L-NORADRENALINE IN TREATMENT OF SHOCK IN CARDIAC INFARCTION

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Cardiac infarction is more often than not accompanied by shock. Usually it is transient and passes off as the pain abates under the influence of morphine. In some patients it persists and appears to contribute to an early fatal issue, while, in a few, shock gravely complicates the clinical state during a period of several days or even a week in an illness which in four cases out of five ends in death. It is in this last group that physicians have felt the lack of therapy to combat peripheral circulatory collapse, in which pressure may fall to levels that can hardly, if at all, be recorded, with disappearance of pulse and loss or clouding of consciousness. Intravenous infusions of hypertonic glucose, plasma, blood, and dextran have been used, and slight success has been claimed. In spite of its obvious possibilities, adrenaline has been discarded in this condition; it may raise the pressure but the risk of ventricular fibrillation is too great. On the other hand, other pressor drugs of the sympathomimetic amine series have been shown to raise the blood pressure without increasing the rate or the work of the heart. It was the claim of anaesthetists that the laevorotatory form of noradrenaline secured their patients against serious falls of pressure during major operations which led us to the use of this substance in cardiogenic shock. In this paper we report the results of the use of L-noradrenaline bitartrate ("levophed") in the six instances in which we have employed it for this purpose.

Material and Methods

We have, so far, treated only six patients suffering from shock in myocardial infarction with infusions of L-noradrenaline bitartrate, restricting this treatment to those patients whose lives we judged to be immediately threatened by shock. As L-noradrenaline is a sufficiently powerful overall vasoconstrictor to be effective in doses ranging from 5 to 40 μg. a minute when used in the treatment of any peripheral vasomotor collapse (Swan, 1952), we ensured a sufficient dilution by adding 4 ml. of 1/1,000 L-noradrenaline bitartrate solution to a litre of isotonic solution either of 5% dextrose or of 4.3% dextrose in 0.18% saline, thus giving a drug strength of 4 μg. per ml. Normal saline as a vehicle was avoided in view of the danger of introducing excess of sodium ions into the circulation when heart failure existed or might supervene. Intravenous drip infusions were set up with one or other of these solutions, and preparations were made to continue the infusions for periods of a few hours to a few days. The concentration of drug necessary to keep the blood pressure at a chosen level varied greatly with each patient, but it was sometimes found that drip rates of more than 36 drops a minute were required. As this would entail giving a total infusion of more than three litres in 24 hours, the concentration of the L-noradrenaline bitartrate was increased as much as necessary—on one occasion to 64 ml. per litre—so as to be able to reduce the drip rate by the same factor. By this means the risk of circulatory overloading was abolished, although the control of the blood pressure by adjustment of drip rate became less sensitive.

In accordance with the main indication already mentioned, the use of L-noradrenaline infusion was considered whenever the systolic blood pressure was progressively falling in cardiogenic shock or when it was found to be 80 mm. or less for more than 24 hours, especially in the presence of a very small pulse pressure and oliguria. That we have been reluctant rather than anxious to employ this treatment is shown by the fact that two of our six patients were pulseless when the infusion was begun.

The presence of a nurse capable of measuring the blood pressure reliably was found to be essential. Throughout the whole period of the treatment vigilant attention had to be given to the drip rate, which might spontaneously vary with corresponding and perhaps dangerous fluctuations in blood pressure, which was generally kept between 100 and 110 mm. systolic. It was found that there was a direct and immediate relationship between drip rate and the blood pressure; with a turn of the regulating screw the pressure could be raised or lowered at will. On one or two occasions when the infusion was brought to an end the blood pressure fell abruptly; it therefore became our rule to discontinue the infusion by degrees while a close watch was kept on the blood pressure.

