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L-*NOR*ADRENALINE AS A VASOCONSTRICTOR

BY

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It is proposed to examine the physiological actions of some of the vasopressor drugs in present use, and to show that L-*nor*adrenaline 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-*nor*adrenaline 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 (Bülbring 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 *nor*adrenaline 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 *nor*adrenaline was present in urine and suprarenal extracts, whilst Gaddum and Goodwin (1947) showed that electrical stimulation of sympathetic nerves in

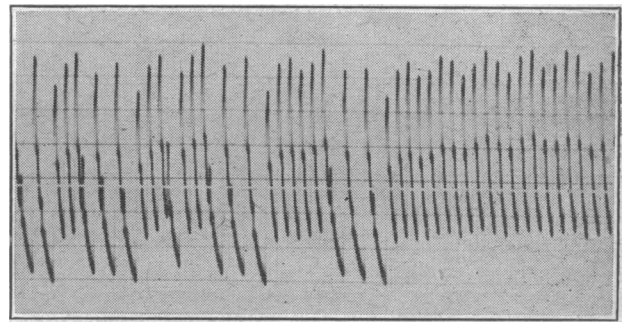
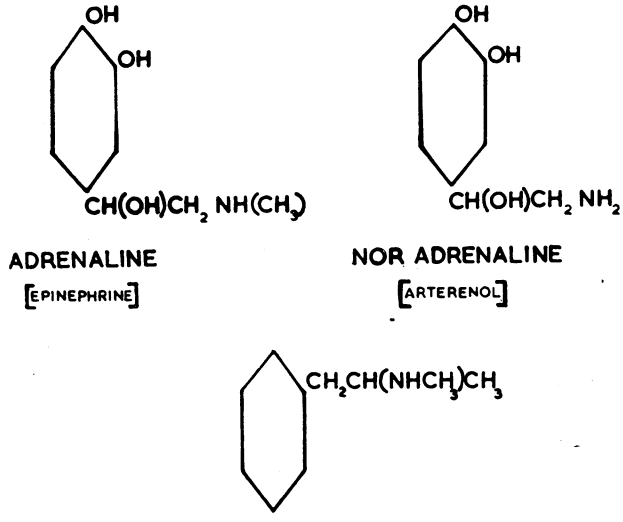


FIG. 1.—Showing part of a continuous pulse record after the patient had been given 15 mg. of methedrine intravenously to raise the pressure following pentamethonium bromide. The gross irregularity of cardiac rhythm is well shown.

all probability liberated *nor*adrenaline. In 1948 Tullar resolved racemic synthetic *nor*adrenaline into its optical isomers—D-*nor*adrenaline, acting mainly on the smooth muscle of the bronchi, and L-*nor*adrenaline, which acts on blood vessels (see Graph).



Since then L-*nor*adrenaline has been found widely distributed in most nerves containing adrenergic fibres (von Euler, 1951). It has been suggested that *nor*adrenaline is merely a precursor of adrenaline with no independent function, but most investigators regard L-*nor*adrenaline as the chemical transmitter of sympathetic nerve endings, being responsible for reflex vascular effects, whereas adrenaline is mainly concerned with metabolic activities (von Euler, 1951). Investigation of its physiological activity in man has shown that it is an extremely powerful overall vasoconstrictor with either no change or a slight decrease in the minute-volume of the heart (Goldenberg *et al.*, 1948). It produces a marked bradycardia and an almost similar rise in the systolic and diastolic pressures (Swan, 1949; Barcroft and Konzett, 1949). This is in distinct contrast to adrenaline and methedrine, following which there is no rise in diastolic pressure, or only a mild increase compared with the rise in systolic pressure (Table I). The only parts

TABLE I.—*Comparison of Physiological Actions of Adrenaline, Methedrine, and L-noradrenaline*

Substance	Cardiac Output	Systolic	Dia-stolic	Pulse	Muscle Flow	Skin Flow	Peripheral Resist-ance
Adrenaline	+++	+++	0	+	++	−	−−
Methedrine	++	+++	+	0	− +	−	+ − −
L-*nor*-adrenaline	0	+++	+++	−−	− −	−−	+++

+ = An increase. − = A decrease. 0 = No change.

of the vascular bed in animals which have been found to respond to *nor*adrenaline with vasodilatation are the coronary arteries and possibly the intestinal vessels (Burn and Hutcheon, 1949). It has not, as yet, been shown whether coronary dilatation occurs in man, but the fact that it occurs in animals suggests that it is a preferable constrictor drug to post-pituitary extract, which is known to produce marked coronary constriction. A further point of interest appears to be the comparison of toxicity between L-*nor*adrenaline and adrenaline, since it has been shown in mice that L-*nor*adrenaline was eight times less toxic than adrenaline (Tainter *et al.*, 1948).

