Quarterly Journal of Medicine, New Series XLVII, No. 185, pp. 1–20, January 1978

Plasma Noradrenaline and Adrenaline Concentrations and Dopamine-β-hydroxylase Activity in Patients With Shock Due to Septicaemia, Trauma and Haemorrhage

C. R. BENEDICT AND D. G. GRAHAME-SMITH

From the M.R.C. Unit and University Department of Clinical Pharmacology, Radcliffe Infirmary, Oxford

Accepted 14 July 1977

SUMMARY

Plasma adrenaline and noradrenaline concentrations and dopamine-β-hydroxylase activities were measured in patients with septicaemic, traumatic or haemorrhagic shock. Irrespective of the type of shock plasma adrenaline and noradrenaline concentrations were increased above the normal range. This is in keeping with the clinical features of increased sympathetic nervous system and adrenal medullary activity present in these patients. Plasma dopamine-β-hydroxylase activities were within the normal limits in all forms of shock indicating the poor relationship of this measurement to sympathetic nervous system activity. In patients who died plasma noradrenaline concentrations remained persistently elevated above normal while in those who survived there was a rapid decline towards the normal range.

INTRODUCTION

It has been proposed that by estimating noradrenaline and adrenaline concentrations and dopamine-β-hydroxylase activity (DβH) in plasma one might get an idea of the activity of sympathetic nervous system and adrenal medullary function. Previous studies in humans have mainly measured these factors in clinical states (e.g., hypertension, thyrotoxicosis) and in physiological states (e.g., tilt studies, cold pressor test) in which an increase in sympathetic nervous system activity and adrenal medullary function is likely to be small. It would be useful to investigate the changes in noradrenaline and adrenaline concentrations and DβH activity in plasma in clinical conditions with *marked* increase in sympathetic nervous system and adrenal medullary activity. Such studies might put into perspective the changes found in other clinical conditions and would record the range of changes likely to be found in clinical conditions with critical pathological stress.

Some of the features of the clinical syndrome of shock such as pale, cold, sweating skin, tachycardia, vasoconstriction and pupillary dilatation are accepted as being due to increased activity of the sympathetic nervous system and adrenal

medulla. The evidence that the activity of sympathetic nervous system and adrenal medulla is increased in states of shock is derived chiefly from experimental animal studies. Gernandt, Liljestrand, and Zotterman (1946) demonstrated that haemorrhage greatly increased efferent impulses in the splanchnic nerves of the cat and that the impulse frequency returned to the control value after transfusion. Beck and Dontas (1955) similarly recorded a marked increase in the electrical activity of splanchnic nerves in both cats and dogs after haemorrhage. Lundgren, Lundwall, and Mellander (1964) estimated that haemorrhage was associated with an increase in sympathetic impulse frequence from control values of less than 1 per second to frequencies as high as 7 per second.

The activation of the sympathetic nervous system and adrenal medulla also results in an increase in plasma adrenaline and noradrenaline concentrations and as early as 1917 Bedford demonstrated an increase in circulating catecholamine concentration following haemorrhage in experimental animals. Since then other workers have demonstrated that plasma adrenaline and noradrenaline concentrations increase following haemorrhagic shock in animals (Walton, Richardson, Walton, and Thompson, 1959; Rosenberg, Lillehei, Longerbeam, and Zimmerman, 1961; Watts and Wertfall, 1964; Millar and Benfey, 1958). Similar increases in plasma catecholamine concentration have been demonstrated in animals during endotoxic shock (Hall and Hodge, 1971; Jacobson, Mehlman, and Kalas, 1964; Lillehei, Longerbeam, Block, and Manax, 1964; Rosenberg *et al.*, 1961; Spink, Reddin, Zak, Peterson, Starzecki, and Seljeskog, 1966; Prager, Ernest, and Seaton, 1975).

In contrast, knowledge of plasma adrenaline and noradrenaline concentrations or their changes following traumatic, haemorrhagic or septicaemic shock in man is scanty. Rhoads and Howard (1963) measured the urinary excretion of adrenaline and noradrenaline in man after trauma and demonstrated high concentrations which remained elevated for several days. Similar observations have not been made in patients with septicaemic shock. Nor have there been any studies on the influence of states of shock on circulating DβH, which is released with noradrenaline from sympathetic nerve terminals (Axelrod, 1972).