Case 1

A man aged 49 was admitted to hospital at 2 p.m. on June 16, 1952, on account of sudden very severe pain in the centre of the chest and vomiting. For three years he had had angina of effort; there had been cardiographic evidence of old antero-septal cardiac infarction, and the blood pressure was usually 140/90. He was extremely ill and shocked, and was drenched in sweat. The temperature was 97° F. (36.1° C.), and the heart sounds were distant. The systolic blood pressure was 60. Injections of morphine totalling ¾ gr. (50 mg.) were needed for relief of pain, and an intramuscular injection of 12,500 units of heparin was given. Although the condition improved during the day, the pressure during the following morning varied between 70 and 65 mm. systolic. In spite of intravenous injections of nikethamide, the pulse at the wrist disappeared, the extremities being cold and clammy.

An intravenous infusion of 20 oz. (570 ml.) of plasma failed to bring improvement. To a second similar quantity 4 ml. of 1/1,000 L-noradrenaline was added. Immediately this had started, the pressure rose to 100 and was maintained at 90 by an infusion rate of 60 drops a minute. Thereafter, the infusion was continued with 4.3% dextrose in 0.18% saline containing 16 ml. of 1/1,000 L-noradrenaline per litre; a drip rate of 36 drops a minute sufficed to keep the systolic pressure in the neighbourhood of 90 (Fig. 1). The condition of the patient remained critical, in spite of oxygen administration and maintenance of the drip throughout the day; on one occasion when it accidentally stopped the patient at once became pulseless. A pint (570 ml.) of plasma alone brought no improvement, but renewal of the L-noradrenaline infusion at once restored the pulse, while the pressure rose to 95 and later 115. The drip had to be maintained continuously for 48 hours, but when it was then discontinued the pressure fell slowly from 120 to 85, at which level it remained. An electrocardiogram showed antero-posterior infarction of the heart.

The patient made a gradual recovery in spite of temporary congestive heart failure, and he was discharged from hospital on July 27. Two months later he was readmitted in severe left ventricular failure, which in spite of every effort worsened and ended fatally on October 19, about four months after the onset.

Necropsy showed fibrotic scars of cardiac infarctions involving the posterior and lateral walls of the left ventricle and the anterior wall in the neighbourhood of the septum. The right coronary artery and the circumflex branch of the left coronary were occluded 2 cm. from the origin in each case.

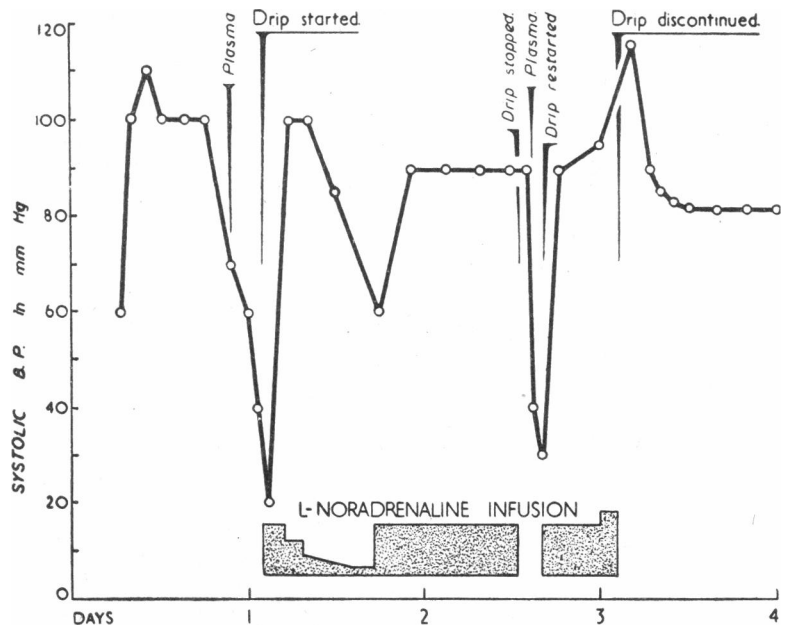

FIG. 1.—Graph showing rise of systolic pressure during intravenous infusion of dextrose–saline containing L-noradrenaline, 4 ml. 1/1,000 solution to the litre, in a patient with severe cardiac infarction and shock (Case 1).

