The first is severe and is characterized by weight loss and *ketosis* as well as hyperglycaemia; it occurs at any age, but mainly in the young, and their plasma contains no available insulin but renders the rats insensitive to subsequent insulin injections. They require insulin treatment to live.

The second type consists mainly of middle-aged obese diabetics, females being more numerous, and is distinguished by the absence of ketosis and loss of weight. Their plasma contains available insulin, roughly 70% of normal controls, but does not make rats insensitive to insulin. Their diabetic state is easily controlled by diet alone, especially when obesity is thereby reduced.

The experiments were first carried out at the Baker Institute and the Alfred Hospital, Melbourne, and later in the Departments of Diabetes and Chemical Pathology, King's College Hospital, London, where Professor C. H. Gray deserves our best thanks. We also wish to thank Miss M. Sandiford for invaluable assistance, Dr. E. Reid for a sample of growth hormone, and Messrs. Boots Pure Drug Company for an expenses grant.

REFERENCES

- Bornstein, J. (1950). *Aust. J. exp. Biol. med. Sci.*, **28**, 87, 93.
 — and Lawrence, R. D. (1951). *British Medical Journal*, **1**, 732.
 — and Trehwella, P. (1950). *Aust. J. exp. Biol. med. Sci.*, **28**, 569.
 — (1951). *Med. J. Aust.*, **1**, 119.
 Hartroft, A. W. (1950). *Proc. Amer. Diabetes Ass.*, **10**, 46.
 Lawrence, R. D. (1951). *British Medical Journal*, **1**, 373.

TREATMENT OF TROPICAL ULCERS

BY

H. D. OBRIEN, M.B., B.Ch., B.Sc., F.R.C.S.I.

Surgeon, Overseas Food Corporation Hospital, Nachingwea, Tanganyika

There is already a fairly extensive literature on tropical ulcers, but the results of treatment appear to be still unsatisfactory, and towards the end of each rainy season in Tanganyika the number of ulcer cases attending hospital is embarrassing. The wide diversity of treatments recommended suggests that none is wholly satisfactory, and a study of the literature is not very helpful, as published series are often small and lack definition of the character of the ulcers treated and of criteria of cure. The results of various forms of treatment used in a series of 368 unselected in-patients treated mostly by one surgeon in two Tanganyikan hospitals may therefore be of value.

Geographical Factors and Incidence

In the present series the ulcers were all of the sloughing or phagedenic type so well described by Clements (1936), and all occurred in Africans, of whom most were employees of the Overseas Food Corporation. They were treated in two hospitals, of which one (K) is situated in Central Province on the edge of the Masai Plateau, a relatively dry scrub-land at about 4,000 feet (1,220 metres) above sea-level, with an annual rainfall of 10–15 in. (25–38 cm.). The second hospital (N) is in Southern Province, in miombo forest land at an altitude of about 1,000 feet (305 metres) and with a rainfall of 35–40 in. (89–102 cm.). In the latter region there seems to be a considerably higher incidence of yaws, bilharziasis, ankylostomiasis, and secondary anaemia than in Central Province. Nevertheless the types of ulcer seen in the two regions are essentially

similar, though involvement of bone and tendon appears to be slightly commoner and more extensive in the south. The veldt sore or desert sore type of ulcer was not found among Africans in either region.

The magnitude of the problem is illustrated by Table I, which is extracted from monthly reports by the two hospitals concerned. These do not exactly coincide with the periods covered by the present series. The relatively higher percentage of out-patient ulcer cases at hospital N compared with hospital K is probably due to the inclusion of a number of cases of secondary yaws.

TABLE I.—Incidence of Tropical Ulcers in Hospital Patients (African)

	Hospital N January 1 to December 31, 1949		Hospital K April 1, 1949, to March 31, 1950	
Out-patient department, new attendances:				
All cases	8,405		22,548	
Ulcer cases	1,141		984	
Percentage of ulcer cases	13.6		4	
	No.	Days in Hospital	No.	Days in Hospital
In-patient department, cases discharged:				
All cases	1,719	26,180	3,546	34,139
Ulcer cases	111	2,881	147	4,096
Percentage of ulcer cases	6.4	11.0	4.2	12.0

The overall average stay in hospital of the 368 cases was 26.5 days, and most patients were recommended relief from duties for about seven days after discharge, so that the expense in hospital treatment and the loss of man-power from this cause are very considerable.

Aetiology

Nutrition.—It is generally accepted that tropical ulcers occur in the underprivileged and undernourished classes (Pattanayak, 1944; Marsh and Wilson, 1945; Rao *et al.*, 1945; Pran Nath Luthra, 1946; Triloki Nath, 1946; Blank, 1947; Adamson, 1949), and this is further confirmed in the present series as shown in

TABLE II.—Incidence of Ulcers by Occupation

Occupation	No. of Cases
Employees { Unskilled labourers	174
Semi-skilled	15
Office workers, etc.	0
Dependants of employees	6
Non-employees (local peasants)	52

247

Table II. While the rations provided for labourers were adequate in calorie and vitamin content, many of the men had been undernourished for many years and had never undertaken heavy physical labour. They mostly developed ulcers before they had been long enough in the employment of the Corporation to have derived much benefit from the better food provided. In addition to their poorer physical condition, the labourers are more exposed to trauma and dirt than sedentary workers.

Circulatory Factors.—Typical phagedenic ulcers occur almost exclusively below the knee (Earle, 1942; Pattanayak, 1944; Rao *et al.*, 1945; Seshadrinathan, 1945; Pran Nath Luthra, 1946; Triloki Nath, 1946), and this is further demonstrated in Table III. What the connexion is between this regional incidence and circulatory inadequacy is not within the scope of this paper, but it should be noted that none of the cases

TABLE III.—Regional Incidence of Ulcers

Below knee, not specified ..	60	Finger	1 (with yaws)
Leg, knee to ankle	96	Elbow	1 " "
Ankle and heel	104	Arms and legs ..	1 " "
Foot	46	Buttock	1 (malignant)
Toe	11	Scalp	1 (atypical)
		Forearm	1 " "
	317		6

showed varicose veins, and small ulcers secondary to filarial elephantiasis and nutritional oedema are not included. It should be noted, however, that labourers rarely wear shoes or stockings, and their lower extremities are constantly exposed to injury by thorns or bamboo stems, etc., concealed in the long grass found at the end of the rainy season.