Use of L-Noradrenaline in Clinical Anaesthesia

As L-*nor*adrenaline appeared to offer certain physiological advantages over other vasopressor drugs, it was decided to undertake a clinical trial to determine the efficacy of this drug in the control of the blood pressure during surgical operations.

An intravenous infusion of L-*nor*adrenaline was administered to 69 cases in the course of this trial (Table II). In every case a satisfactory response was obtained

TABLE II

Thoraco-lumbar sympathectomy	8
Coronary ischaemia	3
Severe haemorrhage	2
Prevention of hypotension following thiopentone sodium	24
Spinal analgesia	5
Pentamethonium or hexamethonium compounds	24
Mitral valvulotomy	3
	69

and the blood pressure was controlled at the required level. The period of administration varied from five minutes to six hours. It must be emphasized, however, that most cases of hypotension are best treated with posture in the Trendelenburg position along with a blood transfusion to replace any blood loss. Nevertheless, L-*nor*adrenaline would appear to be a drug that on occasion may be of exceptional value. The anaesthetist must be prepared to undertake personal supervision of the infusion throughout the administration. If the drip goes too fast the blood pressure may become dangerously high, and if it becomes too slow, owing to a change in the position of the arm or of the needle, it may become dangerously low. The closest attention to the rate of the drip and to the height of the blood pressure is constantly required.

Administration of L-Noradrenaline

L-*nor*adrenaline is administered by intravenous infusion. Owing to its instability it is kept in ampoules in an acid solution such as ascorbic or N/10 hydrochloric acid, and is added to normal saline just before use.

The most convenient method of setting up the infusion is to add 4 ml. of 1:1,000 *nor*adrenaline (≡4 mg.) to 1 litre of normal saline, or 2 ml. of 1:1,000 *nor*adrenaline to 0.5 litre of normal saline. This gives a solution with a strength of 4 γ per ml. of normal saline. The drip is then tested to find out how many drops falling into the inspection chamber are equivalent to 1 ml. The quickest method of ascertaining this is to run the drip into a glass measure or an inverted 2 ml. syringe with the nozzle occluded. With most saline and blood transfusion sets this appears to lie between 15 and 25 drops per ml. The average dose required for a healthy subject of 70 kg. weight is 20 γ a minute, but may vary from 5–35 γ a minute according to the level at which the blood pressure is controlled.

The infusion is started slowly (30–40 drops a minute), and is increased gradually at one-minute intervals until the optimum level of blood pressure is obtained by frequent blood-pressure readings. A sensitivity may be shown by hypertensive patients, and small doses will maintain a constant level of pressure; whereas larger

doses than usual are necessary after using pentamethonium or hexamethonium compounds. This difference may be accounted for by the large rise in pressure required to return the blood pressure to its former level in a patient lacking sympathetic tone. The only satisfactory guide to dosage lies in observation of the effect produced, by comparing blood-pressure readings recorded at frequent intervals; once the blood pressure has been stabilized it is remarkably easy to maintain it at the desired level. The danger of excessive dosage is mainly that too high a blood pressure may cause a cerebral haemorrhage, but slowing of the drip rate will produce an almost immediate fall of such an accidental hypertension to the required level.

Indications for Use of L-Noradrenaline

Following this clinical trial it was considered that the intravenous infusion of L-*nor*adrenaline might be of advantage in the following cases.

Phaeochromocytoma. — Chromaffin-cell tumours contain a high percentage of *nor*adrenaline, so that on their removal there may be a sudden precipitous fall of blood pressure. It has already been shown that an infusion of L-*nor*adrenaline can satisfactorily control the pressure until the patient's own vascular system has become adapted to the sudden change (Swan, 1951b).

Profound Hypotension Following the Second Stage of Thoracolumbar Sympathectomy.—An infusion of L-*nor*adrenaline has been found of advantage in combating the dramatic fall in blood pressure commonly associated with surgical intervention in such cases (Goldenberg *et al.*, 1949).

Other Surgical Operations on Patients with Severe Hypertension or Disease of the Coronary Arteries.—Cerebral thrombosis is a well-known cause of post-operative morbidity in hypertensive patients. In severe disease of the coronary artery a fall in blood pressure may seriously embarrass the myocardium, leading to increased irritability, with the consequent risk of ventricular fibrillation (see Fig. 2). The profound fall in blood pressure which is so apt to follow the intravenous injection of short-acting barbiturates is easily prevented by the simultaneous injection of L-*nor*adrenaline.

