the noradrenaline. Their cold clammy extremities became warm and dry and the whole clinical picture of severe shock was altered dramatically. Nor did they require further blood at any time during their stay in hospital, which suggests that their blood loss had been reasonably replaced. The point that the beneficial effect of noradrenaline might have been obtained equally well by additional transfusions appeared highly unlikely at the time and there was an ever-present danger of overloading the already failing circulation.

In Case 4 the rising pulse and temperature, the diarrhoea, and the sudden onset of complete collapse without evident haemorrhage suggested an overwhelming toxæmia as the aetiological factor. Whether this resulted from peritonitis or bowel infection was at the time an academic question, and from past experience the administration of noradrenaline held out some hope of temporary recovery, while the simultaneous use of oxytetracycline was designed gradually to control the infection. The use of noradrenaline in severe toxic states has been described by Skelton *et al.* (1952) and Kurland and Malach (1952), with encouraging immediate results, although ultimate survival depended on the subsequent successful treatment of the underlying disease.

The use of noradrenaline requires constant supervision. Initially the blood pressure should be taken every minute and the drip rate varied according to the response. When the blood pressure is stabilized a reading every five to ten minutes should be sufficient. A concentration of 4 ml. in 1,000 ml. of glucose-saline was adequate in the first three cases. In the fourth case the concentration was doubled two hours after onset, since with a rate of 80 drops a minute signs of pulmonary oedema were beginning to develop. In cases of cardiac infarction where excessive infusion would overload the circulation, concentrations of 8 ml. and 16 ml. have been used (Smith and Guz, 1953).

Grayson and Johnston (1952) suggested that infusions of more than an hour or two may cause liver damage. In this small series the drug was given for six, twenty-three, four, and eleven hours without obvious ill effects.

Barlow *et al.* (1953) consider the results of noradrenaline so dramatic and reliable that in acute hypotensive states the use of other vasopressors has largely been discontinued. When the orthodox methods have failed it certainly seems justifiable to try the effect of noradrenaline.

Summary

The successful use of noradrenaline in four cases of severe peripheral circulatory failure is reported.

The cause of shock in two cases was haemorrhage and post-operative collapse; in one case post-anaesthetic aspiration of gastric contents combined with anoxia; and in the fourth case, toxæmia.

Three patients made a complete recovery. One patient died from pulmonary embolus thirty days later.

The use of noradrenaline is advocated as a last resort when the usual methods of resuscitation have failed.

The method of administration is described.

My thanks are due to Mr. J. W. M. Sutherland, who operated on Cases 1 and 4, for permission to publish them; to Dr. J. R. Kyles for his interest and help; and to the house-surgeons whose all-night vigils were so willingly undertaken and so amply rewarded.

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SKIN NECROSIS FOLLOWING INTRAVENOUS NORADRENALINE

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Intravenous L-noradrenaline, because of its general vasoconstrictor properties, is of great value in hypotensive states, but on occasion it may produce extreme local vasoconstriction that results in necrosis of tissues. This complication has occurred five times in three recent cases, in which the use of noradrenaline in an intravenous drip was followed by gangrene of the skin and subcutaneous tissues overlying and around the recipient vein. In each case the drug was administered in 5% dextrose or normal saline solutions through a metal cannula tied into a superficial vein. The patients had shown a marked degree of shock before the infusion was begun.

The case reports are given in some detail, as we believe that they indicate the pathogenesis of the complication and its means of prevention.

Case 1

A girl aged 18 was admitted to the Liverpool Royal Infirmary suffering from chronic ulcerative colitis. A subtotal colectomy with ileo-colic anastomosis was performed on January 18, 1955. Her post-operative condition was good until the early hours of January 21, when she was found to be in a state of extreme shock with a feeble pulse of 140 a minute and a systolic blood pressure of 40 mm. Hg. No cause for the collapsed condition was evident. Since the operation intravenous dextrose and saline with oxytetracycline had been given through a cannula tied into the left internal saphenous vein at the ankle. An infusion of 0.5 litre of 5% dextrose containing 2 mg. of noradrenaline was then begun through the same apparatus. The blood pressure rose to 80–90 mm. Hg, but after 150 ml. of the solution had been given in just under an hour it was noticed that the skin on the inner aspect of the left leg was mottled blue and white in colour, and very cold. The drip was stopped and the cannula removed.

