the difference between observer means is significant at the 5% level (Table III). This is rather surprising, as observed differences in leg lengths might be expected to be free from any systematic bias affecting a single measurement. The bias could depend on the order of the two measurements or on the handedness of the observers; but Observer 3 was left-handed and measured the left leg first, whereas the other three observers were right-handed and measured the right leg first.

The departures from the general mean are small, though significant, and are judged unimportant. The general mean (+0.036 in.—0.91 mm.), having a standard deviation of only ± 0.009 in. (± 0.23 mm.), is significantly greater than zero, but again is small. It is not possible from the data to say to what extent it is due to a real average difference in the patient's leg lengths or to a persistent bias in the observers.

The systematic differences between observers, though significant, are small, the main source of variation being an experimental error which would arise even with repeated determinations by one observer. What is much more important from the clinical standpoint is that the variations between observers are negligible compared with the residual variation, since the latter measures the variation to be expected if a single observer continued to make independent measurements on the same patient. This experimental error has a standard deviation of about $\frac{1}{4}$ in. (3 mm.), so that once in 20 times a single reading will be more than $\frac{1}{4}$ in. (6 mm.) out. Greater accuracy could be achieved by taking the average of several independent readings.

Conclusion

The overall degree of accuracy of the measurement of leg lengths is such that differences of $\frac{1}{4}$ in. (12.5 mm.) or more may be accepted as diagnostically significant, but differences of less than $\frac{1}{4}$ in. are not reliable unless based on the average of at least four measurements.

Thanks are due to Squadron Leader D. J. E. Cheshire, Flight Lieutenant C. E. A. Thomas, and Dr. C. P. Finch for measuring many legs. Permission to publish this paper was granted by the Director-General of Medical Services of the Royal Air Force

REFERENCE

Schilling, R. S. F., Hughes, J. P. W., and Dingwall-Fordyce, I. (1955). *British Medical Journal*, 1, 65.

TREATMENT OF SEVERE SHOCK BY NORADRENALINE

REPORT OF FOUR CASES

BY

I. E. W. GILMOUR, M.B., F.R.C.S.Ed.

*Surgeon, Leith Hospital; Late Assistant Surgeon,
Kirkcaldy General Hospital*

L-Noradrenaline bitartrate ("levophed") is a powerful peripheral vasoconstrictor drug which produces a rise in both systolic and diastolic pressures (Swan, 1949). The clinical indications for its use include the treatment of hypotensive circulatory states due to a lowering of the peripheral resistance (Churchill-Davidson, 1951). In the following four cases the intravenous infusion of L-noradrenaline caused a dramatic sustained rise in blood pressure and appeared to be a major factor in the recovery from seemingly irreversible shock.

Case 1

A man aged 57 had a partial gastrectomy for duodenal ulcer performed by Mr. J. W. M. Sutherland in May, 1950. He was well until 4 a.m. on February 12, 1953, when he suddenly developed a severe haematemesis and was admitted

to hospital. He was transfused with 7 pints (4 litres) of blood, and the blood pressure rose satisfactorily to 120/70. In the evening he collapsed again, and the blood pressure fell to 70/40. Surgical intervention seemed imperative, and at operation an hour later a stomal ulcer was found at the site of anastomosis and a second higher gastrectomy done. The operation lasted two and a half hours and 4 pints (2.3 litres) of blood was given intravenously. Forty minutes after operation the blood pressure was 60/40, and the patient was severely shocked. Methylamphetamine hydrochloride (15 mg. intravenously, 15 mg. intramuscularly) had no effect.

Half an hour later, in a last attempt to raise the blood pressure, intravenous noradrenaline was started, 4 ml. in 1,000 ml. of glucose-saline. At a rate of 20 drops a minute the blood pressure rose to 100/50 within a few minutes. The drip rate was increased to a maximum of 40 drops a minute within the next half-hour and the blood pressure rose steadily to 130/70. Thereafter ten-minute blood-pressure readings were taken and the drip rate was adjusted to keep the systolic pressure at 130. For an hour the rate varied between 20 and 30, and then gradual "weaning" from the drip was begun until it was finally stopped six hours after its commencement. Slow but steady improvement followed, but on the seventh post-operative day a phlebotrombosis developed in the right leg. Anticoagulants were given and the swelling subsided, but unfortunately on March 14 he developed sudden pain in the chest and died in two hours. Post-mortem examination revealed a large pulmonary embolus.

Comment.—Initial shock due to haemorrhage aggravated by operation.

Case 2

A man of 78 was admitted to hospital on October 26, 1954, with acute retention of urine. On examination he was fit and active for his age. The tongue was clean, and the heart and lungs were clinically normal. The blood pressure was 166/96. The bladder was distended to 2 in. (5 cm.) below the umbilicus. Rectal examination revealed an adenomatous enlargement of the prostate.