Case 2

A woman aged 67 was admitted for an operation on her left hip. Clinical examination showed no cardiovascular abnormality save a blood pressure of 170/90. The operation was performed at noon on September 22, 1952. There had been little trauma or blood loss, but near the end of the operation she suddenly collapsed and became pulseless. Surgical shock was diagnosed, and an intravenous plasma infusion containing 4 ml. of 1/1,000 L-noradrenaline to the pint (570 ml.) was given, whereat the blood pressure became measurable at 80. On surgical grounds the infusion was changed to whole blood, and later to normal saline, but always with the same addition of L-noradrenaline, and at the rate of 40 to 60 drops a minute. Eleven hours after the start of the operation the patient regained consciousness. She had pain at the site of the operation, but nowhere else.

On the next day the condition had further improved. There was still no cardiac pain and the heart sounds were faint. Continuance of the L-noradrenaline–saline drip, now changed to 0.18% saline, enabled the blood pressure to be kept at about 100 mm. systolic, and the level could be raised or lowered at once by quickening or slowing the drip.

On September 24 an electrocardiogram revealed that the unsuspected cause of the collapse had been a large through-and-through antero-lateral infarction of the heart. The patient remained dependent on the L-noradrenaline infusion; although she was not breathless and the urinary output remained good, the sacrum and legs became oedematous. Fluid-balance charts revealed that 6 pints (3.4 litres) more fluid had been taken in than had been excreted in the previous 36 hours. This was remedied by quadrupling the concentration of L-noradrenaline and reducing the rate of the drip to 15 to 20 a minute. Heparin and biscoumacetate were then started. The L-noradrenaline administration had to be continued for five days, when a very gradual cessation was begun; any sudden reduction in drip rate was followed by an abrupt and dangerous fall of systolic pressure, so that the process of cessation took 72 hours to complete. The systolic blood pressure then remained at 85 mm., with a pulse of 100 a minute. During the next two months in hospital, the pressure fluctuated between 90/50 and 105/70, which was the reading on discharge. Seven months later there was no dyspnoea or angina, and the blood pressure was 105/70.

Case 3

A man of 53 was admitted at 6.30 p.m. on May 8, 1953, with a history of a sudden onset of severe retrosternal pain. He had vomited twice and sweated profusely. The extremities were cold, the temperature being 96.2° F. (35.7° C.), and the pulse regular at 36 a minute. The blood pressure was 80 systolic. The heart sounds were faint and the cervical veins engorged.

Electrocardiography confirmed the clinical presumption of complete A-V block and showed auricular fibrillation as well as patterns of an extensive posterior cardiac infarction. The blood pressure fell steadily in spite of general measures to combat shock, and one hour after admission it was 55 systolic, the patient looking as if about to die. The pulse rate was 40 a minute. As soon as an infusion of dextrose–saline containing 4 ml. of 1/1,000 L-noradrenaline per litre was started he looked better and uttered some words. At an infusion rate of 20 drops a minute the blood pressure rose swiftly to 80–115 systolic. Within 15 minutes of the infusion being started there was a sudden reversal to normal rhythm at 80 a minute (Fig. 2).

After one and a half hours of this treatment the drip rate was gradually slowed without fall of the blood pressure, and during the next two hours the L-noradrenaline concentration in the infusion was halved. It was discontinued after a total duration of just over three hours. During the next two months there was uninterrupted convalescence with improving effort tolerance. At a later examination the heart was found to be not enlarged and the pressure remained around 130/80.