The objectives of this investigation have been (i) to study over a period of time the changes in plasma adrenaline and noradrenaline concentrations and DβH activities in individual patients with septicaemic, traumatic or haemorrhagic shock and septicaemia without shock; (ii) to relate the changes in noradrenaline and adrenaline concentration and DβH activity in plasma to severity of shock, clinical observations and outcome; (iii) to see if in patients with good clinical evidence of increased sympathetic nervous system and adrenal medullary activity there are related alterations in concentration of plasma noradrenaline, adrenaline and DβH and whether these changes can be used to monitor sympathetic nervous system and adrenal medullary function.

PATIENTS

(*1*) *Patients with septicaemic shock*

The definition of septicaemic shock was the syndrome consisting of all of the following: systolic blood pressure less than 90 mmHg or 30 mm less than the

TABLE 1. *Clinical details of the patients with septicaemic shock*

	Age (years)	Sex	Admission		Sweating (S) Pallor (P) Cyanosis (C)	Organism isolated from blood	Source of infection	Drugs given	Comment
			Blood pressure (mmHg)	Pulse (beats/ min					
1	64	M	80/40	140	S, P	Klebsiella aerogenes	(?) CVP catheter	gentamicin lincomycin	Total oesophagectomy for carcinoma of oesophagus; primary haemorrhage shortly after surgery; 5 litres of blood given: in ITU developed septicaemia; died 23 days after surgery.
2	52	M	85/50	135	S, P but warm. Later cold with cyanosis	Proteus mirabilis	Peritonitis following gut surgery	gentamicin penicillin prednisolone	Died 5 days after development of shock. In renal and hepatic failure for last two days.
3	83	F	90/60	136	P, C and cold	E. coli	faecal peritonitis	gentamicin	Intestinal resection for Crohn's disease; died 4 days after onset of shock.
4	34	M	80/45	155	S, P but warm. Later cold with cyanosis	E. coli	Peritonitis subphrenic abscess multiple abscesses in lung, liver, spleen, kidney and brain.	ampicillin cloxacillin gentamicin	Haemorrhagic necrotising pancreatitis; following surgery developed rigors and became shocked. Died 5 days later.
5	67	M	70/?	120	S, P but warm. Later cold with cyanosis	Klebsiella aerogenes	Infarcted ileum following mesenteric embolism	gentamicin	Laparotomy carried out to remove the infarcted bowel but developed shock and died 7 days later.
6	50	F	90/65	130	S, P, C and cold	Pseudomonas pyocyaneus	Peritonitis following resection for carcinoma of colon	carbenicillin gentamicin	Developed shock 24 hours after resection, hepatic and renal failure 72 hours after surgery and died on the fourth day after onset of shock
7	38	F	70/?	120	S, P, C and cold	Klebsiella aerogenes Staph. aureus	Traumatic rupture of rectum and faecal peritonitis	cloxacillin gentamicin hydro-corusone	Forty-eight hours after surgical repair of anastomosis patient developed shock and died 78 hours later.
8	46	M	85/50	132	S, P but warm. Later cold with cyanosis	Proteus mirabilis	Pelvic abscess following gut surgery	gentamicin lincomycin	Fifteen days after surgery developed rigors and became shocked, developed acute hepatic failure and died four days after onset of shock.
9	39	F	80/?	146	S, P, C and cold	E. coli	Infarcted ileum following (?) mesenteric thrombosis	gentamicin	Four days after surgical resection of the necrotic bowel became shocked, developed renal failure and died five days later.
10	44	M	90/40	130	P and cold	E. coli	Lung abscess	gentamicin lincomycin	Developed widespread pneumonic consolidation, respiratory failure and later hepatic failure. Died four day after onset of shock.

systolic pressure prior to development of septicaemic shock; tachycardia of 120 per minute; oliguria of less than 20 ml per hour; a positive bacteriological culture from blood.