A self-retaining Foley catheter was inserted and the patient underwent a retropubic prostatectomy the following morning. The operation was without incident and lasted fifty minutes. Approximately 10 oz. (285 ml.) of blood was lost. The blood pressure at the conclusion was 140/80.

Two hours after operation bladder lavage was carried out and some clots were removed. The pulse rate was 86 and the blood pressure 136/78. Two hours later there was a marked deterioration. The patient was pale and sweating, pulse rate 120, blood pressure 80/60. A pint (570 ml.) of blood was given rapidly intravenously. Since there was no significant improvement a second pint was given intra-arterially. Preoccupied by the resuscitative measures, it was not noticed until after the intra-arterial transfusion that the bladder was distended and not draining. Manipulation of the catheter soon produced about 20 oz. (570 ml.) of heavily blood-stained fluid. Following the transfusions and release of tension in the bladder there was a moderate improvement. At 7 p.m. the blood pressure was 130/70 and the pulse rate 100. During the evening there was persistent blood-stained soakage from the wound followed by a further deterioration in the general condition.

A third pint of blood was started intravenously, and at 11 p.m. the wound was reopened under general anaesthesia. There was some venous oozing from the prostatic veins, which was controlled by a pack. At the end of the operation the blood pressure was only 60/40 and the patient seemed unlikely to survive. A noradrenaline drip, 4 ml. in 1,000 ml. of glucose-saline, was started. Within ten minutes, at a drip rate of 30 drops a minute, the blood pressure rose to 110/80 and was maintained at over 100 systolic by a drip rate varying between 20 and 25 a minute. Blood pressure readings were taken at 10-minute intervals throughout the night. At 10.30 a.m. the drip was stopped. Within five minutes the blood pressure fell to 70/40. Five minutes

after restarting the drip the blood pressure rose to 122/60. It was continued until the evening, when the rate was gradually slowed and the blood pressure was maintained. At 10.30 p.m. the drip was finally stopped without any concomitant fall in blood pressure, and thereafter the patient continued to improve. He was discharged home on the twenty-first day.

Comment.—Shock due to distension of bladder with blood aggravated by haemorrhage and second operation.

Case 3

A heavily built man of 43 was admitted to Victoria Hospital, Kirkcaldy, on October 19, 1954, with haematemesis and melaena. A barium meal in July, 1954, had shown a duodenal ulcer. Bleeding persisted over the next twenty-four hours, and he was transferred to the General Hospital for operation on October 20. Prior to operation he had received 5 pints (2.9 litres) of blood and 2 pints (1.1 litres) of "dextraven." His blood pressure on admission and before operation was 160/100, although it had fallen to 90/60 before transfusion was started. At operation no peptic ulcer was found. The liver and spleen were normal, but the entire alimentary tract contained a large quantity of blood. A high partial gastrectomy was performed. The operation was uneventful and lasted one and a half hours. When the patient was about to be taken to the ward he suddenly vomited and inhaled blood-stained stomach contents. He was immediately bronchoscoped and intubated. With pure oxygen he recovered, but his blood pressure, which at the end of operation was 160/100, dropped to below 60 systolic. The endotracheal tube was removed in half an hour, but within a few minutes he became cyanosed and then grey; respiration stopped and the pulse slowed to 10–15. Death seemed imminent.

Intubation, oxygen, and assisted respiration brought a dramatic improvement. First the pulse rate increased and the volume became stronger, followed by spontaneous respirations and loss of cyanosis. This sequence of events occurred on four further occasions, after the last of which the attacks did not recur. During these episodes 1 pint (570 ml.) of blood was given. The blood pressure, however, could not be raised above 70–80. Methylamphetamine hydrochloride, 15 mg. intravenously, had no significant effect. It seemed certain that the patient would soon die unless the blood pressure could be raised above 100 mm. Hg systolic. An intravenous infusion of noradrenaline, 4 ml. in 1,000 ml. of glucose-saline, was begun at 2 a.m., and the blood pressure quickly became stabilized at 140/90 with a drip rate of 18 drops a minute. Blood pressure readings were taken at five-minute intervals. At 5 a.m. the drip rate was slowed to 7 drops a minute, and at 6 a.m. the infusion was stopped and the blood pressure maintained. Despite the development of paralytic ileus and a partial disruption of the wound he made a complete recovery and was discharged on November 16.

Comment.—Shock due to inhalation of gastric contents and anoxia.

Case 4

A woman aged 20 was admitted to hospital on January 14, 1955, for observation as a case of possible ectopic pregnancy. On examination she was not shocked. The blood pressure was 130/80, pulse 76, and temperature normal. The diagnosis remained in doubt until the following day, when a vaginal examination revealed a soft mass in the right tube. At operation a tubal pregnancy was confirmed and the tube excised. About 10 oz. (285 ml.) of blood was removed from the peritoneal cavity.

On the second day she complained of upper abdominal pain and the pulse had risen from 80 to 110. On the third day the pulse rose to 120 and the temperature to 101° F. (38.3° C.), and in the afternoon she passed three loose green stools and vomited twice. At 8 p.m. her condition deteriorated further. She looked toxic and was sweating freely.