Trauma.—Opinion on the influence of trauma in starting ulcers appears to vary, but it must be remembered that it is often difficult to obtain an accurate history from an African, and that the original trauma may be very minor. Adamson (1949) obtained a history of injury in 112 of his 114 cases, while Ransford (1948) states that 311 of his 641 cases had a spontaneous origin. Radhakrishna Rao *et al.* (1945) say the origin was generally traumatic in their 127 cases, while Ramachandra Rao *et al.* (1949) got a history of injury in only 14 out of 38 cases. In the present series reliable histories were obtained in 209 cases, of which 181 attributed the ulcer to an injury. It seems probable that in the vast majority of cases infection must enter through a break in the skin, which is usually minor, and may be caused by an insect bite.

Infection.—Infection is generally mixed, but in most acute and subacute cases there is an overwhelming preponderance of Vincent's organisms (*Borrelia vincentii* and *Fusiformis fusiformis*) (Earle, 1940; Costa, 1944; Seshadrinathan, 1945; Blank, 1947; Adamson, 1949; Rao *et al.*, 1949). Pattanayak, however, in 144 examinations of exudate found spirochaetes in only 8 and fusiforms in 52. In the present series exudate from 144 acute and subacute ulcers was examined microscopically, and Vincent's organisms, singly or combined, were found in 126. Experience seemed to show that the earlier the ulcer was examined the more often were Vincent's organisms found. Spread of infection may be by flies, which cluster densely round the afflicted, but Clements (1936) attributed much infection to the habit of indiscriminate spitting among his patients, associated with a high incidence of oral infection. Tanganyikan Africans do not chew betel and do not spit very much, but Table IV shows that the mouth is probably a reservoir of infection. The habit of applying a first-aid dressing of saliva to a minor wound is by no means confined to Africans, and this would appear to be a likely method of conveying infection.

TABLE IV.—Incidence of Vincent's Organisms in Mouths and Ulcers

			No. of Patients
Ulcer positive, mouth positive ..	..	..	37
" " " negative	..	..	4
" " " positive	..	..	2
" " " negative	..	..	1

Coincident Disease.—Some degree of malnutrition was very common among ulcer patients, and in Southern Province chronic malaria, ankylostomiasis, helminthiasis, bilharziasis, and yaws were present singly or in combination in roughly half the patients. The only statistical survey done in the present series was of the Kahn reaction in 95 patients in Southern Province, where yaws was common and syphilis rare. Of these

cases, 38 had positive reactions, 48 were negative, and 9 doubtful positive. It was not felt that yaws played more than a minor part in increasing susceptibility to ulcers, but bone changes were commoner and more extensive in patients with a positive Kahn reaction.

Clinical Condition and Complications

The various phases of development of the phagedenic ulcer and its progress to chronicity or healing have been repeatedly and admirably described elsewhere (Clements, 1936; Blank, 1947). It may, however, be necessary to reiterate that these ulcers are painful, tender, and very offensive, and that they spread very rapidly in the early phases, with complete destruction of skin and often of underlying tissues also. Earle (1942) stated that in Trinidad and Tobago he never saw regional lymphadenopathy or involvement of muscle, periosteum, or bone, but experience in Tanganyika has been less favourable. Of 135 consecutive acute and subacute cases seen at hospital K, 59 showed regional lymphadenopathy, 34 had some degree of fever on admission (excluding cases with positive blood slides for malaria), 12 had tendon involvement, 8 had bone involvement, 3 had muscle involvement, and 2 had abscesses due to burrowing infection from the ulcer. The incidence of bone and tendon involvement was if anything higher at hospital N. The metastatic non-suppurative osteoperiostitis referred to by Early and Bharucha (1944) was found in one case only.

General Treatment

All writers on this subject agree that general constitutional treatment is essential. The ideal is rest in bed in hospital, with an adequate diet rich in protein and supplemented with vitamins. Blank (1947) and Hallinan (1950) stress the importance of vitamin-B complex given in the diet or locally, but in the present series no special supplement of this vitamin was used.

The importance of vitamin C in wound-healing is generally accepted, and Adamson (1949) has shown that tissue levels of this vitamin are reduced in patients with florid ulcers, but tend to increase again as the ulcer heals. This is in accordance with the demonstration by Harris *et al.* (1937) that there is increased utilization of vitamin C in infections. In the present series vitamin C was given on general principles to all cases, usually in the form of ascorbic acid tablets, 100 mg. daily.

Cod-liver oil (Charters, 1943; Rao *et al.*, 1945) has been widely used as a local application, and the normal African diet tends to be deficient in fat. Local application of cod-liver oil is very offensive and repugnant to a patient already afflicted with a stinking ulcer, and this method was not used in the present series, but all cases received fat-soluble vitamins in the form of crude cod-liver oil or vitaminized shark oil in doses of 2 dr. (7 ml.) daily. Supplementary calcium, as recommended by Charters (1943) was not given, and extra milk and meat were advised only for the very debilitated and chronic cases.

Absolute rest in bed was ordered for all active ulcer cases, but in practice it is found to be impossible to keep Africans in bed without recourse to mechanical means of restraint.