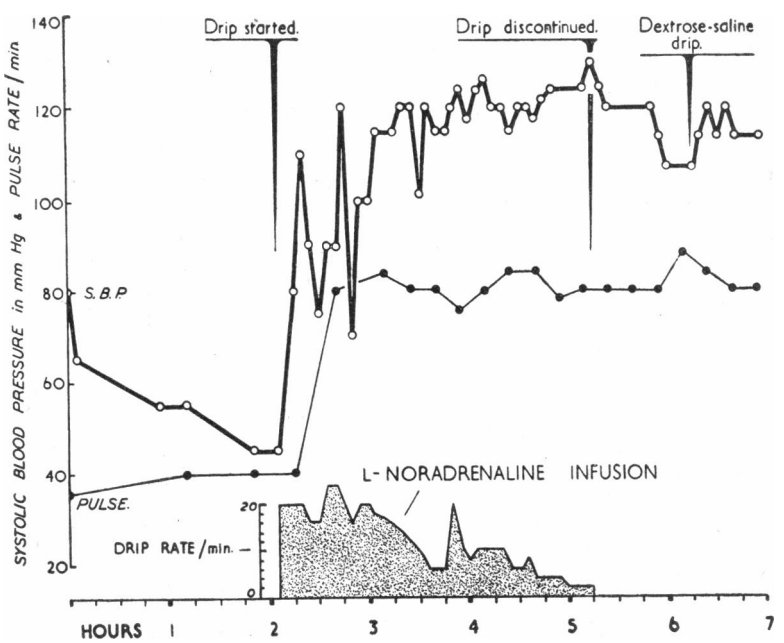

FIG. 2.—Graph showing rise of systolic pressure during intravenous infusion of dextrose–saline containing L-noradrenaline in varying concentration. Case 3, suffering from acute posterior cardiac infarction with initial complete A-V block and auricular fibrillation.

Case 4

A woman aged 73, a patient of Dr. D. I. L. Gleed, of Finchley, was seen in consultation on March 15, 1953. She had for nine years suffered from angina of effort, and had latterly been taking 50 trinitrin tablets weekly. At noon she was seized with an attack which caused collapse with loss of consciousness. She was grey and sweating with a weak pulse at 60 a minute. She vomited twice.

Examination six hours after the onset showed the patient still shocked, with a pulse of 72 and blood pressure 105/75. An electrocardiogram showed extensive postero-lateral infarction of the heart. Admission to hospital took place the same evening, when the pulse had quickened to 100 and the pressure had fallen to 90 systolic. Signs of congestive heart failure were developing, and there was pericardial friction to the left of the sternum.

At 1.30 a.m. that night renewed collapse occurred with sweating and unconsciousness; the systolic pressure fell to 50 and the pulse was hardly perceptible. At 2.5 a.m. an intravenous infusion of dextrose–saline containing 2 ml. of 1/1,000 L-noradrenaline per litre was started. Instantly the condition improved, the systolic pressure rising to 80 and later to 100. Throughout the day of March 17 the condition remained fairly satisfactory in that, despite sweating and chilliness of the extremities, the pressure was maintained at the same level by adjustment of the drip rate. Electrocardiography that evening showed that right bundle-branch block had now developed. The white cells numbered 31,200 per c.mm. During the following night the condition again became very grave, the pulse becoming weaker, with increasing signs of collapse. The drip rate was increased, but in spite of this and of an intravenous injection of theophylline with ethylenediamine the heart rate increased to 100 while the pulse became imperceptible. Death took place 66 hours after the onset of the illness.

Necropsy showed a recent infarction in the interventricular septum extending to the adjacent parts of the anterior and posterior walls of the left ventricle. The anterior part of the septum had become thinner, with the beginning of dilatation in this part of the ventricle. The remainder of the myocardium showed diffuse patches of fibrosis. Patches of calcified atheroma were found in both coronary arteries and their main branches. While the vascular lumen was in places much reduced, no occluding thrombus could be found.

Case 5

A woman of 75 was seen in consultation with Dr. Alan Strachan, of Sutton, on April 18, 1952, when she was in a state of cardiogenic shock. This had set in at 10 a.m. that day, about half an hour after an injection of morphine and atropine preparatory to dental extractions. It later transpired that three years previously a similar injection for gallstone colic had been followed within a few minutes by collapse, with pallor and a thready pulse. On that occasion there had been swift recovery after an injection of nikethamide, but in the present attack pain had developed around the trunk at the level of the diaphragm. The foot of the bed was raised and oxygen was given. The condition improved, but the pain persisted, later centring over the right upper quadrant of the abdomen.

