ment excreted, but to the amount of pigment retained. As in the human cases, it seems probable that the pigment is retained chiefly because of the failure to excrete; in the rabbit experiments, however, it is difficult to see what causes the renal failure other than the injected solution of myohæmoglobin or some impurity therein. The alternative possibility exists, therefore, that the retention of pigment may initiate renal failure. Further experiments are in process and no full answer can yet be given, but these human cases illustrate that arguments based on the failure to produce renal failure in animals with concentrations in the urine and total amounts injected on a basis of body-weight much greater than in human crush cases do not eliminate myohæmoglobin as a causative agent in man.

ALKALI THERAPY

The fact that five cases whose urine was rapidly made alkaline showed no renal failure, whereas one case subject to exactly the same trauma of a similar duration and extent, but without alkalinisation, subsequently developed uræmia is no complete proof of the efficacy of alkali. While the pH of the urine was changed from 5·5 to 6·7 within two hours, it was not until eighteen hours after release that alkali therapy was started. We know that in air-raid casualties with only slight injuries no renal failure will develop, alkali or no alkali. Case 3 was really the only one in which there is the possibility that alkalinisation affected the course. It is possible that the lesser degree of urinary acidity seen initially in this case compared with other air-raid cases with a similar extent of lesion, together with the absence of clinical "shock" with its resultant oliguria, is the correct explanation of the lack of renal impairment. Unfortunately the corresponding data on case 2 which would have thrown light on this point are not available.

SUMMARY

Of 12 patients who had been pinned down in a shelter by other bodies, one died of other injuries soon after release; one developed a high grade of uræmia but ultimately recovered; and the other 10 showed every grade of injury from severe muscle damage to skin erythema only, and all recovered.

The course was similar to that of the "crush syndrome"—ischæmic muscle necrosis following burial beneath debris as the result of aerial bombardment—but less severe, perhaps because of the short time of compression (1½–2½ hours).

Quantitative estimation of myohæmoglobin, creatine and potassium excretion gave a basis for the calculation of the amount of muscle damaged; this was the best guide to the severity of the lesion and ran parallel to the duration of albuminuria and to the local plasma loss as calculated from (*a*) hæmoconcentration, (*b*) Crooke and Morris's figures for dye distribution and (*c*) limb swelling.

No conclusions can be drawn as to the efficacy of alkali therapy.

PLASMA-VOLUME DETERMINATIONS BY THE EVANS BLUE METHOD

An estimation of plasma volume by the Evans blue method of Crooke and Morris (1942) was made on 4 patients (cases 3, 4, 5 and 6). The results are shown in fig. 4, in which the apparent plasma volume is plotted against the time after injection of the blue dye. The curves are typical, showing that the concentration of the dye remained constant throughout the first hour and thereafter the dye disappeared at the usual rate of about 5% per hour. The true value is represented, therefore, by the average of three readings taken during the first hour. These are as follows:

Case	*Plasma vol. in litres*	*Plasma vol. % body-weight*
6	2·11	4·83
5	3·03	4·59
3	1·55	3 82
4	2·11	3·63

The average normal is taken as 5% body-weight with a normal range of 4·5–5·5%. There was a significant reduction in plasma volume in cases 3 and 4, but in the other two patients it was within the normal range.

These estimations were made between 3·15 and 4 PM, some 17 hours after release from compression.

(*Continued at foot of next column*)

LOCAL THERAPY OF WAR WOUNDS

II. WITH SULPHASUXIDINE *

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THE investigation of succinyl sulphathiazole ('Sulphasuxidine') in the Central Pathological Laboratory, MEF, confirmed its claim to be a drug of interesting and valuable properties. When taken by mouth it is to a small extent broken down to sulphathiazole in the intestinal tract, and while absorption is very slight even when doses of 60 g. are taken daily, all organisms except fæcal streptococci are eliminated from the fæces, and clinical improvement in dysentery is manifest. Its use in colonic surgery, and in the management of abdominal gunshot wounds, is clearly indicated.

It was decided to investigate its properties as a local therapeutic agent in infected gunshot wounds.

Absorption of Sulphonamides

One of the main problems in all sulphonamide therapy is to ensure that neither the rate nor the degree of absorption is great enough to cause severe toxic symptoms or other complications due to sulphonamide poisoning. This problem becomes particularly acute when these drugs in the powder form are applied to open wounds. It is therefore not irrelevant at this stage to give a few examples of the rates of absorption encountered when various sulphonamide derivatives were applied externally or given intraperitoneally or intramuscularly. The examples given below include: some burn cases which were treated with sulphonamide powders or emulsions; 2 cases of sulphadiazine given intraperitoneally; 1 case of sulphathiazole given in the same way; and comparisons of absorption rates of sulphanilamide, sulphathiazole and sulphasuxidine in rabbits. Only the absorption is dealt with, the clinical results being discussed elsewhere.