As the peripheral veins were collapsed a similar cut-down drip with tied-in cannula was set up in the right internal saphenous vein at the ankle, using 2 mg. of noradrenaline in 0.5 litre of 5% dextrose. Marked pallor of the skin overlying the vein was noticed immediately, and one hour later there was a mottled discoloration similar to that in the left leg. The patient's general condition improved and the blood pressure was maintained at over 100 mm. Hg, but immediately the drip was slowed the pressure fell. Nine hours later the discoloration on the inner aspect of each leg had condensed to a uniform purple ellipse of skin about 4 in. (10 cm.) wide extending from 1 in. (2.5 cm.) above each skin incision almost to the knee. No further noradrenaline was given, and 5 ml. of 0.5% procaine and 50 mg. of papaverine sulphate were injected into the drip before it was stopped.

50 ml. of 0.5% procaine containing 2,000 units of hyalase and 80 mg. of papaverine sulphate were infiltrated subcutaneously around the affected part in each leg. Twenty-

four hours later the patient's general condition was good and the systolic blood pressure was 110 mm. Hg. The legs were painful and the areas of discoloration, which were insensitive to touch, had diminished in size and each was surrounded by a red raised zone of erythema. Further diminution in the extent of the involved skin took place, especially in the right leg, over the next week. On February 9 the necrotic tissue, consisting of skin and superficial fascia, was excised from each leg. On the right there were two areas of slough measuring $3\frac{1}{2}$ by $1\frac{1}{2}$ in. (9 by 3.8 cm.) and $1\frac{1}{2}$ by 1 in. (4.4 by 2.5 cm.), and on the left an area of 9 by 3 in. (22.8 by 7.6 cm.). Three weeks later skin grafting was successfully carried out, and on discharge on April 27 the legs were healed.

Only about 0.5 mg. of noradrenaline was given through the left internal saphenous vein, but the infusion had already been running for about 60 hours before the noradrenaline was begun. In the right leg a total of 10 mg. of noradrenaline in 2 litres of fluid was given over a period of ten hours. The maximum concentration used was 8 mg. per litre of dextrose or saline solution.

Case 2

A married woman aged 63 was admitted to the David Lewis Northern Hospital, Liverpool, suffering from a carcinoma of the posterior vaginal wall infiltrating the rectum. At operation on February 1, 1955, panhysterectomy and synchronous combined abdomino-perineal resection of the rectum with the posterior vaginal wall were performed. Just before the conclusion of the operation the patient's blood pressure fell to an unrecordable level and the pulse rate rose to 130 a minute. Two pints (1,140 ml.) of blood had already been given through a needle inserted percutaneously into a vein of the right forearm. A further pint (570 ml.) of blood containing 10 mg. of noradrenaline was given through the same apparatus with improvement in the patient's general condition and a rise in blood pressure. After operation the infusion was continued with 5% dextrose containing noradrenaline in a concentration of 12 mg. per litre. After a total of 3 litres of fluid had been given in a period of 24 hours the needle slipped from the vein and there was a slight leak of the solution into the subcutaneous tissues of the forearm before the drip was stopped. No local complications resulted. There was an immediate fall in blood pressure, necessitating intravenous noradrenaline being started, and being continued as follows:

February 2 and 3.—In 48 hours 6 litres of fluid containing 72 mg. of noradrenaline was given through a cannula tied into a vein on the dorsum of the right foot. The vein thrombosed and the infusion stopped spontaneously. No local complications developed.

February 4–8.—In five days 15 litres of fluid containing 180 mg. of noradrenaline was given through a needle inserted into a vein in the right forearm. The infusion stopped spontaneously because of venous thrombosis. There was local oedema but no other tissue reaction.

February 9.—In 24 hours 3 litres of fluid containing 36 mg. of noradrenaline was given through a needle in a vein in the right antecubital fossa. The vein thrombosed, but there were no other local complications.

On February 10 an infusion was started through a cannula tied into a vein at the left ankle. After 48 hours the skin over the vein on the inner aspect of the leg was cold and showed a blue-white discoloration. There was no swelling and the infusion was running freely when it was discontinued. The vein had received 6 litres of fluid containing 72 mg. of noradrenaline.

February 12 and 13.—In 48 hours through a needle in a left forearm vein 6 litres was administered containing 72 mg. of noradrenaline.