At the consultation that evening there was pain across the lower part of the back with a bruised feeling in the upper part of the abdomen. The patient was shocked though not in distress; the pulse was regular at 64 a minute, and the blood pressure was 85 systolic. The clinical state did not permit thorough examination, but the heart sounds were heard softly at all areas, and there was no pericardial friction or gallop. There was no tenderness in the abdomen; arterial pulsation was felt readily in the feet. An electrocardiogram showed low voltage in standard leads, intraventricular conduction defect, and lateral subendocardial ischaemia. It was concluded that acute coronary insufficiency had followed a sudden severe fall of blood pressure as a result of abnormal sensitivity to an injection of morphine and atropine.

During the following day or two the condition fluctuated; the symptoms lessened but the blood pressure remained at 80 systolic. On April 22, four days after the onset, an intravenous drip infusion of dextrose–saline containing 4 ml. per litre of 1/1,000 L-noradrenaline was set up at 6 p.m. The blood pressure began to rise within a minute or two, and reached 90 after ten minutes. It then increased steadily to 120 at the end of 30 minutes. Slowing the drip was followed at once by a drop to 110, and this level was maintained without difficulty for four hours (Fig. 3). At the end of this time the systolic pressure was 105, and one litre of the infusion had been given. It was then discontinued.

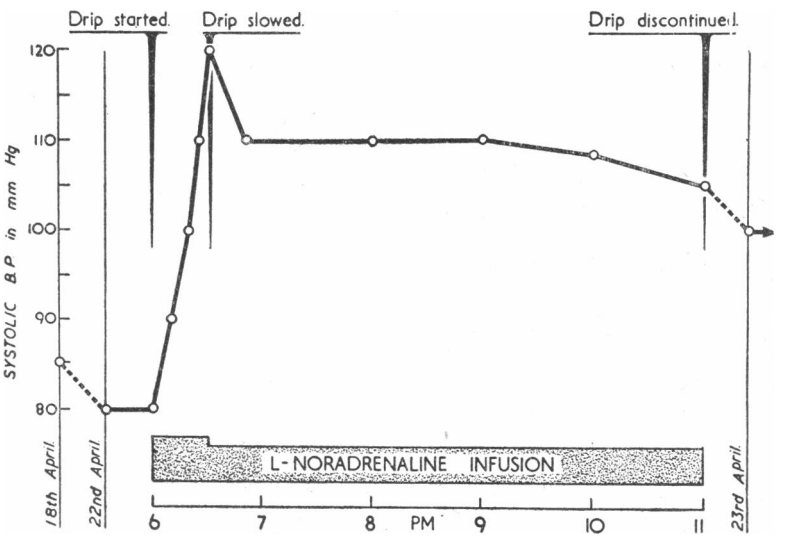

FIG. 3.—Graph showing rise of systolic pressure resulting from intravenous infusion of dextrose–saline containing L-noradrenaline started on the fourth day of cardiogenic shock due to acute coronary insufficiency (Case 5).

On the following morning the general condition had much improved and the pressure was 100. Three months after the onset the patient was up and about quietly, with a blood pressure of 110/75. The cardiogram showed regression of the patterns representing myocardial ischaemia. Radioscopy showed mild left ventricular hypertrophy, normal hilar shadows, and clear lung fields.