Collapse under Spinal Analgesia. —Recent work has suggested that the fall in blood pressure associated with spinal analgesia is largely due to a reduction in cardiac output while the effective peripheral resistance remains unchanged (Rovenstine *et al.*, 1942). If, on the other hand, the peripheral resistance is reduced as well, then circulatory collapse ensues (Pugh and Wyndham, 1950). This suggests that those cases which, without excessive blood loss, show circulatory collapse during spinal analgesia have a reduced cardiac output and lowered peripheral resistance. The latter can be effectively raised by an infusion of L-*nor*adrenaline.

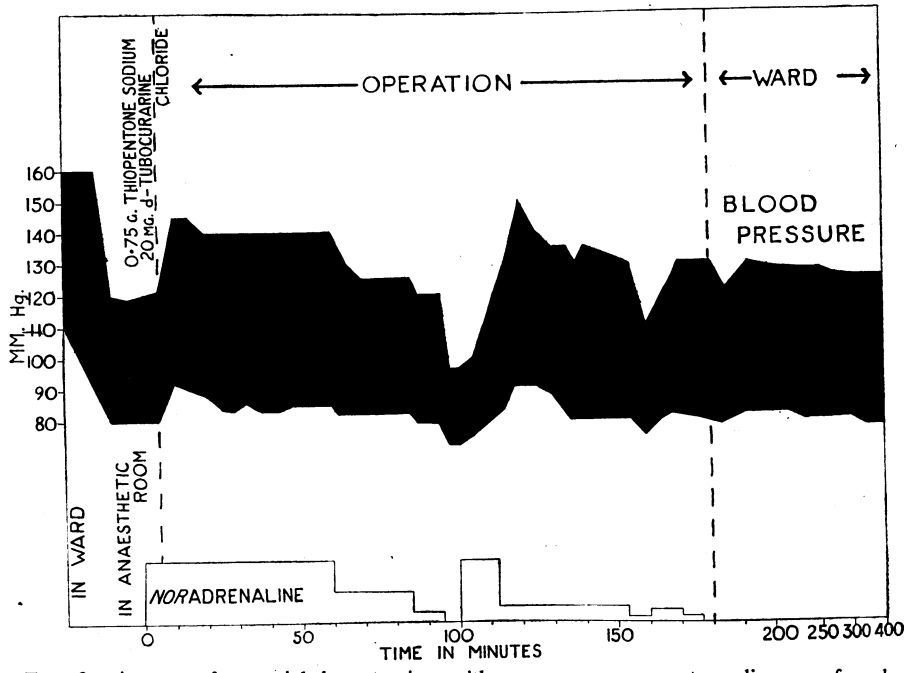


FIG. 2.—A case of essential hypertension with severe coronary artery disease referred by the cardiologists with the opinion that a fall in blood pressure during the surgical operation would have dangerous consequences. The infusion of *nor*adrenaline was started before the induction of anaesthesia with thiopentone sodium. Two hours after the operation had begun an attempt was made to discontinue the infusion. This resulted in a sharp fall in blood pressure, which was rapidly overcome by restarting the infusion. At the close of the operation the patient was able to maintain an adequate level of blood pressure unaided.