Parenteral Penicillin and Sulphonamides

Penicillin locally or by injection has been used by many recent writers (Pran Nath Luthra, 1946; Blank,

1947; Denhoff and Kolodny, 1947; Pinkerton, 1947; Whitestone, 1947; Rao *et al.*, 1949), and the drug is now comparatively cheap, although Whitestone says its use by injection in ulcer cases is extravagant. Penicillin was given parenterally to patients treated by Schedules I, III, V, VI, and VII (see Appendix) in this series. At first crystalline penicillin G was given in three-hourly doses of 25,000 units, but when procaine penicillin became available at a slightly lower cost than the crystalline salt this was used as a routine in doses of 150,000 units twice daily. This dose is probably unnecessarily high, but the preparation available contained 300,000 units per ml., and the average African orderly cannot be relied on to withdraw less than 0.5 ml. from a bottle without wastage. The most satisfactory dosage schedule, and that mostly employed in Schedule VI cases, was to give penicillin from two to four days from admission, followed by four doses of 150,000 units at the time of grafting, two doses being given before grafting and two after. Parenteral penicillin was found to eliminate pain and stench from nearly all cases within 24 hours. Cases with bone involvement usually received larger doses than those described above, and each bone operation was performed under an "umbrella" of penicillin.

The average dosage of penicillin per case treated by skin grafting is shown in Table V. The smallest amount

TABLE V.—*Dosage of Penicillin Per Case*

Schedule	No. of Cases	Average per Case
I	58	1,191,000 units
III	46	1,095,000 "
V	37	934,000 "
VI	44	1,909,000 "
VII	25	532,000 "

of penicillin was used in Schedule VII, but these cases also received "sulphatriad," which proved a good deal more expensive than equivalent treatment with penicillin, and showed no special advantages. The next smallest amount was used in Schedule V, but these patients were also receiving local antibiotic treatment two or three times a day, and the exact amount of antibiotic in the dressings could not be calculated. The largest dosage of penicillin was used in Schedule VI, but, with increasing confidence in this method, dosage was progressively reduced without adversely affecting results, and could probably be still further reduced.

Local Treatment

This is divisible into two stages, the first being to arrest local infection, and the second to assist sound healing. Treatment should be acceptable to the patient, and as economical as possible in staff and material.

A wide variety of local applications have been recommended, such as eusol and flavine (Adamson, 1949), penicillin lotion (Blank, 1947; Denhoff and Kolodny, 1947; Whitestone, 1947), sulphanilamide powder (Earle, 1940; Pattanayak, 1944; Mina, 1945; Rao *et al.*, 1945; Pran Nath Luthra, 1946; Rao *et al.*, 1949), tincture of iodine (Mina, 1945), pure carbolic (Pran Nath Luthra, 1946; Smyth, 1946; Hallinan, 1950), potassium permanganate 1/1,000 (Shircore, 1944) or 5% (Stock, 1945), silver nitrate and iodoform (Bullen, 1942), warm, moist dressings (Walker-Taylor, 1945), torula yeast (Hallinan, 1950), and cod-liver oil (Rao *et al.*, 1945). These methods require the attention of trained dressers

several times a day, and fairly large amounts of dressings are used. They must often be painful, especially in the early stages, when the ulcer is extremely tender, and some of the strong antiseptics recommended must inevitably cause further destruction of tissue.

Excision of ulcers (James, 1932; Clements, 1936) and débridement (Rao *et al.*, 1945; Pinkerton, 1947) have been advocated, but they require general anaesthesia and must result in removal of a certain amount of viable tissue. I have occasionally employed both methods, particularly when there has been bone or tendon involvement with delay in separation of necrotic tissue, but in most cases cleansing was done without anaesthesia and was confined to wiping or snipping away obvious sloughs. Excision and primary skin grafting, as recommended by James (1932), are probably effective and time-saving in small superficial ulcers, but the method was not used in the present series.

Occlusive therapy, first developed by Winnett Orr (1929) for infected fractures, and later applied to the treatment of varicose ulcers by Dickson Wright (1930), has been advocated by many (Bullen, 1942; Irvine, 1944; Marsh and Wilson, 1945; Triloki Nath, 1946), and has the great advantages of being economical in dressings, dressers, and doctor's time, while reducing the liability to repeated secondary infections and being of great value in reducing pain. The patient with a plaster cast on his leg is less likely to do much walking, and is less subject to gravitational oedema, than one with a simple gauze bandage. Granulations forming under a plaster cast are richly vascular and suitable for early grafting. All patients treated under Schedules VI and VII of the present series had such casts, while in the other schedules casts were employed in many cases with tendon or bone involvement.

Methods to improve local circulation, such as spinal procaine injection (Price, 1945) or extradural block (Ransford, 1948), have been advocated, but the technique is neither easy nor devoid of danger, and cannot be delegated to African orderlies. Such methods were not attempted.

Skin Grafting

Nearly all ulcers will in time heal completely no matter what treatment is used, but except in the smallest ulcers the process is slow, and in larger ones unstable scars and contractures are apt to develop. One case (not included in this series) with a very chronic ulcer was found to have developed malignancy in the scar.

The proper dressing for any healing ulcer is skin, and skin grafting has been used extensively for tropical ulcers (Clements, 1936; Irvine, 1944, 1945; Walker-Taylor, 1945; Pinkerton, 1947; Whitestone, 1947). Most writers on this subject recommend the use of Reverdin pinch grafts, which are eminently suitable for application to infected surfaces but are very tedious to apply on ulcers of over 7 sq. in. (45 cm.²) such as occurred in nearly 30% of the present series. Thiersch grafts are rapidly and easily cut under local analgesia with an ordinary hollow-ground razor, and if applied as a patchwork of small pieces allow an adequate escape of secretions in most cases.

In the present series it was assumed that all but the smallest ulcers would require skin grafting, and local treatment could be divided into three stages—namely, preparation of the ulcer area, application of a graft, and aftercare of the grafted area.

Methods used in cleansing and preparing the ulcer prior to grafting are classified under seven treatment schedules in Table VI and in the Appendix.