Case 6

A man of 61 who had been treated for cardiac infarctions in 1948 and December, 1952, was under periodic observation until, in the summer of 1953, he began to complain of dyspeptic symptoms, and a barium meal examination led to a diagnosis of carcinoma of the pylorus. Partial gastrectomy was performed by Mr. Norman Lake on August 20, with complete removal of a pyloric carcinoma. During the operation the patient never received less than 30% oxygen. Soon after the operation was started he became shocked and the pulse was faint and irregular. He was transfused with 2 pints (1,140 ml.) of blood, and after return to the ward the blood pressure was 130/90. During the next 36 hours the blood pressure fell gradually to 80/65, and he appeared to be moribund. It was judged that this illness was due to infarction of the heart, but cardiography could not be carried out at once. It was decided to give L-noradrenaline.

The infusion of dextrose–saline containing 8 ml. of 1/1,000 L-noradrenaline per litre was begun at a rate of 26 drops a minute. The blood pressure quickly rose to 110/85. In order to maintain this pressure it was necessary to raise

the drip rate to 40 drops a minute, and after 18 hours to double the concentration of L-noradrenaline and reduce the infusion rate from 40 to 30 drops a minute. At this stage a cardiogram showed antero-septal and postero-lateral infarctions. After a further six hours it was necessary to double the concentration again, and yet again seven hours later. The L-noradrenaline concentration was then 64 ml. per litre and the infusion rate 36 drops a minute. Over the next 12 hours the blood pressure was maintained at 110/85 with no further increase in concentration of the drug, and with a decrease in the rate of infusion to 24 drops a minute. The patient then suddenly developed a pulmonary embolism and died at 1.30 a.m. on August 25, one and a half hours after the onset of this complication.

The necropsy confirmed that there was a massive pulmonary embolism involving the whole right lower lobe. The anastomosis of the stomach remnant to the jejunum was intact and no evidence of secondary neoplastic deposits was found. There was severe widespread atheroma of the coronary arteries. A large antero-septal infarction and a small postero-lateral infarction of the heart were present. There were also three old infarctions involving the posterior and lateral walls of the heart. In the left ventricle a great part of the muscle had been replaced by fibrotic tissue.

Discussion

The shock in myocardial infarction needs no special treatment if it is slight. It is upon the treatment of severe and continuing cardiogenic shock that controversy has centred. While some clinicians have employed oxygen, infusions of hypertonic glucose solutions, and stimulants such as nikethamide, these methods have not given constant or convincing results. There has naturally been a temptation to use pressor substances such as adrenaline and ephedrine, and, although they have been advocated in the past by Fishberg (1937), they have been generally condemned on account of the risk of inducing ventricular fibrillation (Eggleston, 1947; Wood, 1952).

The introduction of noradrenaline, and particularly of L-noradrenaline, the optical isomer which acts mainly upon blood vessels, has revived interest in the use of pressor substances in shock. This compound is the most powerful overall vasoconstrictor known and it lacks many of the pharmacological actions that have rendered adrenaline and ephedrine dangerous in cardiac infarction. Thus, in contrast to adrenaline, it does not increase the rate of the heart or the cardiac output; this is the result of reflex vagal cardioinhibition, for L-noradrenaline stimulates mildly, but definitely, the isolated mammalian heart and the heart of the human under the influence of atropine. Also, whereas adrenaline raises the systolic pressure by its profound cardiac effects and hardly influences or actually lowers the diastolic pressure because of muscle vasodilatation, L-noradrenaline increases both systolic and diastolic pressure as a result of the marked generalized vasoconstriction (Goldenberg *et al.*, 1948). Moreover, Reale *et al.* (1950) have shown that, in the healthy subject, intravenous L-noradrenaline does not increase the oxygen consumption, as does adrenaline. Additional support for the use of this substance in shock due to heart disease comes from Burn and Hutcheon (1949), who have shown that L-noradrenaline is a coronary vasodilator in dogs and cats, but species differences exist and no work has been found on the action of the drug on the adult human coronary artery.