On February 14, for the first time since the operation, the patient's blood pressure was maintained at 100 mm. Hg without artificial aid. The inner aspect of the left leg showed a dark-blue area of necrotic skin measuring 8 by $1\frac{1}{2}$ in. (20

by 3.8 cm.) overlying the recipient vein. The lower limit of discoloration was $\frac{1}{4}$ in. (1.9 cm.) above the skin incision.

Ten days after operation a vesico-perineal fistula developed and on February 23 this was repaired through a supra-pubic transvesical approach. On February 29 laparotomy was necessary for small-bowel obstruction and an entero-anastomosis to short-circuit obstructing adhesions was performed. During this operation the patient's blood pressure fell to an imperceptible level and a noradrenaline infusion through a tied-in cannula was begun in a vein on the radial aspect of the right wrist. The concentration of the drug was initially 4 μ g. per ml., but this was later increased to

FIG. 1

FIG. 2

FIG. 1.—The forearm in Case 2, showing the extent of skin necrosis and its relation to the incision. FIG. 2.—The leg in Case 2 during the stage of separation of sloughs.

8 μ g. per ml. After 26 hours, when a total of 8 mg. of noradrenaline had been given in 1.5 litres, the radial aspect of the forearm became oedematous and the skin showed a discoloration identical with that in the leg. The drip was running freely until it was discontinued. Twenty-four hours later there was an area of necrotic skin measuring 6 by $1\frac{1}{2}$ in. (15 by 4.4 cm.) over the course of the recipient vein on the forearm. The lower limit was 1 in. (2.5 cm.) from the skin incision (Fig. 1).

The areas of necrosis on the forearm and leg were treated with eusol applications and the sloughs gradually separated, leaving granulating surfaces (Fig. 2).

Case 3

A man aged 49 was admitted to the Liverpool Royal Infirmary complaining of dysuria. A difficult urethral dilatation for stricture was performed under general anaesthesia on March 10, 1955. Six hours later he had a rigor and was unable to pass urine. Eighteen hours after the operation he was found to be in a state of collapse with rapid, feeble pulse and a systolic blood pressure of 65 mm. Hg. Only a few drops of blood-stained urine had been passed. As the limb veins were collapsed a drip infusion of noradrenaline in 5% dextrose solution was started through a cannula tied into the right internal saphenous vein at the ankle. There

was a satisfactory response and the blood pressure was maintained at about 120 mm. Hg. A moderately distended bladder was drained by suprapubic cystostomy, performed under local analgesia.

Forty-six hours after starting the infusion it was found that there was a strip of skin measuring 7 by 1½ in. (17.8 by 3.8 cm.) overlying the internal saphenous vein in the leg, which was purple in colour and was surrounded by a zone of erythema; the discoloration began 1 in. (2.5 cm.) above the incision. The drip was immediately stopped. The discoloured area of skin gradually decreased in size, and eighteen days later a slough of skin and subcutaneous tissue measuring 2½ by ¾ in. (6.4 by 1.9 cm.) was excised.

After further urethral dilatation the patient was able to pass urine normally. The leg was healed when he was discharged on April 29.

Initially, the concentration of noradrenaline solution used was 4 µg. per ml., but later, because of oliguria and raised blood urea in spite of high fluid intake, the quantity of intravenous fluid was reduced and a concentration of 16 µg. per ml. was used to maintain the blood pressure. In all, 66 mg. of noradrenaline was given in 7 litres of fluid during a period of 46 hours.

Discussion

We believe that the necrosis of tissue is due to intense prolonged arteriolar vasoconstriction produced by a high local concentration of noradrenaline. Deterling and Apgar (1951) recorded a case of skin sloughing following paravenous leakage of the solution. Greenwald *et al.* (1952) described two cases in which skin necrosis in the leg occurred in shocked patients; they thought that there was direct extravasation of noradrenaline into the subcutaneous tissues, probably due to the needle or cannula slipping from the vein. In Bergmann's (1953) three cases, however, a cannula or "polythene" catheter had been tied into the vein, and he thought that the hydrostatic pressure of the entering fluid was higher than the venous pressure and that noradrenaline solution passed along the tributaries of the vein and thence to the capillary and arteriolar bed, causing vasoconstriction and ischaemia. In our cases a tied-in-cannula had been used on each occasion when the complication subsequently occurred. The strict localization of the necrosis to the skin and subcutaneous tissues overlying and around the recipient vein, combined with the fact that its distal limit corresponded with the position of the tip of the cannula, suggests that the solution diffused through the vein, possibly owing to ischaemia of its wall caused by constriction of the vasa vasorum. There was no venous thrombosis, because in each instance the infusion was running well when skin discoloration was noticed. The skin incisions used for insertion of the cannulae healed by first intention.