TABLE VI.—Primary Treatment Schedules

Schedule	Outline of Treatment	Cases Treated
I	Multiple dressings of hypertonic saline with parenteral penicillin injection	59
II	Multiple dressings with various antiseptics	56
III	Multiple dressings with antiseptics and parenteral penicillin	58
IV	Multiple dressings with various antibiotic preparations	74
V	Multiple dressings with antibiotics and parenteral penicillin	51
VI	Single application of antibiotic, plaster cast, and parenteral penicillin	44
VII	Single application of antibiotic, plaster cast, parenteral penicillin in small dosage, and sulphatriad by mouth	26
	Total	368

In Schedules I to V the time to graft was determined by inspection of the ulcer surface, but in the last two schedules grafting was done in most cases seven days after the primary dressing. In the vast majority of these cases Thiersch grafts rather than Reverdin were employed, as they were so much quicker to cut and apply. Pedicle or cross-leg flap grafts were used when an extensive area of bone was exposed and it was clear that a split-thickness graft would produce an unstable scar.

The donor area was prepared with cetyltrimethylammonium bromide (C.T.A.B.), spirit, and saline, and infiltrated with 1% procaine. While this was taking effect the dressing was removed from the ulcer, and pus and debris were wiped away, residual sloughs and superficial sequestra, if present, were removed, and a compress of 10-volume hydrogen peroxide was applied. Returning to the donor area, split-thickness grafts were cut and spread on "tulle gras" preparatory to cutting up into "postage stamps," and a hydrogen peroxide compress was applied to the donor area to arrest oozing. The ulcer was again exposed, and any oozing was controlled by hot saline or hydrogen peroxide compresses. When dry the recipient area was dusted with a powder consisting of crystalline penicillin, 10,000 units, with sulphathiazole, 0.6 g., and mag. carb. pond. to 1 g. (P.S.P.), and the grafts were laid on with great care to ensure against overlapping and curling of the edges. If any part of the recipient area showed residual sloughs or the possibility of infection it was not covered by grafts, which were instead laid around the potential danger. No fibrin, thrombin, or red-cell fixative for the graft was used, but when the granulations had been covered the skin around the ulcer was painted with benzomastiche, and stretched lengths of sterile crêpe bandage were glued on. A pad of fluffed gauze or wool was next firmly bandaged on, and the part was enclosed in a light plaster cast. The donor area was dusted with P.S.P., any unused pieces of graft were replaced, and a dry dressing was firmly bandaged on. The patient was returned to the ward with instructions to remain in bed.

The graft was inspected six to eight days after operation, and in most cases in Schedules V, VI, and VII it was possible to apply an Unna-paste bandage, or its proprietary equivalent, and discharge the patient the following day.

To obtain the best results, every case must be treated on its merits, but, so far as possible, in Schedules VI

and VII the routine was adopted so as to obtain some idea of its efficacy. Nevertheless, in a few cases with bone or tendon involvement the primary dressing was left on for more than a week, or was renewed for a further period, while in a few cases with small ulcers grafting was done earlier or not at all.

Ancillary Surgical Procedures

A number of cases requiring major bone operations, such as major sequestrectomy, local resection, or exostomy, have been excluded from the series as being outside the scope of an investigation of the treatment of ulcers, but Table VII analyses the procedures used in the 368 cases of the series.

TABLE VII.—Surgical Procedures Used in Treatment of Ulcers

Procedure	No. of Cases
Thiersch or Reverdin grafts	314
Preliminary bone operation	5
Pedicle or cross-leg graft	5
Amputation	4
Healed without grafting	29
Refused treatment or absconded before graft	11
Total	368

Amputation was done in one case of extremely severe ulcer with pathological fracture of both bones of the leg, and was accomplished by a quick snip with a pair of scissors. This patient subsequently developed a severe attack of bacillary dysentery and died. Hers was the only death in the series. In three other cases amputation was used in cases of terminal digital ulceration with involvement of nail-bed and phalanx, and this treatment appears to be the quickest way of dealing with such cases. The amputation amounts to little more than excision and suture of the ulcerated area.

Importance of Simplicity in Treatment

In most African hospitals bacteriological methods of assessing sterility of the recipient area for a graft are not available, and experience showed that absolute sterility was not necessary. All stages of each treatment have been done at various times by African orderlies, and Table VIII shows that the African staff were capable of cutting and applying skin grafts with results comparable to those of the European staff. Of course, some selection has necessarily occurred here, as the African staff performed on the simpler types of cases, and were not allowed to do bone operations, flap grafts, or amputations. These Africans were trained operating-room staff, but not qualified hospital assistants.

TABLE VIII.—Results of Grafts by Different Operators

Results	Surgeon	African Staff
Good (90% cover or better)	158 (60.5%)	33 (60%)
Fair (50–80% cover)	94 (36.0%)	12 (21.9%)
Poor (40% or worse)	9 (3.5%)	10 (18.1%)
Total	261	55

Note: Results were assessed by eye on the sixth to the eighth day. The results of 95 grafts done by other Europeans are excluded for the sake of simplicity, but were no better than those done by the Africans. The total number of grafts exceeds the total number of patients in the series because some patients had more than one ulcer, or were grafted more than once.

Results

The following results are based on records of the 314 patients who received Thiersch or Reverdin type grafts. Records were unfortunately not complete in all cases, so that the totals in the different tables will be found to vary.

Most of the patients in the series were employees of the Corporation, and the primary object of treatment was to get the men back to work as soon as possible. It was a secondary object to get the men out of hospital quickly, hence many patients were discharged before their ulcers were completely healed. The effectiveness of treatment cannot therefore be measured only by comparison of length of stay in hospital, but must be qualified by the condition at discharge. This was recorded as "healed" when there was complete epithelial cover for the whole ulcer, although the donor area was generally not completely healed at this stage. In cases recorded as "almost healed" there was epithelial cover for 90% or more of the ulcer surface, and the residual bare areas were of clean granulations likely to heal spontaneously under ambulant treatment either in an occlusive dressing or by repeated dressings at unit dressing stations. Cases with 80% or less of epithelial cover were classified as "unhealed."