In experimental myocardial ischaemia in dogs produced by tying a coronary artery, Corday *et al.* (1949) demonstrated the harmful effects of hypotension on the infarcted zone and showed that such effects could be reversed by correcting the hypotension. In addition, Sayen *et al.* (1952) have shown that an L-noradrenaline infusion causes a rise in oxygen tension in the ischaemic zone, an effect greater than that produced by pure oxygen inhalation, while no ectopic beats or other arrhythmias were observed during the course of the infusion. On the other hand, Wiggers (1952) has pointed out that such experiments have been performed on dogs in which intercoronary anastomoses are better developed than in man, and he groups noradrenaline with adrenaline and ephedrine as potentially dangerous in myocardial infarction owing to the increase in the work of the heart and the risk of ventricular arrhythmias.

After weighing all such clinical and experimental evidence, it remains clear that even serious risks might be accepted when the blood pressure in cardiogenic shock is progressively dropping, when the pulse is disappearing, and death wellnigh at hand.

Some work on the use of L-noradrenaline in the shock attending myocardial infarction in man has already been published. Miller and Baker (1952) employed this treatment in seven such patients. A rise of blood pressure was produced in four and in no instance was there any arrhythmia. Six of the patients died. The criterion for use in these cases was a systolic blood pressure of 80 or less continuing for four hours, and they concluded that the results might have been better had infusion been started earlier. Maintenance of infusion until the improvement in the circulatory state was established, and gradual rather than abrupt cessation was advised. More favourable results have been reported by Kurland and Malach (1952), who treated with L-noradrenaline 14 patients suffering from shock due to cardiac infarction. In 12 cases there was a significant pressor response, but the ultimate results were disappointing, as five died from 1 to 41 days after recovery from the state of shock and only four ultimately survived. No arrhythmias that could be attributed to the infusion were observed, although these workers recorded intense venous spasm, phlebitis, and ulceration of the skin at the site of the infusion as occasional complications.

Although our series of six cases is a small one the results are encouraging, since four of these patients survived for four months or more. Three of them were still alive at intervals of six to thirteen months after infarctions which caused grades of shock so severe and prolonged that death appeared to be imminent. In no case did L-noradrenaline cause harm. In spite of the increase in systemic and pulmonary resistances heart failure was never induced by the treatment.

In this grave state of cardiogenic shock there are two elements; the shock and the underlying myocardial injury. Study of our cases endorses what must have been the clinical impression of many—that the degree of shock is not necessarily proportional to the extent of the infarction. If shock is severe and the lesion is gross, then a fatal issue may be determined by the extreme disorganization of the heart. But when, as is sometimes the case, a lesser injury is attended by grave shock, then there is the possibility of recovery and subsequent reasonably good myocardial function, if the critical phase of shock can be surmounted, as exemplified in three of our cases. In the three patients who have died, necropsies have revealed multiple infarctions, old and new, representing a high degree of myocardial damage.

Summary

Six patients in severe shock due to cardiac infarction have been treated by intravenous infusions of dextrose–saline containing L-noradrenaline (levophed). In all of them a fatal issue appeared imminent or probable, the systolic blood pressure falling to levels between 45 and 80, and in two instances the wrist pulse disappearing.

In each case the start of the infusion was followed at once by clinical improvement, the systolic pressure rising to levels between 90 and 100, while the pulse again became palpable; where consciousness had been lost it was regained.

Two patients who had had previous infarctions responded in this way to the infusion, but died within three and four days, recent as well as old infarctions being proved at necropsy.

The remaining four patients made good recoveries after discontinuance of the infusions. Although one died of congestive heart failure four months after the cardiac infarction, the other three were alive and active at intervals ranging from six to thirteen months afterwards, their lives apparently having been saved by the treatment.

The criteria for infusion of L-noradrenaline are discussed and the methods and precautions necessary for its use described.

We are indebted to Dr. N. S. Plummer and Mr. David Trevor for allowing us to study their patients (Cases 3 and 2); to Dr. Alan Strachan, of Sutton, for his help in the clinical observations and treatment of Case 5; to Dr. D. I. L. Gleed, of Finchley, for her initial records of Case 4; to Dr. W. Evans for the pathological reports on Cases 1 and 4; and to Dr. H. Neville Stafford for the necropsy report on Case 6.