CASE A.—Extreme third-degree burns of both legs; powdered with 17 g. of sulphanilamide, three weeks after injury. The rise of blood concentration was as follows:

Hours after powdering ..	½	1	2	3	4	5	7½	10½	23	26
Blood concentration (mg. per 100 c.cm.)	6·9	11·4	13·3	13·3	14·4	17·0	16·1	17	15·1	13·0

CASE B.—Treated with 35 g. of sulphanilamide after only 35 min. delay. The blood concentration after 6 hours was 25 mg. per 100 c.cm.; after 24 hours 16·7 mg., followed by a gradual fall.

Several cases were treated with sulphaguanidine and sulphathiazole powders, the burns being of the same order of severity as those in cases A and B. With these two drugs the blood value was far lower.

* Part I, dealing with penicillin, appeared last week.

(*Continued from previous column*)

I am indebted to Sir James Walton, Mr. W. H. Rothwell, Dr. I. A. J. McCready and Dr. A. J. Watson for allowing me to see patients under their care; to Dr. A. C. Crooke and the nursing staff for their help; to Miss Stead (for whose services we are dependant on a grant from the Medical Research Council) who performed the biochemical analysis; and to Dr. Keith Simpson for giving me access to post-mortem material and allowing me to quote his own report.

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CASE C.—Sulphathiazole, 10 g., was put on an extensive second-degree, patchy third-degree, burn 4 hours after injury and the blood concentration never rose above 3 mg. per 100 c.cm.

The low level was maintained when sulphaguanidine was used, characteristic figures being 5·7 mg.; 3·5 mg.; 1·1 mg. If the drugs were applied in the form of an emulsion, however, the blood concentration remained low even in the case of sulphanilamide. Figures obtained with sulphanilamide and soft-paraffin emulsion included 1·2 mg.; 0·94 mg.; 3·8 mg.; 1·4 mg. One fatal case was noted after treatment with sulphanilamide in which the blood concentration reached 40 mg. In many of these cases the urinary concentrations tended to be high. These results show that it is dangerous to use the more soluble sulphonamide drugs in the powder form over wide areas.

Two patients on whom appendicectomies were being performed received powdered sulphadiazine intraperitoneally. This drug has a low solubility (13 mg. at 37° C. and pH 7·2) and the rate of absorption was low. After 10 g. intraperitoneally at 10.30 AM on Oct. 23 the blood concentrations were:

Date in Oct. 1942	23	23	23	23	24	24	25	26	28
Time ..	12.30 PM	2.30 PM	6.30 PM	10.55 PM	10.30 AM	6.30 PM	10.30 AM	10.30 AM	10.30 AM
Conc. of free drug (mg. per 100 c.cm.) ..	1·8	2·2	2·7	3·2	2·2	1·8	1·4	1·04	0·46

The second set of figures are not reliable since the patient had received sulphanilamide by mouth before the operation; however, the increase in blood concentration followed a similar course to the one shown above.

One patient received 10 g. of sulphathiazole intraperitoneally at 11 AM on Jan. 9, and the figures for the blood concentration were:

Date in Jan. 1943	9	9	9	10	12
Time ..	2 PM	4 PM	6 PM	12 Noon	12 Noon
Conc. of free drug (mg. per 100 c.cm.)	4·07	5·28	5·4	2·6	0·37

STUDIES ON SULPHASUXIDINE

The advent of sulphasuxidine seemed to introduce obvious advantages. When this drug is given orally the amount of absorption is extremely low, the blood value being about half that found with sulphaguanidine even when the dosage exceeds 20 g. daily. It seemed possible that if sulphasuxidine was put into a wound or on a burn, a reservoir of free sulphathiazole would be produced as the drug was slowly broken down. Previous workers had claimed that sulphasuxidine is split by bacteria to yield free sulphathiazole, and because of this it seemed possible that external application would provide a continuous potential source of free sulphathiazole, the rate of breakdown being roughly proportional to the severity of the infection. The rate of absorption and degree of breakdown were compared with those of sulphanilamide and sulphathiazole.

Some experiments were carried out with sulphanilamide, sulphathiazole and sulphasuxidine based on the experiment of Hawking.[1] A transverse incision was made in the lumbar muscles of rabbits (weight 1000 g.) and 0·25 g. of drug, made into a paste, was inserted. The fascial covering of the muscle was sutured and any surplus drug wiped away. The skin wound was also closed; 6 and 24 hours later the rabbits were killed and transverse slices of lumbar muscle about 0·5 cm. thick were taken at various distances from the wound. Heart blood, and muscle from the opposite thigh, were also taken. The concentration of free drug was then determined, the results being expressed as mg. of drug per 100 c.cm. of blood or per 100 g. of muscle (table I).