There were six men and four women aged from 34 to 83 years. All the patients, once diagnosed as having septicaemic shock, were transferred to the intensive care unit. Their clinical details, blood pressure and heart rate at the time of transfer to the intensive care unit and their clinical outcome are given in Table 1.

(*2*) *Patients with septicaemia without shock*

All the patients had fever with rigors, a known source of infection and positive bacteriological culture from blood. There were four males and two females aged from 29 to 70 years. The clinical details of the patients are given in Table 2. These patients were usually observed until they became afebrile after starting treatment with antibiotics and all of them eventually went home.

TABLE 2. *Clinical details of the patients with septicaemia without shock*

	Age (years)	Sex	Admission		Sweating (S) Pallor (P) Cyanosis (C)	Organism isolated from blood	Source of infection	Drugs given	Comment
			Blood pressure (mmHg)	Pulse (beats/min)					
1	70	M	120/70	102	S but warm	Klebsiella aerogenes	Pelvic abscess	gentamicin lincomycin	Anterior resection for carcinoma of rectum; discharged 34 days after diagnosis of septicaemia.
2	66	M	105/80	100	S, P but warm	E. coli	Peritonitis	gentamicin	Carcinoma of head of the pancreas causing obstructive jaundice. By-pass surgery; discharged 29 days after surgery.
3	50	M	95/60	120	warm	Staph. aureus	Bilateral basal pneumonia	cloxacillin	Discharged 16 days after diagnosis of septicaemia.
4	50	M	180/70	110	warm	Staph. aureus	(?) C.V.P. catheter	ampicillin cloxacillin gentamicin	Discharged 12 days after diagnosis of septicaemia.
5	46	F	120/80	110	S but warm	E. coli	(?) following ureteric catheterisation	gentamicin	Discharged 16 days after diagnosis of septicaemia.
6	29	F	130/75	106	—	E. coli	Unknown	gentamicin	Developed fever and rigors after an abortion; discharged 30 days after diagnosis of septicaemia.

(*3*) *Patients admitted after road-traffic accidents*

Patients admitted within six hours of a major road-traffic accident with shock were investigated. All the patients had a systolic blood pressure of less than 90 mmHg, a tachycardia of more than 120 per minute and were clinically shocked at

the time of admission. After the initial clinical assessment and surgical treatment of their injuries they were transferred to the intensive care unit. There were six men and three women aged from 16 to 81 years and their clinical details are given in Table 3.

TABLE 3. *Clinical details of the patients admitted after road-traffic accidents*

	Age (years)	Sex	Admission		Sweating (S) Pallor (P) Cyanosis (C)	Nature of the injuries	Comment
			Blood pressure (mmHg)	Pulse (beats/min)			
1	81	M	50/?	95	S, P, C and cold	Fractures of C.6 vertebrae, mandible, L. clavicle, 10 ribs on L. side (flail segment), R. radius, sup. and inf. pubic rami (bilateral) L. tibia and fibula, L. femoral condyle; diastasis of symphysis pubis and sacro-iliac joints; pelvic retro-peritoneal haematoma.	Patient was unconscious from the time of admission until death eight days after admission. Six litres of blood given.
2	52	F	80/55	148	S, P, C and cold	Multiple fractures of pelvis, R. scapula and clavicle, L. tibia; ruptured mesentery, retro-peritoneal haematoma.	Transfused 11 litres of blood; cardiorespiratory arrest; died 6 days after admission.
3	17	M	90/65	148	S, P	Ruptured spleen, torn renal vein, L. haemopneumothorax, fracture of r. radius.	Laparotomy and splenectomy. Transfused 10 litres of blood; discharged 55 days after admission.
4	43	M	90/60	125	P, C	Haemopneumothorax, R. flail segment (fracture of 8 ribs), R. knee joint dislocation and fracture of tibia and femur.	Transfused two litres of blood; recovered and sent home three months after admission.
5	63	M	80/40	100	S, P, C and cold	Haemopneumothorax, compound fracture of R. humerus and fracture of 6 ribs on R. side.	Transfused four litres of blood; recovered and sent home 37 days after admission.
6	18	M	85/55	120	P, C and cold	Crush fracture of pelvis, fractures of L.4 and L.5 vertebrae and L. femur; fracture dislocation of sacro-iliac joint; lacerated rectum and ext. iliac vein; ruptured L. psoas muscle.	Transfused seven litres of blood and underwent laparotomy and vascular surgery. Recovered and discharged three months after admission.
7	16	M	90/60	130	P, C and cold	Fracture of 9 R. side ribs and flail segment; haemopneumothorax, fracture of R. radius, humerus and clavicle; ruptured spleen.	14 litres of blood. Splenectomy carried out. Recovered and discharged 78 days after admission.
8	49	F	60/?	130	P, C and cold	Ruptured spleen and R. kidney; fracture of R. lower four ribs; torn quadratus lumborum and psoas on R. side.	Six litres of blood; developed acute renal failure and died six days after surgery for removal of spleen and kidney.
9	58	F	90/70	130	P, C and cold	Fractures of both femurs, fibulae and tibiae; crush injuries of feet and pelvis; torn rectum and R. femoral artery.	10 litres of blood given; developed acute renal failure and died four days after surgery.