Bergmann (1953) was of the opinion that the duration of the noradrenaline infusion was important, and found that, of eight recorded cases of skin gangrene, seven did not occur until the second day. In Case 1 of our series the complication occurred in both legs. The infusion in the right lasted for ten hours; in the left the vein lining had probably been damaged by the previous infusion, for sixty hours, of dextrose and saline solutions containing oxytetracycline. Noradrenaline was infused for only one hour. It is evident, therefore, that skin necrosis may follow a short period of intravenous noradrenaline therapy.

We believe that the two important factors resulting in tissue necrosis are shock and a high concentration of noradrenaline in the recipient vein. The latter is related more to the technique of administration than to the concentration of the drug in solution.

In our three cases, and in all other recorded cases of this complication of noradrenaline therapy, a common factor has been the presence of severe protracted arterial hypotension. The resulting hypoxia of the skin and subcutaneous tissue in the limbs renders them unable to withstand the further reduction in oxygen tension produced by the local vasoconstriction.

With regard to the second factor, in Case 1 the maximum concentration of noradrenaline solution infused by cannula in the left leg was only 4 µg. per ml. We have had experience of one case of prolonged hypotension and anuria in which a concentration of 32 µg. per ml. was used without local complications. With this patient the drug was given through a needle placed in an antecubital vein percutaneously. A similar technique has been used in many cases of prostatectomy performed under spinal analgesia without ill effect, although transient blanching of the skin overlying the vein has on occasion been noted. Case 2 received noradrenaline infusions of equal concentrations into seven superficial veins. Skin necrosis occurred over two of the three veins in which a tied-in cannula was used. With the four percutaneous infusions there were no local complications. This evidence indicates that the concentration of the drug in the solution as administered is not significant, but that the actual concentration in the vein lumen is extremely important. When the noradrenaline is given through a needle inserted percutaneously into a large vein it is rapidly diluted by the circulating blood, whilst if a tied-in cannula is used the recipient vein contains noradrenaline solution only and is thus exposed to a high concentration of the drug until it is joined by a large tributary.

When noradrenaline is to be given to a shocked patient we suggest that the complication of skin gangrene may be prevented by administering the solution either through a needle into a large superficial vein or, if the veins are collapsed and a cut-down is necessary, through a polythene tube passed far enough proximally to enable its tip to lie in a vein of considerably greater diameter than its own. Both these methods allow rapid dilution of the drug by the venous blood stream. If the skin overlying a vein receiving noradrenaline shows colour changes other than slight blanching the infusion should be stopped immediately. The early injection of procaine and papaverine into the vein may possibly relieve the local vasoconstriction and prevent tissue necrosis or reduce its extent.

Summary and Conclusions

Five instances of skin necrosis following intravenous noradrenaline are recorded in three patients. The pathogenesis of the lesions is discussed, and it is concluded that the main factors in its development are arterial hypotension and infusion through a tied-in cannula. It is suggested that the complication may be avoided by using a technique which permits rapid dilution of the drug by the circulating blood.

We are grateful to Professor Charles Wells, Mr. J. B. Oldham, and Mr. J. Howell Hughes for permission to record these cases and for their interest and advice in the preparation of this report. The skin grafting in Case 1 was performed by Mr. R. P. Osborne.

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The British Dietetic Association has issued a pamphlet on the functions and status of dietitians (Leaflet BDA/4), as it considers the position of dietitians in the hospital service needs clarification. "At the present time," it observes, "there is a shortage of qualified dietitians, insufficient to allow the proportion of even one to every hospital of 150 beds or more. The British Dietetic Association therefore urges that steps should be taken wherever dietitians are employed to ensure the utmost economy of staff and administration, so that dietitians are being used only for the very specialized work for which they have been trained, and are given adequate assistance by qualified cooks and by cleaners."