1. Hawking, F. *Brit. med. J.* 1941, i, 263.

TABLE I—CONCENTRATION OF SULPHONAMIDES AT VARIOUS DISTANCES FROM AN EXPERIMENTAL WOUND, AND IN THE BLOOD, 6 HOURS AND 24 HOURS AFTER APPLICATION

Sulphonamide and period of application	Muscle concentration (mg./100 g.)				Blood concentration (mg./100 c.cm.)
	Sides of Wound	1–2 cm. away	4 cm. away	Opposite thigh	
Sulphanilamide (6 hr.)	220	29	1·7	1·8	2
Sulphanilamide (24 hr.)	20	3·7	3·6	1·1	Trace
Sulphathiazole (6 hr.)	Solid drug still present	185	14	2	0·4
Sulphathiazole (24 hr.)	230	26	6	4	0·5
Sulphasuxidine (6 hr.)	F: 0·75 T: 243	F: 47 T: 14	F: 3·6 T: 4·7	F: 3·4 T: 4·6	F: trace T: 0·82
Sulphasuxidine (24 hr.)	A low uniform concentration in all specimens amounting to about 1 mg. per 100 g. The amount of water used in extracting the specimen was too large for accurate estimation.				..

F = free. T = total.

These results are in agreement with those observed in the treatment of burns. The more soluble sulphanilamide rapidly reaches a maximum concentration and is rapidly excreted, whereas sulphathiazole diffuses far more slowly. In the case of sulphasuxidine there is a progressive and decreasing difference between the free and the total drug demonstrating once more the capacity of plasma to break down sulphasuxidine into the free compound.

Further experiments were carried out to show the rates of absorption when sulphanilamide, sulphathiazole and sulphasuxidine were put in the peritoneal cavity of a rabbit, the drugs being suspended in lanoline and in saline. The blood concentrations were estimated 24 and 48 hours afterwards and all the rabbits were killed after 7 days (table II).

TABLE II—RATES OF ABSORPTION OF SULPHONAMIDES FROM PERITONEUM OF THE RABBIT

Experiment	Concentration (mg. per 100 c.cm. of blood) after:		
	24 hr.	48 hr.	7 days
1. Sulphanilamide in saline, 10 c.cm. of 20% suspension	4·0	0·89	Large fat clot in peritoneum.
2. Sulphathiazole in saline, 10 c.cm. of 20% suspension	1·1	2·2	Nil abnormal.
3. Sulphathiazole in lanoline, 10 c.cm. of 20% suspension	0·83	0·62	Fat clot as in 1.
4. Sulphasuxidine in saline, 10 c.cm. of 20% suspension	F: Faint trace T: 2·3	F: 0·5 T: 2·3	Nil abnormal.
5. Sulphasuxidine in lanoline, 10 c.cm.	F: Nil T: 0·6	F: 0·6 T: 1·5	Fat clot as in 1.

F = free. T = total.

As was expected, these experiments showed greater absorption from the saline than from the lanoline; and, as before, the more soluble sulphanilamide was absorbed the quickest. The fat clot on section showed a high degree of organisation. It had all the appearances of fatty tissue (i.e., alveoli with fine fenestration); on the outside was a layer of coagulated lymph and medial to this an area of intense infiltration with polymorphs and large mononuclear cells.

A few experiments were carried out in vitro to determine the degree of breakdown of sulphasuxidine in various fluids. A very small amount of the drug is liberated when a tablet is broken and shaken with water. This breakdown increases with rise of temperature and with increase of time between suspension and estimation, but even after 24 hours at 37° C., a 0·5 g. tablet in 100

c.cm. of water gave a concentration less than 0·5 mg. In suspension with dilute acids or alkalis the breakdown is increased. One of the main difficulties of estimating the breakdown is that the estimation must be carried out in acid solution, and hence there is a danger of increasing the breakdown; in alkaline solutions there is a danger of causing precipitation. The drug is completely broken down to free sulphathiazole by heating with mineral acids on a water-bath. A suspension of the drug in the presence of fæcal matter showed a concentration of free sulphathiazole three times as great as the control. Suspensions in plasma or serum or pus showed a considerable increase in breakdown as compared with suspensions in water, and this remains true even if the serum has been heated to 56° C. for two hours. Figures varied widely, as the following show:

—	Sulphasuxidine, 0·5 g., plus:			
	Pus (10 c.cm.)	Pus (5 c.cm.) and saline (5 c.cm.)	Water (10 c.cm.)	Saline (10 c.cm.)
Concentration of free sulphathiazole after 17 hr. at 37° C. (mg./100 c.cm.)	150	56	9·0	9·3

Other samples gave lower figures, such as 46 mg. per 100 c.cm.; 35 mg. and 42 mg., when estimations were carried out as above using 10 c.cm. of pus; 2 samples of pleural fluid gave values of 45 mg. and 25 mg.