The abdomen was moderately distended and only a few bowel sounds were heard. She passed three more green stools, which did not contain any blood or mucus. The blood pressure dropped to 80/40. Her conjunctivae were well coloured and there was no evidence of haemorrhage. A provisional diagnosis of peritonitis or a severe intestinal infection or necrotising enteritis was made. A pint (570 ml.) of blood was started at 11 p.m., by which time her blood pressure was unrecordable and her pulse was weak and irregular. The abdomen was more distended and bowel sounds were now absent. At 1.30 a.m. her extremities were cold and cyanosed. She was drowsy and apathetic. The blood and 250 ml. of normal saline had been given without any improvement.

A second drip with noradrenaline, 4 ml. in 1,000 ml. of glucose-saline, was started, and 1 g. of oxytetracycline was added to the first drip. Within fifteen minutes the blood pressure was 84/60 with a drip rate of 80 drops a minute. By increasing the rate to 100 a minute the blood pressure rose to 108/60 in an hour. Two hours later the dose of noradrenaline was doubled (8 ml. in 1,000 ml.), and the drip rate slowed to 60 a minute without any fall in pressure. This rate was maintained for three hours and then halved. The blood pressure did not fall. Further gradual reduction in the rate was possible, and the drip was finally stopped eleven hours after its commencement. The blood pressure was then 110/70. During the next three days she passed a total of 26 loose stools. No specific pathogenic organisms were cultured from these, but the clinical picture seemed to be that of a bowel infection rather than a peritonitis. Her temperature and pulse gradually subsided and she was discharged on the fifteenth day.

Comment.—Shock due to toxæmia.

Discussion

It is felt that noradrenaline should be used only when other "orthodox" methods have failed. In surgical practice the majority of cases of shock respond to adequate and prompt restoration of a deficient blood volume. Cases that respond in this way have already a normally functioning peripheral vasoconstrictor mechanism, and the additional constricting effect of noradrenaline is not required.

In Case 1 blood replacement that appeared to be adequate had no significant effect, although intra-arterial transfusion was not tried. It is obvious that the peripheral vasoconstrictor mechanism needed boosting. Similar cases have been described by Cappe and Pallin (1951), Churchill-Davidson (1951), and Shanahan (1955).

The primary collapse in Case 2 appeared to be due to distension of the bladder with blood. Some improvement followed intravenous and intra-arterial transfusions, but continued oozing from the prostatic veins and the administration of a second anaesthetic caused a profound peripheral circulatory failure, from which recovery seemed unlikely. As it was considered that the blood loss had been fully replaced no further transfusions were given. The administration of noradrenaline as a last resort resulted in an immediate elevation of the blood pressure and ultimate recovery.

In Case 3 the aspiration of gastric contents into the tracheo-bronchial tree, combined with anoxia in a patient who had undergone gastrectomy for haematemesis, caused a different mechanism of peripheral circulatory failure. The blood loss had been fully replaced and the most urgent initial treatment was to establish an adequate airway and to remove gastric contents from the trachea and bronchi. The repeated bronchoscopies and intubations lasted forty minutes. When this crisis was overcome and spontaneous breathing re-established the systolic blood pressure could not be raised above 80 mm. Hg. Ten minutes after starting noradrenaline the blood pressure rose to over 100 and was soon stabilized at 140/90.

These three cases illustrate common catastrophes in surgical practice. They responded almost immediately to

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.

REFERENCES

- Barlow, M. B., Ginsberg, H., and Gottlich, J. (1953). *S. Afr. med. J.*, **27**, 564.
 Cappe, B. E., and Pallin, I. M. (1951). *Anesthesiology*, **12**, 728.
 Churchill-Davidson, H. C. (1951). *British Medical Journal*, **2**, 1551.
 Grayson, J., and Johnston, D. H. (1952). *Ibid.*, **1**, 547.
 Kurland, G. S., and Malach, M. (1952). *New Engl. J. Med.*, **247**, 383.
 Shanahan, E. F. (1955). *Brit. J. Anaesth.*, **27**, 31.
 Smith, K., Shirley, and Guz, A. (1953). *British Medical Journal*, **2**, 1341.
 Skelton, J. A., Mills, L. C., and Moyer, J. H. (1952). *Fed. Proc.*, **11**, 391.
 Swan, H. J. C. (1949). *Lancet*, **2**, 508.

SKIN NECROSIS FOLLOWING INTRAVENOUS NORADRENALINE

BY

J. HUMPHREYS, M.B., F.R.C.S.

Surgical Registrar

J. H. JOHNSTON, M.B., F.R.C.S.

Senior Surgical Registrar

AND

J. C. RICHARDSON, M.B., F.F.A.R.C.S., D.A.

Senior Anaesthetic Registrar

United Liverpool Hospitals

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-