To test the practical significance of these recorded results, 110 unselected cases were told to report back to the surgeon for a personal check of healing instead of reporting to the unit dressing station or hospital outpatient department. Those who reported back were followed up until completely healed and fit for full duties. Many of them could probably have gone back to work earlier in a partially healed condition. The first check-up visit was five to seven days after discharge. The results are given in Table IX.

TABLE IX.—*Follow-up of Cases*

Condition at Discharge	No. Told to Report	Discharged "Fit"			Readmitted
		No. Reported Back	Total Days to "Fit"	Average Days to "Fit"	
Healed	21	11	78	7.1	Nil
Almost healed ..	73	37	279	7.5	1
Unhealed	16	3	25	8.3	1
Total	110	51	382	7.5	2

The two cases readmitted were taken in 5 and 11 days after discharge and were redischarged "fit" after 14 and 11 days respectively. If their additional period of disability be added to the total days of disability in the respective categories, it will be seen that the average period of disability after discharge in 38 cases classed as almost healed is now 7.8 days, while for 4 cases unhealed at discharge the period is increased to 10.8 days. It will thus be seen that there is not much difference in post-hospital disability between healed and almost healed patients, while the unhealed take about three days longer to return to work healed. The minimum period from grafting to discharge was found to be about seven to eight days, but the donor area usually took 14–21 days to heal soundly, so that it was customary to recommend about seven days excused duty to all patients discharged in about the minimum period after grafting. Unless patients can be returned to light duties with unhealed donor areas, it does not at present seem possible to get men back to work in less than 14 days from the date of grafting.

It was considered that the site of the ulcer might influence the rapidity of healing, but Table X shows that this is not an important factor. The 254 cases here analysed were all treated by skin grafting after any of the seven treatment schedules.

TABLE X.—*Influence of Site of Ulcer on Stay in Hospital*

Site	No. of Cases	Average Days in Hospital
Leg	96	25.4
Ankle and heel ..	104	24.1
Foot	46	24.3
Toe	8	26.0
Total	254	24.7

Foot and toe ulcers are usually smaller than leg ulcers, but, owing to their special liability to injury in a shoeless population, these patients were detained in hospital until healed, while those with leg and ankle ulcers were often discharged before healing was complete. It would seem that there is not much difference in healing time between ulcers at different sites.

Without skin grafting, large ulcers will obviously heal more slowly than small ones, but when grafts are used there should not be very much difference, and this is partly borne out by the results shown in Table XI.

TABLE XI.—*Effect of Size of Ulcer on Stay in Hospital*

Size of Ulcer	No. of Cases	Average Days in Hospital
Large—3 in. (7.5 cm.) or more in diameter	63	27.5
Medium—1–3 in. (2.5–7.5 cm.) diameter ..	132	23.4
Small—less than 1 in. (2.5 cm.) diameter ..	19	25.9
Total	214	24.8

From this table it is seen that patients with large ulcers stay a little longer in hospital, and this is probably because they are more likely to have tendon and bone involvement. However, in assessing the values of different forms of treatment it will be necessary to consider the proportion of large, medium, and small ulcers in each treatment group. This is shown in Table XII. It will be noted that in all schedules the incidence

TABLE XII.—*Incidence of Different-sized Ulcers and Effect on Stay in Hospital, by Treatment Groups*

Schedule	Large Ulcer		Medium Ulcer		Small Ulcer	
	No.	Average Days in Hospital	No.	Average Days in Hospital	No.	Average Days in Hospital
I	15 (31.4%)	31.4	29 (55.8%)	26.3	2 (3.8%)	22.0
II	7 (25.0%)	29.1	12 (42.9%)	26.2	4 (14.3%)	34.2
III	13 (40.6%)	36.0	7 (22.5%)	31.0	3 (9.4%)	29.3
IV	11 (22.0%)	25.3	22 (44.0%)	26.3	2 (6.0%)	37.5
V	3 (11.1%)	22.3	18 (66.7%)	20.2	2 (7.4%)	16.0
VI	11 (26.8%)	18.2	27 (65.8%)	17.6	3 (7.4%)	21.7
VII	3 (13.0%)	20.0	17 (74.1%)	17.7	2 (8.6%)	16.0
Total	63		132		19	
Ulcers of unspecified size						214 (84.3%)
Grand total						40 (15.7%)
						254 (100%)

Note: The percentages in parentheses refer to the incidence of each size of ulcer among the total cases treated by the particular schedule.

of small ulcers—that is, less than 1 in. (2.5 cm.) in diameter—is low. As in Table XI, patients with large ulcers are fit for discharge slightly later than those with medium ulcers. The shortest periods in hospital in each size group were obtained by Schedules V, VI, and VII, but this is further analysed in Table XIV, in which the condition of the ulcer at discharge is taken into consideration.

The possible effect of duration of the ulcer is considered in Table XIII, taking into consideration the

TABLE XIII.—*Effect of Duration of Ulcer on Stay in Hospital*

Schedule	Condition of Ulcer			
	Healed and Almost Healed		Unhealed	
	No.	Average Days in Hospital	No.	Average Days in Hospital
(A) <i>Ulcers Less than 6 Weeks from Onset to Admission</i>				
I	12	24.2	—	—
II	17	30.1	1	34
III	25	31.6	—	—
IV	41	24.2	5	26
V	22	21.5	2	22.5
VI	37	18.2	1	16
VII	21	17.8	2	17
Totals	175	23.4	11	23.5
(B) <i>Ulcers More than 6 Weeks from Onset to Admission</i>				
I	5	23.0	—	—
II	14	32.0	2	32.5
III	11	33.0	3	51.6
IV	9	37.2	1	25.0
V	10	18.9	—	—
VI	2	26.0	1	21.0
VII	2	17.5	—	—
Totals	53	29.0	7	38.0

condition on discharge. This table shows that the older ulcers take longer to heal than the more recent ones, and this may be because they tend to be larger and more likely to involve bone and tendon. Thus the average stay for two cases of more than six weeks' duration treated by Schedule VI was 26 days, and this rather poor result was attributable to one case with extensive involvement of the tendo Achillis in which it was not possible to graft until 22 days after admission. Regardless of duration of the ulcer, the best results are obtained by Schedules V, VI, and VII, with the exception of the instance above mentioned.