Estimations were also carried out on the fluid from wounds into which 20% sulphasuxidine in lanoline had been put. About 30 c.cm. were usually put into the wound and an estimation of the free drug in the wound fluid was made after 24 hours. The amount of free sulphathiazole varied considerably, figures including: 2·2 mg. per 100 c.cm., 2·6 mg., 32 mg., 27 mg., and 35 mg. The blood concentrations never exceeded 1 mg. of free drug. In one case where powdered sulphasuxidine was put into the wound, a concentration of 150 mg. was found in the wound fluid. This result was unreliable owing to solid particles of the powder still remaining.

CONCLUSIONS ON ABSORPTION

Experimental findings suggest that:

1. The probable rate of absorption of sulphonamide drugs can be forecast from a knowledge of their solubilities.
2. The most soluble are most likely to produce dangerously high concentrations and are best used in suspension.
3. The breakdown of succinyl sulphathiazole into free sulphathiazole in ordinary solvents—including plasma, cerebrospinal fluid and fluid from wounds—is too small to produce a dangerous blood concentration.
4. The breakdown is increased by rise of temperature.

Therapeutic Tests

Sulphasuxidine applied locally in the form of a 20% anoline cream appeared to limit quickly and effectively the gram-positive flora, to control suppurations and accelerate healing. No toxic or irritant properties of any kind were noted. Absorption was less than 1 mg. per 100 c.cm. of blood. The cream was heated to 40° C., and then applied to wounds with a syringe used as a grease-gun.

It is quite possible that other sulphonamides applied in this way would have given equally good results; however, the "reservoir" potentialities of sulphasuxidine are, at present, a unique feature from a theoretical point of view. If this drug is used intraperitoneally, the lanoline cream should not be used, as it acts as a foreign body. Probably a microcrystalline form would be best.

Results in 8 cases are set out in table III.

DISCUSSION

HEALING OF WOUNDS

This series of cases is a small one. For this there are several reasons—the length of time taken on account of the individual care required, the movement of patients to other centres necessitated by Service conditions, and the number of other duties in a routine laboratory. Moreover, most wounds are encased in plaster and are inaccessible. The results are presented in an attempt to encourage the local treatment of wounds, and in the belief that this is not carried to its logical conclusion at present. If it be granted that sulphonamide prophylaxis by local application is of value, and if it is further established that its action, owing to breakdown and absorption, is temporary, then it is reasonable to suggest that repeated application can extend the prophylactic value. The same argument holds for penicillin treatment; observation shows that one application will not give permanent results, and the process must be continued. Similarly, all local applications must be made on a raw surface; pus must be removed.

Up to the present, the number of Allied wounds have fortunately been few compared with the numbers in the last war. The total allied casualties in the battle of El Alamein were less than those inflicted in two days of the Somme battle. Surgeons in this war to date cannot speak from anything like the experience of those of the last war. They have however modified greatly last-war methods, in particular with regard to closed-plaster technique.

The advantages of this method are obvious even to one not a surgeon. The relief of pain, and ease of nursing of a patient with the severest injuries is striking. It is obviously admirable for a large number of cases, but it does interfere with local treatment of infection.

One compromise is the use of a window in the plaster, and this has been used in some of the cases described. Its disadvantages are: first, the risk of new infection, though this in our opinion is more than balanced by the benefit of the therapy; and the more serious disadvantage that the wound tends to bulge out through the window, compressing the edges, and causing pain. Here a further compromise is possible. After a period during which the wound is locally treated, it may finally be covered in plaster, and the unequal pressure readjusted.

Three cases in this series were disappointing. One was a compound fracture of femur, infected with hæmolytic *Staph. aureus* and hæmolytic streptococci. It showed no reaction at all to penicillin, even applied thrice daily in a 1% solution, and even though the organisms in vitro proved susceptible; it did not react to sulphathiazole microcrystals, to sulphasuxidine, or to proflavine. Two others showed an initial reaction to penicillin, but then regressed to their former bacteriological picture; and sulphasuxidine also proved ineffective. These were both compound fractures with exposed bone, and all were first treated at least a month after wounding.

One of these cases was then treated with proflavine powder, and the wound was covered with a wire cage. It scabbed over, and the profuse suppuration ceased. On two occasions associated with the lighting up of wounds elsewhere this wound too became active, and brisk suppuration set in; but when the pus had been cleaned away the infection again subsided, and was eventually put up in closed plaster, well on to complete healing.