(*4*) *Patients with haemorrhagic shock*

Patients who sustained a large, fast haemorrhage either after natural causes (see below) or after surgery were investigated. Four men and two women aged from 47 to 80 years formed this group. Their clinical details are given in Table 4.

At the time of admission to the intensive care unit these patients had a systolic blood pressure less than 90 mmHg, tachycardia of over 120 beats per minute and peripheral vasoconstriction and were considered to be in haemorrhagic shock.

TABLE 4. *Clinical details of the patients with haemorrhagic shock*

	Age (years)	Sex	Admission		Sweating (S) Pallor (P) Cyanosis (C)	Cause of bleeding	Comment
			Blood pressure (mmHg)	Pulse (beats/min)			
1	80	M	90/60	140	S, P, C and cold	Ruptured abdominal aortic aneurysm.	Three litres of blood given during and after surgery. Initial oliguric but later recovered. Discharged 12 days after surgery.
2	67	M	75/?	130	S, P, C and cold	Ruptured abdominal aortic aneurysm.	Eight litres of blood transfused; developed acute renal failure and died 48 hours after surgery.
3	47	M	80/40	136	S, P, C and cold	Primary haemorrhage from left gastric artery.	Partial gastrectomy for duodenal ulcer with gastro-jejunostomy. Two litres of blood given. Discharged 18 days after surgery.
4	71	M	60/?	144	S, P, C and cold	Ruptured abdominal aortic aneurysm.	Anuric for over 18 hours; six litres of blood given; no urine output after surgery; died 24 hours after surgery.
5	67	F	45/35	132	S, P, C and cold	Perforation of sigmoid colon. Septicaemia queried but no organisms isolated.	Transfused 10 litres of blood; developed acute renal failure and died 24 hours after surgery.
6	68	F	65/40	148	S, P, C and cold	Primary haemorrhage from (?) inferior mesenteric artery.	Intestinal resection for Crohn's disease; six litres of blood given. Developed renal failure and died four days after surgery.

METHODS

Immediately after admission to the intensive care unit the following variables were monitored continuously: systolic and diastolic blood pressures using an indwelling arterial cannula in a peripheral artery, the pressure being recorded by an external transducer (Hewlett Packard 1280C 02, Hewlett Packard and Co., Massachusetts, USA); heart rate from lead II of the electrocardiogram and central venous pressure. Frequent clinical examinations were made to determine the respiratory rate and to assess peripheral signs of vasoconstriction. Patients who received isoprenaline or noradrenaline infusions were excluded from the study as those drugs interfere with the assay for plasma adrenaline and noradrenaline.

Five ml venous blood samples were collected after 30 minutes of bed rest following admission to the intensive care unit or when the diagnosis of septicaemia was made and then at four-hourly intervals for the first 12 hours, at six-hourly intervals for the next 36 hours and then at eight or twelve-hourly intervals until the patient died or up to four to ten days after admission in survivors. Patients with septicaemia without shock were observed until they became afebrile. The patients received only the following drugs: antibiotics, diamorphine or pethidine, pancuronium, frusemide, mannitol (20 per cent), potassium supplements, low molecular weight dextran infusions (Rheomacrodex or Dextran 40) heparin, intravenous fluids including amino acid mixtures and lipid supplements and either nitrazepam or diazepam.