Tables XI and XII do not take into consideration the condition of the ulcer at discharge, while Table IX shows that this bore a relation to the period of disability after discharge. Table XIV shows the overall figures

TABLE XIV.—*Overall Results of Treatment by Skin Grafting*

Schedule	Condition at Discharge				Refused Treatment
	Healed and Almost Healed		Unhealed		
	No.	Average Days in Hospital	No.	Average Days in Hospital	
I	53 (91.4%)	26.6	5 (8.6%)	27	0
II	39 (88.6%)	30.0	5 (11.4%)	38.8	4
III	42 (91.3%)	32.4	4 (8.7%)	46.5	4
IV	54 (90.0%)	26.6	6 (10.0%)	25.8	1
V	35 (94.6%)	20.7	2 (5.4%)	22.5	1
VI	42 (95.5%)	18.5	2 (4.5%)	18.5	0
VII	23 (92.0%)	17.7	2 (8.0%)	17.0	0
Totals	288	25.3	26	29.0	10

for ulcers treated by skin grafting or offered skin grafts, relating total days in hospital to condition at discharge and treatment schedules. This table shows that the highest percentages of healed and almost healed ulcers are obtained by Schedules V, VI, and VII, and that this is achieved in considerably shorter time than by other methods.

There is yet another way in which treatments can be compared, and that is on the condition of the graft at the first dressing, as mentioned already in another connexion in Table VIII. That this bears a relation to the duration of stay in hospital and to the condition of the ulcer at discharge is shown in Table XV.

TABLE XV.—*Time from Grafting to Discharge*

Condition on Discharge	Condition of Graft at First Dressing					
	Good		Fair		Poor	
	No.	Average Days	No.	Average Days	No.	Average Days
Healed	78	12.2	26	17.3	4	14.8
Almost healed	99	10.4	59	16.2	11	20.8
Unhealed	2	14.0	12	18.1	8	18.1
Total	179	11.2	97	16.6	23	18.8

Note: Definition of condition of graft as in Table VIII.

It is apparent from this table that good results at the first dressing are associated with a higher proportion of patients discharged as healed or almost healed, and this is effected in a shorter average time than in cases having fair or poor results at the first dressing. Hence the method yielding the highest proportion of good results at the first dressing is likely to be associated with a short stay in hospital.

Table XVI relates the condition of the graft at the first dressing with the method of treatment used in preparing for the graft.

TABLE XVI.—*Results of Grafts Related to Treatment Schedule*

Schedule:	I	II	III	IV	V	VI	VII	Total
No. treated	58	44	46	60	37	44	25	314
Good result	23	20	22	19	26	40	15	165
% good	39.7	45.4	47.8	31.7	70.3	90.8	60.0	52.6

Discussion of Results

Study of Tables XII, XIII, XIV, and XVI suggests strongly that, regardless of size, position, or duration of the ulcer, the best results were obtained with Schedules V, VI, and VII, and of these Schedule VI is probably the best. But before coming to any definite conclusion it is advisable to consider certain other factors, some of which cannot be statistically demonstrated.

Desertions and Refusal of Treatment.—If a treatment schedule does not produce rapid relief from pain, or if it is in itself painful or offensive, the African patient is likely to refuse further treatment or to abscond from hospital. Table XIV shows that no patients undergoing treatment by Schedules I, VI, and VII absconded, while only one absconded or refused treatment in Schedules IV and V. A patient with a plaster is less likely to abscond than one with an ordinary dressing, and this in itself is a recommendation for schedules VI and VII. In addition it was found that the combination of plaster cast and parenteral penicillin therapy generally eliminated pain and stench within 24 hours, so that the confidence of the patient was gained early.

Economy of Trained Staff.—In Schedules VI and VII trained staff is required for the initial dressing, the skin graft, and the final dressing. Otherwise treatment in these schedules is reduced to administration of penicillin and medicines. Although ambulation was discouraged, patients in these two categories in fact looked after themselves, and mostly were able to visit the latrine on their own, so that the use of bed-pans and urinals was reduced to a minimum.

Economy of Dressings.—Sterilized dressings were used in all forms of treatment, and, even in the early stages of ulcers, bandages were so soiled that it was impossible to launder and use them again. It is clear that less gauze, wool, and bandages are used, and there are fewer calls on the autoclave

when patients are undergoing treatment in plaster casts than when ordinary dressings are used, and this saving probably offsets the extra cost of the plaster bandages.

Economy of Drugs.—Penicillin is now a comparatively cheap drug, and its use as the procaine salt causes little inconvenience to patients or staff. It is impossible to draw up exact costings, but, on a conservative estimate, three days of penicillin treatment on the lines prescribed above cost about as much as one day's stay in hospital, and Schedules V, VI, and VII certainly saved several days in hospital.

Economy of Doctor's Time.—It is advisable for the doctor to be present at the first and final dressings and at the skin graft, but otherwise he need not visit the patient or spend time inspecting dressings if Schedules VI and VII are followed. The actual treatment in each phase of these schedules can be carried out by trained African orderlies.

Comparison with Other Published Series

The published results that I have surveyed are not easy to compare, as series are often small and there is rarely accurate definition of size and extent of ulcers, presence of complications, and condition at discharge.

Marsh and Wilson (1945) reported 85 cases treated in plaster casts; of these 59 were healed in an average of just over two weeks, but there is no definition of the size and complexity of the ulcers, and 26 patients defaulted. Pattanayak (1944), using ten different treatment schedules on 90 cases, found infrequent dressings of a sulphonamide most favourable, and in 8 cases so treated the average duration of the disease was 22.2 days. Earle (1940), using local sulphapyridine therapy, found that 14 out of 38 recent cases were favourably influenced and healed in two weeks. Godkin (1950) treated 80 cases with oral sulphonamides and grafting. The average size of ulcer was 1.5 in. (3.75 cm.) in diameter, and the average stay in hospital 19.5 days, and all patients were completely healed on discharge. This does not coincide with my experience, but perhaps the cases in Godkin's series were uncomplicated, since no mention of complications was made.