No-one can observe the process of healing in wounds without being impressed by certain facts. The minimum interference with a surface is essential; to drag off adherent dressings, and even soft-paraffin gauze, is to inflict pain, and to delay healing. In many cases a wire cage applied on top of the window, above the plaster, and covered with cotton-wool, is the best "dressing;" the wound surface is left open. Secondly, aspiration of pus and the use of many-tail bandages to avoid all movement of the limb, gives the patient ease and makes him look forward to the dressing, not with apprehension but with relief.

Finally, gross as is the disturbance caused by a suppurating wound to a patient's general well-being, the converse is equally true: a wound showing no tendency to heal undergoes a profound change when the patient's general condition improves; attention to his diet, his psychological state, his general comfort are all part of the essentials of wound treatment. While this argument can scarcely be pursued without leaving the confines of pathology, it is within the province of that craft to insist that the increased metabolism of fever, the gross protein loss of suppuration, the diminished appetite caused by the malaise of sepsis all render the dietetic control of such a patient an urgent problem. It may, indeed, be the greatest single necessity; in its absence other methods are relatively useless, in its presence the need for them far less.

TABLE III—EIGHT CASES TREATED WITH SULPHASUXIDINE CREAM (SX. CR.) OR SULPHASUXIDINE POWDER (SX. P.)

Case and date	State of wound and progress	Treatment	Smear (S) and Culture (C)
CASE 1	Patchy 3rd degree diesel-oil burns, both hands; sl., suppuration	Sodium sulphate	..
Nov. 6, 1942	Cleaned and dressed	10 c.cm. of sx. cr. on each hand	S: pus cells + +; gram-pos. cocci and gram-neg. bacilli in mod. nos. C: no hæmolytic streptococci; *Staphylococcus albus*; coliform bacilli
Nov. 10	Both hands healing. Small patch 3rd degree, rt. hand, not healed	7·5 c.cm. of sx. cr. on each hand	S: pus cells +; few gram-pos. cocci and gram-neg. bacilli. C: a few *Staph. albus*
Nov. 11	Blood concentration: nil	..	..
Nov. 16	No discharge; all areas healing well	5 c.cm. of sx. cr. on each hand	S: a few pus cells; no organisms. C: sterile
Nov. 17	Blood conc.: nil	..	..
CASE 2 Nov. 2, 1942	Gutter-wound rt. shoulder, 4 × 2 in., extending down and in from post. axillary border over wing of scapula. Slightly dirty	Eusol dressings and oral sulphonamides	..
Nov. 8		Sulphonamides stopped, after 21 g. given	..
Nov. 10	Wound v. dirty and foul smelling; fair amount of discharge	10 c.cm. of sx. cr. over shoulder	S: pus cells + + +; gram-pos. cocci in large nos. C: hæm. *Staph. aureus*, and hæm. strep., mod. growth
Nov. 11	Blood conc.: 0·2 mg. per 100 c.cm.	..	..
Nov. 15	No discharge; wound pink and healthy; pt. feels well	10 c.cm. of sx. cr.	S: pus cells + +; few gram-pos. cocci. C: hæm. *Staph. aureus*, a few colonies
Nov. 19	Clean wound; no discharge	4 g. of sx. p. to wound. Final treatment	S: few pus cells. C: sterile
Nov. 20	Blood conc.: nil	..	..
CASE 3 Nov. 9, 1942	Foul-smelling severe wound of lt. thigh with great skin loss and gross infection; oozing dark green pus from pocket connected with surgical incision on other side. Pt. felt well. Eusol used to deodorise, not applied to wound	20 c.cm. of sx. cr.	S: pus cells + + +; heavy infection with gram-pos. cocci and gram-neg. bacilli. C: hæm. strep.; *Staph. albus*; coliform bacilli
Nov. 12	Copious discharge, foul-smelling, greenish-yellow; much pus aspirated from pocket	Same	S: pus cells + + +; gram-pos. cocci in large nos. C: free from hæm. streps.
Nov. 13	Much less discharge and smell; tissues looked healthy. Pt. much better	,,	S: pus cells + + +; mod. nos. gram-pos. cocci. C: hæm. strep., mod. growth
Nov. 14	Little discharge; still a little pus collecting in deep pocket; dull pain below wound during night	,,	S: pus cells + +; mod. amount of gram-pos. cocci. C: hæm. strep., mod. growth
Nov. 15	Pt. fit; no discharge; clean passage from wound to incision on other side	,,	S: pus cells + +; mod. nos. gram-pos. cocci. C: hæm. strep., mod. growth
Nov. 17	No discharge; nothing aspirated; tissues healthy	,,	S: pus cells +; a few gram-pos. cocci. C: hæm. strep., a few cols.
Nov. 19	No discharge; tissues healthy	,,	S: A few pus cells; a few gram-pos. cocci. C: hæm. strep., 4 cols.
CASE 4 Oct. 23, 1942	Through-and-through wound, lt. thigh	Sulphanilamide and soft-paraffin gauze	..
Nov. 3	Dirty entry and exit wounds, heavily infected, much loss of skin; connected by drains; exuding large amount of foul-smelling greenish pus	10 c.cm. of sx. cr. to wounds	S: pus cells + + +; mod. nos. gram-pos. cocci. C: hæm. *Staph. aureus*, free growth; coliform bacilli
Nov. 4	Blood conc.: nil	..	..
Nov. 5	Both wounds healthy; little discharge; pt. felt well	Same	S: pus cells + +; few gram-pos. cocci and gram-neg. bacilli. C: *Staph. aureus*, 10 cols.: pyocyaneus, a few cols.
Nov. 8	Drain removed; wound healthy, a little discharge	,,	S: pus cells + +; few gram-neg. bacilli. C: pyocyaneus, few cols.
Nov. 9	Blood conc.: nil	..	..
Nov. 11	No discharge from wound; no complaints	,,	Scanty pus cells; few gram-neg. bacilli. C: pyocyaneus, few cols.
Nov. 12	Blood conc.: nil	..	..
Nov. 19	2 dry dressings since last treatment. Ready for skin graft	..	..