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ACUTE DISSEMINATED ENCEPHALOMYELITIS AND ACUTE DISSEMINATED SCLEROSIS

RESULTS OF TREATMENT WITH A.C.T.H.

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The treatment of seven cases of acute disseminated encephalomyelitis with A.C.T.H. was reported in a previous paper, in which the theoretical basis for trial of the drug was discussed (Miller, 1953). The results of treatment were held to be suggestive enough to warrant further trial. Three further cases have now been treated, and they are briefly reported below.

We have also used A.C.T.H. in the treatment of seven patients with acute exacerbations of disseminated sclerosis. Glaser and Merritt (1952) have already reported on the use of the drug in disseminated sclerosis. They treated 33 cases of the disease, giving 80 to 100 mg. daily during a course of 14 days' duration. These were chronic cases, and none had experienced significant remission during the three years preceding treatment, or since the onset of the disease in cases of less than three years' duration. Twelve patients showed significant improvement. The syndromes benefited were spastic-paretic, cerebellar-ataxic, bladder dysfunction, and visual impairment of recent origin. Oculomotor disorders, sensory impairment, and reflex changes remained unaffected. The effects observed appeared during the course of drug administration and rarely persisted for more than seven to fourteen days after the end of treatment. In most cases the disease later resumed its usual course, though these authors believed that subsequent maintenance treatment with 75 to 150 mg. of cortisone daily might possibly retard its progression. They considered that the beneficial effects of the drug represented "secondary physiological phenomena due to the hyperadrenal state," whether produced by interference with abnormal immunological reactions in the central nervous system, suppression of inflammatory and connective-tissue responses, or the effect on nervous excitability of chemical changes related to the profound metabolic disturbance which A.C.T.H. is known to produce. A somewhat similar transitory improvement in cases of established disseminated sclerosis has been reported by Fog (1951).

We have, however, restricted the experimental use of A.C.T.H. to patients with a recent acute exacerbation of unequivocal established disseminated sclerosis. All cases had recently developed an acute neurological episode with some objectively assessable focal disability, either a fresh manifestation of the disease or the sudden aggravation or reappearance of a previous symptom. No patient was showing any sign of spontaneous improvement when treatment was begun, and progressive deterioration was evident in several. It seems reasonable to believe that the onset of an acute neurological episode of this nature signals the development of fresh plaques in the central nervous system. Although there is no general agreement on the pathogenesis of disseminated sclerosis, nor indeed on the histopathological changes present in recent lesions, it seemed justifiable to make a trial of A.C.T.H. in such cases.

We had found apparent improvement in acute disseminated encephalomyelitis, which shows several clinical and pathological similarities to disseminated sclerosis. Moreover, if an abnormal immunological reaction were responsible for such exacerbations (Pette, 1942) there are theoretical grounds for believing it might be aborted by A.C.T.H. There are similar grounds for believing that A.C.T.H. might also lead to the resolution of the acute inflammatory reaction which was considered by earlier authors—for example, Marburg (1906, 1942)—to be the basis of acute episodes of disseminated sclerosis. If, however, the initial change of the disease is demyelination, possibly as a result of enzymatic disorder (Lumsden, 1951), A.C.T.H. would be unlikely to have any effect once the process had begun, although such a view of the disease does not preclude the possibility that long-term administration of the drug might possibly prevent the development of fresh lesions.

It was felt that by selecting our cases on the above lines it would be possible to make an initial assessment of the effects of the drug on a relatively small number of cases, with a view to a more extended trial if the results were suggestive enough to justify this. It may be remarked that the collection of cases satisfying these criteria proved quite unexpectedly difficult.

In all cases of acute disseminated encephalomyelitis and disseminated sclerosis treated, 25 mg. of A.C.T.H. was given intramuscularly every six hours, usually for a period of five days. Repeated eosinophil counts were made, but in all the cases reported adequate adrenal response was obtained with this dosage.