Triloki Nath (1946) reported on 20 cases which healed in an average of 15 days under occlusive therapy with leucoplast. From my experience these must have been small ulcers. Pran Nath Luthra (1946) treated 50 cases with local sulphonamides and was able to discharge them after an average stay of 20 days in hospital, but he does not define the condition on discharge. Whitestone (1947), using local penicillin and skin grafting in 35 cases, reported 33 healed or almost healed in an average of 23.1 days. Rao *et al.* (1949) used local penicillin on 17 patients with small ulcers which healed in 10 days each, while 13 patients with larger ulcers healed in an average of 28 days. Pinkerton (1947), using parenteral penicillin and skin grafts in eight cases, obtained healing in three of his type I ulcers in an average of one month. Hallinan (1950), using local applications of torula yeast, obtained healing in two to three weeks in 15 cases with ulcers less than 1 in. (2.5 cm.) in diameter, but larger ulcers, of 4 to 5 in. (10 to 12.5 cm.) diameter, took four to five weeks to heal. Walker-Taylor (1945) treated 47 cases of ulcers and tropical onychia by minor surgery and skin grafts with an overall average stay of 17.8 days in hospital, but if 12 cases of onychia are excluded the average stay for the remainder was 19 days. James (1932), using excision and immediate skin grafts in 45 cases, obtained complete epithelial cover in 41 cases in an average of 13

days. These ulcers were all apparently less than 3 in. (7.5 cm.) in diameter, and none are reported to have had any complications.

Summary

In my experience the most satisfactory routine treatment for acute and subacute tropical ulcers is by occlusive plaster treatment combined with parenteral penicillin injections and skin grafting.

Results by this method do not differ much from the best results in the literature surveyed, and the method has the advantage of simplicity, which may commend it to those having to deal with large numbers of ulcer patients.

APPENDIX

Details of Primary Treatments

Schedule I.—Hypertonic saline dressings, applied hot or cold three or four times a day.

Schedules II and III.—The antiseptics most used were eusol, alone or combined with hydrogen peroxide; a lotion of equal parts of acriflavine 1/500 and sodium sulphate 5%; and brilliant green 1/500. In addition nearly all cases were cleaned at each dressing with a 1% solution of C.T.A.B. Other antiseptics used were "zipp," gentian violet, ichthammol, and acriflavine 1/1,000 alone. In general, eusol and hydrogen peroxide were found most effective in clearing sloughs and reducing primary infection, while other antiseptics were generally used later to deal with secondary infections, and brilliant green was used in the final stages of preparing the area for grafting.

Schedules IV and V.—The antibiotics used for topical application were (1) a powder of crystalline penicillin, 10,000 units, with sulphathiazole, 0.6 g., and mag. carb. pond., to 1 g. (P.S.P.); (2) a cream containing penicillin 500 units per g.; (3) a lotion, or more often a cream, containing bacitracin 500 units per g. The bacitracin was kindly supplied by Messrs. Commercial Solvents, of New York. A survey of the relative merits of bacitracin and penicillin is to be the subject of a different study, but in general there was no very marked difference in action in these cases. The antibiotics were applied once or twice daily except when a lotion was used, when applications were made three or four times daily.

Schedules VI and VII.—These were adopted in order to avoid the need for repeated dressings, at a time when there were so many ulcer cases that trained staff was not available to carry out the aseptic dressing technique which was otherwise insisted upon. The results were so satisfactory that the method is described in greater detail. Patients were admitted in batches twice a week. A history was obtained, the patient was examined, and smears of exudate were taken from the ulcers and in some cases also from the gums for laboratory examination. A saline dressing was applied, and the first course of penicillin injections was started. The following day each patient was taken to the operating theatre and the ulcer cleaned with C.T.A.B. and gross sloughs snipped off without anaesthesia. No attempt was made to do a thorough surgical toilet. The ulcers were swabbed clean with the mixture of eusol and hydrogen peroxide, dried and dusted with P.S.P., and covered with a dry sterile dressing. The limb was encased in a light plaster cast and the patient returned to the ward with instructions to stay in bed. Six days later the area selected for giving the graft was prepared with C.T.A.B. and the second course of penicillin was begun. The following day, one week after the primary treatment, the patient was returned to the operating theatre for skin grafting.

I am indebted to Brigadier A. Moore Cameron, late R.A.M.C., chief health officer, Overseas Food Corporation, for permission to publish these results; to Mr. J. Darling, surgeon, Overseas Food Corporation, Kongwa, for permission to use much of his material and for help and advice in compiling the results; and to Dr. W. Burkitt, O.F.C. Hospital, Kongwa, some of whose cases are included in the series.