TABLE III—(*continued*)

Case and date	State of wound and progress	Treatment	Smear (S) and Culture (C)
CASE 5	Perforating wound, lt. side chest wall. Fracture of ribs 9, 10 and 11	Sulphanilamide, soft-paraffin gauze, eusol dressings	..
Nov. 11, 1942	V. deep unhealthy-looking wound, tender to touch; copious discharge; fairly foul smell. Compound fracture of ribs; old empyema operation	7 c.cm. of sx. cr.	S: pus cells + + +; mod. nos. of gram-pos. cocci and gram-neg. bacilli. C: hæm. strep., free growth; coliform bacilli
Nov. 12	Mod. amount of discharge, removed by suction; fairly clean wound left; no smell	10 c.cm. of sx. cr.	S: pus cells + +; mod. nos. gram-pos. cocci. C: hæm. strep., free growth
Nov. 13	Little discharge; all tissue pink and healthy	7·5 c.cm. of sx. cr.	S: pus cells +; a few gram-neg. bacilli. C: coliform bacilli, few cols.
Nov. 14	Pt. well; dull pain during the night. No discharge; wound beginning to granulate	6 c.cm. of sx. cr.	S: pus cells +; few gram-pos. bacilli. C: hæm. strep., 7 cols.
Nov. 16	No discharge; no complaints	6 c.cm. of sx. cr.	S: few pus cells; few gram-pos. cocci. C: hæm. strep., 11 cols.
CASE 6 Oct. 26, 1942	Perforating wound, lt. thigh; loss of fair amount of tissue	Sulphonamide and soft-paraffin gauze	..
Nov. 3	Entry wound on inside of thigh; great loss of skin, but not heavily infected; exit wound about 12 in. sq., fairly deep. Drains in position; exuding yellow pus; fairly foul-smelling	20 c.cm. of sx. cr. put on wound: 5 c.cm. on entry, 15 c.cm. on exit	S: pus cells + + +; mod. nos. gram-pos. cocci. C: *Staph. aureus*, mod. growth
Nov. 4	Blood conc.: nil	..	..
Nov. 5	Little discharge; tissue looked healthy; granulation. Pt. looked and felt fit	15 c.cm. of sx. cr. on wound	S: pus cells + + +; few gram-neg. bacilli. C: sterile
Nov. 8	Drain removed on Nov. 7. Wound healthy; much granulation; no discharge. Pt. v. fit	Same	S: pus cells +; few gram-neg. bacilli. C: sterile
Nov. 9	Blood conc.: nil	..	..
Nov. 11	No discharge; tissue healthy. Pt. had use of leg except for straightening out	Same	S: scanty pus cells, few gram-neg. bacilli. C: coliform bacillus, a few cols.
Nov. 12	Blood conc.: nil	..	..
Nov. 19	2 dry dressings since last treated; wound clean, ready for surgical treatment	..	..
CASE 7	Admitted Oct. 15 with cellulitis, rt. forearm and elbow. Large abscess, forearm; adenitis + + +	Sulphonamide powder and soft-paraffin gauze, Oct. 19–22. Abscess opened, Oct. 31. Oral sulphonamide, Oct. 15–Nov. 2	..
Nov. 6, 1942	Sl. discharge from both areas; ulcer resisted treatment	5 c.cm. sx. cr. to forearm	S: pus cells + + +; gram-pos. cocci in clumps + +. C: hæm. *Strep. aureus*, free growth
Nov. 8	No discharge; beginning of granulation; both wounds clean	5 c.cm. to each wound	S: few pus cells; few gram-pos. cocci. C: *Staph. aureus*, mod. growth
Nov. 9	Bl. conc.: nil	..	..
Nov. 12	Forearm wound scarred over; elbow wound clean, but not covering over, probably owing to movement	5 c.cm. of sx. cr. to elbow	S: pus cells +; no orgs. seen. C: sterile
Nov. 18	Elbow wound beginning to heal; no discharge	2·5 g. of sx. p.	Nil abnormal
CASE 8 Oct. 26, 1942	Infected 2nd degree diesel-oil burn of lt. ankle with small 3rd degree area	'Tannafax' applied within 20 min., then eusol for 2 days	..
Nov. 2	Burn 9½ by 4¾ in., dirty and neglected	Cleaned; sx. cr. 30 c.cm. of 20% soln. (6 g.)	S: pus cells + + +; large nos. gram-pos. cocci. C: hæm. strep. *Staph. albus.*
Nov. 3	Blood conc.: nil in 10 hr.; 0·2 mg. in 14 hr.	..	..
Nov. 8	Dressing removed. Only one small area of 3rd degree burn not healing. Remainder covering with skin.	Sx. cr., 20 c.cm. of soln. (4 g.)	S: pus cells + + +; few gram-pos. cocci. C: *Staph. albus*, a few cols.
Nov. 9	Bl. conc.: nil	..	..
Nov. 12	Wound clean; epitholium covering burn. All 2nd degree areas covered. Small pocket of pus around hair follicle	Sx. cr. 10 c.cm. of soln. (2 g.)	S: skin, pus cells +, no orgs.; follicle, pus cells + +, gram-pos. cocci. C: no growth
Nov. 13	Bl. conc.: nil	..	..
Nov. 18	Completely healed	Dry dressing only	..