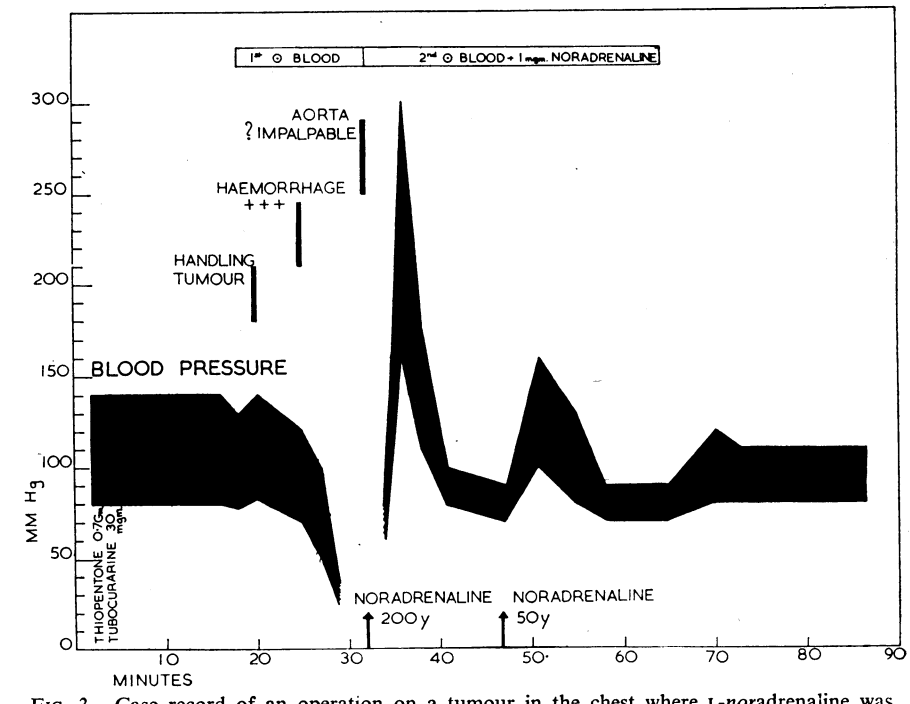


FIG. 3.—Case record of an operation on a tumour in the chest where L-*nor*adrenaline was used for resuscitation after massive haemorrhage. The surgeon remarked that only a "flicker" could be felt in the aorta. The dosage used in this case was obviously far in excess of that required, as is shown by the gross hypertension produced; a critical situation was, however, rapidly reversed.

Sudden Severe Haemorrhage.—The profound and rapid hypotension that follows sudden massive haemorrhage is often difficult to control unless facilities for rapid transfusion therapy are to hand. This can also be countered by an intra-arterial transfusion under pressure if the necessary apparatus is available. During severe hypotension there is an inevitable diminution in the coronary and cerebral blood flow. Another method of increasing the coronary perfusion pressure is to raise the peripheral resistance with L-*nor*adrenaline along with a rapid intravenous infusion. In such an emergency it is a life-saving measure (Fig. 3).

Surgical Operations upon the Heart.—It is customary in cardiac surgery to administer a continuous intravenous procaine infusion in order to reduce the irritability of the cardiac muscle to direct handling. Procaine in large doses reduces the peripheral resistance by generalized vasodilatation and causes a fall in blood pressure. It can be argued that if the peripheral resistance is low the coronary circulation must necessarily suffer. The resulting ischaemia of the cardiac muscle increases its irritability and opposes the intention of the procaine infusion. A combination of procaine and L-*nor*adrenaline has been found satisfactory in such cases.

Following the Use of Pentamethonium or Hexamethonium Compounds.—Pentamethonium iodide and hexamethonium iodide each paralyse autonomic transmission by raising the threshold of the ganglion cell to the acetylcholine released at pre-ganglionic nerve endings (Paton and Zaimis, 1951). This action produces a fall in blood pressure by peripheral vasodilatation. In the event of profound circulatory collapse following the use of the methonium compounds it would seem more physiological to raise the pressure by vasoconstriction with *nor*adrenaline than by an increase in cardiac output with methedrine—the drug usually recommended in such cases. Though a prolonged rise in blood pressure in these cases increases the risk of haematoma formation, L-*nor*adrenaline has been used with advantage to produce a momentary rise in blood pressure to detect major bleeding-points.

Effect of Noradrenaline on the Heart Rate

L-*nor*adrenaline, in conscious volunteers, produces a marked bradycardia (Barcroft and Konzett, 1949; Swan, 1949), which is probably brought about by a vagal reflex from the carotid sinus or aortic arch (Barnett *et al.*, 1950). During the course of this investigation it was noted that a bradycardia did not always occur after pentamethonium bromide. Thus the bradycardia can be prevented if the infusion of *nor*adrenaline is preceded by an injection of:

Atropine Sulphate.—Doses of 1 mg. have been shown to be followed by an increase in heart rate along with an extremely marked rise in blood pressure (Goldenberg *et al.*, 1948). In anaesthetized subjects the normal premedication doses of atropine sulphate and hyoscine hydrobromide do not appear to influence the effect of *nor*adrenaline.

Pentamethonium Iodide.—There is a wide variation in heart rate according to the dose of the methonium compound used. Following doses of 40–80 mg. of pentamethonium iodide a bradycardia ensues on starting the *nor*adrenaline infusion. If, however, a dose of 120 mg. or more is used then a tachycardia is often encountered (Fig. 4). A similar response is seen with methedrine. It appears that small doses of pentamethonium iodide may paralyse the sympathetic ganglia, with a consequent fall in blood pressure, whilst the carotid sinus and aortic arch mechanisms remain unaffected. Large doses produce generalized autonomic paralysis. A further noticeable feature following large doses of pentamethonium is the manner in which the heart rate is closely related to the arterial blood pressure, both rising and falling in unison.