REFERENCES

- Adamson, P. B. (1949). *J. trop. Med. Hyg.*, **52**, 68.
 Blank, H. (1947). *Amer. J. trop. Med.*, **27**, 383.
 Bullen, C. V. (1942). *E. Afr. med. J.*, **19**, 233.
 Charters, A. D. (1943). *Trans. roy. Soc. trop. Med. Hyg.*, **37**, 205.
 Clements, F. W. (1936). *Med. J. Aust.*, **2**, 615.
 Costa, O. G. (1944). *Arch. Derm. Syph., Chicago*, **49**, 260.
 Denhoff, E., and Kolodny, M. H. (1947). *Ibid.*, **55**, 360.
 Earle, K. V. (1940). *Trans. roy. Soc. trop. Med. Hyg.*, **34**, 105.
 — (1942). *Ibid.*, **35**, 241.
 Early, E. P. N. M., and Bharucha, D. R. (1944). *Indian med. Gaz.*, **79**, 200.
 Godkin, S. R. S. (1950). *E. Afr. med. J.*, **27**, 173.
 Hallinan, T. C. (1950). *British Medical Journal*, **1**, 1118.
 Harris, L. J., Passmore, R., and Pagel, W. (1937). *Lancet*, **2**, 183.
 Irvine, C. (1944). *E. Afr. med. J.*, **21**, 143.
 — (1945). *British Medical Journal*, **1**, 120.
 James, C. (1932). *Lancet*, **2**, 1095.
 Marsh, F., and Wilson, H. A. (1945). *Trans. roy. Soc. Trop. Med. Hyg.*, **38**, 259.
 Mina, H. (1945). *British Medical Journal*, **1**, 369.
 Orr, H. Winnett (1929). *Osteomyelitis and Compound Fractures*. Kimpton, London.
 Pattanayak, G. C. (1944). *Indian med. Gaz.*, **79**, 521.
 Pinkerton, J. McL. (1947). *J. trop. Med. Hyg.*, **50**, 243.
 Pran Nath Luthra (1946). *Indian med. Gaz.*, **81**, 169.
 Price, E. W. (1945). *Trans. roy. Soc. trop. Med. Hyg.*, **39**, 83.
 Ransford, O. N. (1948). *Ibid.*, **42**, 267.
 Rao, M. V. Radhakrishna, et al. (1945). *Indian Med. Gaz.*, **80**, 128.
 Rao, V. Ramachandra, et al. (1949). *Ibid.*, **84**, 88.
 Seshadrinathan, N. (1945). *Ibid.*, **80**, 344.
 Shircore, J. O. (1944). *Trans. roy. Soc. trop. Med. Hyg.*, **37**, 345.
 Smyth, E. A. (1946). *J. roy. Army. med. Cps.*, **87**, 141.
 Stock, F. E. (1945). *British Medical Journal*, **2**, 388.
 Triloki Nath (1946). *Indian med. Gaz.*, **81**, 169.
 Walker-Taylor, P. N. (1945). *Lancet*, **2**, 40.
 Whitestone, M. (1947). *Indian med. Gaz.*, **82**, 9.
 Wright, A. Dickson (1930). *Proc. roy. Soc. Med.*, **23**, 1032.

L-NORADRENALINE AS A VASOCONSTRICTOR

BY

H. C. CHURCHILL-DAVIDSON, M.B., B.Chir., D.A.

Senior Registrar, Department of Anaesthetics, St. Thomas's Hospital, London

It is proposed to examine the physiological actions of some of the vasopressor drugs in present use, and to show that L-noradrenaline bitartrate, or arterenol (trade name, "levophed"), is a safe and effective vasoconstrictor drug for the control of blood pressure during surgical operations.

At the present time there are two vasopressor drugs in common use by the anaesthetist. First, adrenaline has been found satisfactory as a continuous drip infusion in cases of hypotension following spinal analgesia (Frankis Evans, 1944). Secondly, D-desoxyephedrine (trade name, "methedrine") is now probably the most frequently used drug for combating low blood pressure following spinal analgesia (Dodd and Prescott, 1943; Anderson, 1946), and its employment has recently been suggested for combating serious hypotension following the use of ganglionic-blocking agents (Hughes, 1951). A close examination of the physiological properties of these drugs reveals, however, that they are not pure vasoconstrictor drugs, whereas L-noradrenaline is probably the most powerful overall vasoconstrictor drug available to the anaesthetist.

Physiological Considerations

Although adrenaline causes constriction of skin and kidney vessels, muscle-blood flow studies show that it produces a vasodilatation during intravenous infusions

of 10 γ /minute (Allen *et al.*, 1946). Muscle-blood-flow studies alone represent only a small proportion of the total peripheral resistance. The blood flow through such large organs as the spleen and liver is difficult to estimate in man. The action of a drug on the muscle vessels, however, gives an indication of its effect on the whole peripheral resistance. It has since been shown that adrenaline produces a marked increase in cardiac output whilst acting as an overall vasodilator. The increase in cardiac output is so great that the clinical effect is that of raised blood pressure (Goldenberg *et al.*, 1948). It has also been shown that adrenaline has an autonomic ganglionic blocking action (Marrazzi, 1939a, 1939b) which becomes evident on stopping the infusion (Bilbring and Burn, 1942). The evidence for this effect in man is small, but may account for the "after-dilatation" that follows the constriction of skin vessels produced by an intravenous infusion of adrenaline (Swan, 1951a) and for the marked fall in blood pressure which is sometimes seen on stopping the adrenaline infusion. It is thus apparent that adrenaline, with its marked effect on the heart, cannot be regarded as a satisfactory pressor drug.

Methedrine was first discovered in 1909 by Ogata and introduced into clinical anaesthesia by Dodd and Prescott (1943). Since that time little work seems to have been done on the muscle-blood flow following the infusion of methedrine, although it has been shown that the effect of intramuscular methedrine was extremely unpredictable and that the muscle-blood flow was increased in every case (Allen, 1948). Further studies using intravenous infusions have shown that there is a short initial constriction followed by a prolonged period of lowered resistance in the presence of a raised blood pressure (Churchill-Davidson and Swan, 1951). The combination of a normal pulse rate with a large pulse pressure in the presence of an increased muscle flow suggests an increase in cardiac output. A pressor dose of methedrine (15–20 mg. intravenously) is usually followed by a dramatic rise in blood pressure of varying duration. There are times, however, when the blood pressure after an initial rise appears to fall below its original level. An example of the way in which methedrine may influence the cardiac rhythm is shown in Fig. 1.

Renewed interest in noradrenaline was first aroused when von Euler (1946) pointed out that it is present in significant amounts in extracts from splenic tissue. The following year Holtz *et al.* (1947) demonstrated that noradrenaline was present in urine and suprarenal extracts, whilst Gaddum and Goodwin (1947) showed that electrical stimulation of sympathetic nerves in

FIG. 1.—Showing part of a continuous pulse record after the patient had been given 15 mg. of methedrine intravenously to raise the pressure following pentamethonium bromide. The gross irregularity of cardiac rhythm is well shown.