SUMMARY (Parts I and II)

Treatment of infected war wounds with the calcium or sodium salts of penicillin rapidly reduced the numbers of gram-positive organisms, including clostridia, staphylococci, streptococci, and corynebacteria. Gram-negative organisms were unaffected. Therapeutic results were excellent.

Experiments with *Penicillium notatum* culture filtrates were promising.

In applying powdered sulphonamides to large absorb-

ing surfaces such as burns, wounds or the peritoneum, there is danger of producing an excessive concentration of the drug in the blood. The more soluble sulphonamides are therefore unsuitable for this purpose.

Experiments showed that plasma and other wound fluids break down succinyl sulphathiazole into free sulphathiazole; but the rate of breakdown is so slow that there is no risk of sulphathiazole being absorbed into the blood in dangerous quantities.

Local application of a lanoline cream containing 20% succinyl sulphathiazole quickly controlled wound infections by gram-positive organisms. No toxic or irritant effects were observed, and the blood contained less than 1 mg. of sulphathiazole per 100 c.cm. This lanoline cream is not recommended for intraperitoneal use.

The surface of wounds should be disturbed as little as possible. Aspiration of pus and the use of many-tailed bandages are recommended.

Attention to the mental state, general comfort, and especially the diet, is an essential part of the treatment of wounds.

These investigations were carried out in the Central Pathological Laboratory, MEF, by the staffs of that laboratory and of the laboratory of the Scottish General Hospital. The post-mortem examinations were carried out by Capt. A. D. Morgan, RAMC. The bacteriological controls were made in collaboration with Sergeant J. Pilling, RAMC, Sergeant L. C. Wilson, RAMC and Private H. Rosenband-Pollack, Palestine ATS.

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EXPERIMENTAL ALLOXAN DIABETES IN THE RAT

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IN 1889 v. Mering and Minkowski demonstrated that total pancreatectomy caused fatal diabetes mellitus in dogs. Their work has led to a great increase in our knowledge of diabetes, partly by promoting more intensive study of glycosuria, partly by directing the morbid histologist to more intimate investigation of the pancreas, but with most practical outcome by initiating the investigations which culminated in the discovery of insulin by Banting and Best (1921). Nevertheless, the classical experiment of over fifty years ago has had little or no influence on the doctrine of the ætiology of diabetes or on its prevention. Joslin (1937), in discussing prevention, refers almost solely to measures calculated to avoid hereditary transmission, and to care in dietary such as will lessen the likelihood of obesity. The value of these practical suggestions need not be doubted, for they refer to recognisable ætiological factors; but it is not claimed that they are based on exact knowledge of the pathogenesis of diabetes or of the part that may be played by disease of the pancreas in initiating the malady.