Noradrenaline and its Effect on Autonomic Ganglia

It has been shown that the prolonged infusion of large doses of DL-*nor*adrenaline in animals is followed by a profound fall of arterial pressure (Blacket *et al.*, 1950), though, as yet, there is no evidence that this effect occurs

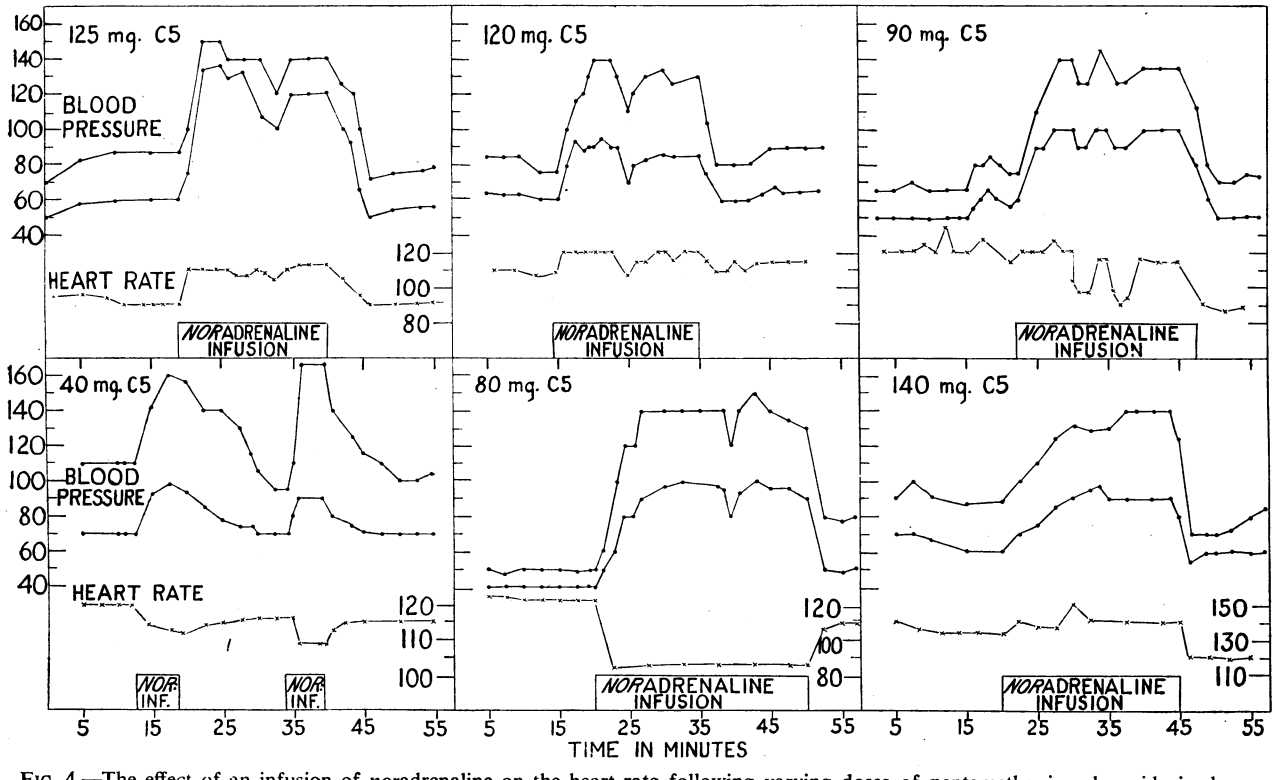


FIG. 4.—The effect of an infusion of *nor*adrenaline on the heart rate following varying doses of pentamethonium bromide is shown. A slowing of the heart rate occurs following small doses of pentamethonium, whereas after large doses a tachycardia is seen.

in man. Since then, it has been suggested that the use of *nor*adrenaline after the pentamethonium or the hexamethonium compound might be followed by a further fall in blood pressure due to the ganglion-blocking action of DL-*nor*adrenaline (Burn, 1951).