In recent years the work which has shown most promise for elucidation of pathogenesis is that of F. G. Young (1937) who discovered that diabetes could be produced in dogs by repeated injections of an extract of the anterior pituitary. Early in the course of the injections definite histological changes could be recognised in the pancreatic islets (Richardson and Young 1938, Richardson 1940). Later, when diabetes had been established for many weeks, the islets were permanently altered. In one case there was profound reduction of β-cells and in another extensive hyalinisation of islets with loss of almost all the specific cells; in this second case there was also a subacute pancreatitis affecting the acinar tissue. This research showed that a diabetic state can be produced by the action of a derivative of body tissue, and there may be deeper significance in the fact that the extract is derived from a gland concerned in the fine adjustment of normal nutrition. Also the histological results suggest that while the effective inoculum is obtained from the hypophysis it acts by influencing the islets of Langerhans.

In a previous paper (Dunn, McLetchie and Sheehan 1943) it was shown that selective necrosis of the pancreatic islets could be produced acutely in rabbits by pure chemicals, particularly alloxan. The first successful results in the production of diabetes with alloxan have since been obtained in rats.

The rats were albinos of a pure Wistar strain, and young adult males were used. They were ordinarily fed on hospital kitchen scraps consisting of potato, egg, meat, fats, and milk puddings. Animals which developed polyuria were supplied with abundant water. On this diet rats normally passed only about 5 c.cm. of urine daily, free from glucose. In earlier experiments the urine was collected on filter-paper in drops exuded when the animal was stretched. Such samples could be tested qualitatively for sugar by Benedict's reagent. In later experiments metabolism cages were available for collection of urine.

ACUTE EFFECTS OF ALLOXAN

The acute effects were examined in seven rats. One (No. 1) was injected intramuscularly and five (Nos. 2, 4, 9, 10, 12) subcutaneously with alloxan equivalent to 300 mg. per kg. body-weight; one (No. 11) received 400 mg./kg. subcutaneously. The clinical and the pathological effects varied. No. 10 showed no evidence of upset and when it was killed on the 4th day the pancreatic islets were normal; No. 4, though ill and off its food, also gave a negative histological result when killed at 48 hrs. In the other five animals well-marked lesions were found.

Nos. 1 and 2, hunched up and weakly, were killed at 6 hours. In both, the islets were universally affected: a large proportion of the cells throughout each islet were shrunken, rounded off and displaced from their attachments: their protoplasm was eosinophil and hyaline, and their nuclei pyknotic: a few cells among these retained normal characters (fig. 2). Two islets in the pancreas of No. 2 were of peculiar structure in having a wide peripheral cuff of large cells free from necrosis and with abundant eosinophil granular protoplasm and large active nuclei. These were judged to be α-cells, restricted to these two islets and surrounding a central mass of β-cells, many of which were necrotic (fig. 3).

No. 9 was ill and did not eat until the second day; glucose and insulin were given; there was glycosuria on the third day. When it was killed on this day the islets showed extensive lesions of later date than in Nos. 1 and 2. Many cells were crumbling to debris, others were loose and rounded off with pyknotic nuclei, and in a state from which recovery appeared doubtful: in contrast a proportion of cells remained in live state with normal or active nuclei; these had normal attachment to stroma and sometimes occurred in short ribbons. At the periphery of the islets there were numerous cells with small bodies and active nuclei; mitoses were very rarely observed.

No. 11 died, cold and drowsy, at 48 hours; there was no glycosuria. The changes in the islets were as in No. 9 but more severe, with more necrotic debris and more cells of doubtful viability, while obviously live cells were fewer. There were, in addition, very pronounced lesions in the small ducts in this pancreas, comprising dilatation and accumulation of wax-like eosinophil masses with leucocyte infiltration in the walls and in the interstitial septa: this lesion could be interpreted as an early pancreatitis.

No. 12 stopped eating on the second day and was hunched up and cold. Injections of glucose were given with insulin and the animal survived until the 4th day when death occurred in coma. The blood-sugar was then found to be only 0·01 g. per 100 c.cm. In the islets in this case most of the cells were normal and in situ, but scattered among these were a number of cells with shrivelled bodies and pyknotic nuclei, while granular debris of broken-down cells occurred here and there.

These few experiments, though they were only first trials, showed that in the rat as in the rabbit the pancreatic islets could be selectively and sometimes severely damaged by alloxan: the β-cells appeared to be chiefly if not exclusively affected. As compared with the lesions described in the rabbit, the necrosis tended to involve individual cells distributed through the islet rather than to destroy completely a central mass of