After the use of pentamethonium bromide an investigation was carried out to determine whether any marked fall in blood pressure occurred on stopping the infusion of L-*nor*adrenaline. With the patient in the anti-Trendelenburg position, repeated doses of pentamethonium were given until no further fall in pressure was induced. The horizontal position was then assumed for ten minutes, after which the blood pressure was raised by an infusion of L-*nor*adrenaline to a marked hypertensive level for a further ten minutes. On stopping the infusion the blood pressure fell precipitously, in four cases to slightly below, in three cases to the corresponding level, and in three cases to slightly above the control value. In no case did it fall below the hypotensive level produced by pentamethonium in combination with a postural tilt. In a control series without pentamethonium the blood pressure returned to slightly above or to the corresponding level in every case.

If these changes represented a ganglionic blocking effect then they would be expected to be most marked in those cases receiving only a small dose of pentamethonium. This was not the case, as is shown in Table III.

TABLE III.—*Showing Changes in the Blood Pressure in Patients Receiving Pentamethonium Iodide Followed by an Infusion of Noradrenaline*

Case No.	Dose of C5 in mg.	Average B.P. Before C5	Lowest B.P. After C5	Average		Average B.P. on Ceasing *Nor*adrenaline	Change
				B.P. in Horizontal Position	Highest B.P. with *Nor*adrenaline		
1	40	110/80	82/60	90/60	160/100	90/60	Nil
2	40	100/62	75/50	95/55	160/90	95/55	,,
3	60	125/80	80/60	105/82	180/120	105/82	,,
4	60	120/80	80/60	100/80	150/100	105/80	Sl. increase
5	60	120/65	60/45	80/40	160/110	85/60	,, ,,
6	80	130/80	40/32	60/50	145/100	74/50	,, ,,
7	90	100/60	55/40	87/60	145/100	75/55	Sl. decrease
8	125	130/90	70/50	80/50	150/130	70/50	,, ,,
9	140	130/70	65/50	84/62	142/92	78/60	,, ,,
10	160	140/80	80/62	90/75	140/98	82/60	,, ,,

After large doses of pentamethonium it is obviously difficult to implicate *nor*adrenaline itself in any further ganglionic blocking effect. The blood pressure, following the initial fall, tended to rise slowly in all cases, and, in view of the removal of some of the compensatory mechanisms by the pentamethonium, these blood-pressure changes do not appear to be of great significance. It is advisable, however, in all cases of L-*nor*adrenaline infusion to slow the rate of infusion gradually over a period so that the patient can adapt himself gradually to the change.

Summary

A study of the physiological actions of adrenaline, methedrine, and L-*nor*adrenaline shows that the pressor activity of adrenaline and methedrine is brought about mainly by an increase in cardiac output, whereas L-*nor*adrenaline acts by a generalized vasoconstriction resulting in an increased total peripheral resistance.

Since *nor*adrenaline is considered to be the physiological transmitter of most adrenergic nerves—responsible for the control of the blood pressure—it is suggested that it is a suitable drug for combating hypotensive circulatory states due to a lowering of the peripheral resistance. An infusion of L-*nor*adrenaline offers a safe and valuable method of controlling the blood pressure. The use of this drug during surgical operations has been described.

I wish to express my thanks to Messrs. Bayer Products Ltd. for making available a generous supply of *nor*adrenaline. I would also like to thank Professor H. Barcroft, Dr. M. D. Nosworthy, and Dr. W. D. Wylie for their helpful criticisms in the preparation of this paper, and Dr. J. D. Laycock and Dr. H. J. C. Swan for permission to use their case as shown in Fig. 3.

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British Railways are to reorganize their medical service so as to bring it more into line with the recommendations of the Industrial Health Advisory Committee (set up by the Government in 1949), which issued its report on February 26 this year. It will be complementary to the National Health Service, as in the case of other large industrial concerns. Under the chief medical officer there is a regional M.O. at each of the headquarters of the six railway regions. Each will be responsible to the chief regional officer for the efficient day-to-day conduct of the whole of the medical services and organization within his region; for conducting routine and special medical examinations; hygiene; first aid; advice on welfare and on all other matters affecting the health of the staff. Each region will be divided into medical areas in charge of a full-time area medical officer responsible to the regional M.O. The area M.O. will advise the district departmental officers and others on medical matters. Big railway workshops will each have a works medical officer. The new organization will call for the appointment of additional doctors, who will be trained for a year in the special technique of railway medicine before taking up their appointments, to become familiar with the causes of illnesses peculiar to the railway industry and outside the scope of the general practitioner. In addition to British Railways staff the new organization will also cover, as necessary, employees of the Road Haulage, Docks and Inland Waterways, and the Hotels Executives—a total of 730,000 people in all.