Plasma adrenaline and noradrenaline concentrations were measured in duplicate by a radioenzymatic method (Hörtnagl, Benedict, Grahame-Smith, and McGrath, 1977) and plasma DβH activities by a photometric method (Nagatsu and Udenfriend, 1972). The data, expressed as mean ± S.E.M. were analysed using Student's two-tailed unpaired '*t*' test.

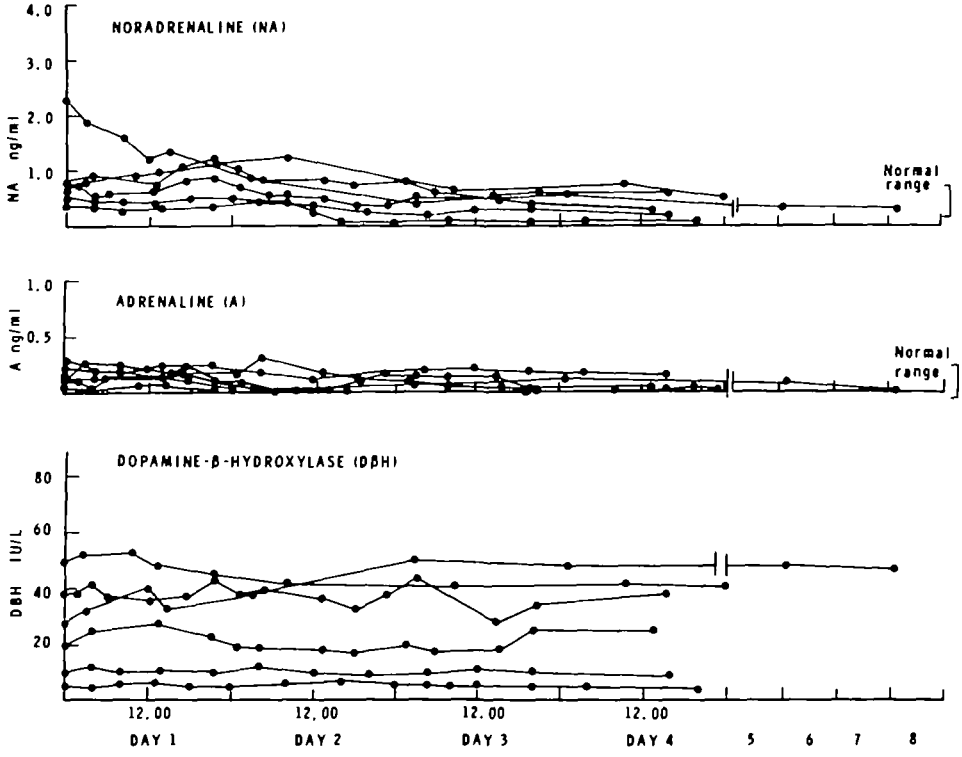

FIG. 1. Plasma noradrenaline, adrenaline and dopamine-β-hydroxylase level in patients with septicaemia without shock.

RESULTS

(*1*) *Plasma adrenaline and noradrenaline concentrations and DβH activities in patients with septicaemic shock and comparison with the values in patients with septicaemia without shock* (see Figs. 1 and 2)

The groups were matched for age and sex.

Plasma adrenaline concentrations

The plasma adrenaline concentrations in patients with septicaemia without shock were 0·27 ± 0·08 ng/ml at the time of diagnosis, only slightly higher than the upper limit of normal values in healthy people. There was a slight increase in the next 18 hours and then a gradual decline until the end of the period of study. In contrast the plasma adrenaline concentrations in patients with septicaemic shock at the time of admission were significantly higher (1·19 ± 0·20 ng/ml) than the

concentrations in patients with septicaemia without shock ($p < 0.005$). Increased concentrations remained significantly elevated in almost all the patients until they died (Fig. 2).

Plasma noradrenaline concentrations

Plasma noradrenaline concentrations in patients with septicaemia without shock at the time of diagnosis (0·90 ± 0·28 ng/ml) were not significantly different from

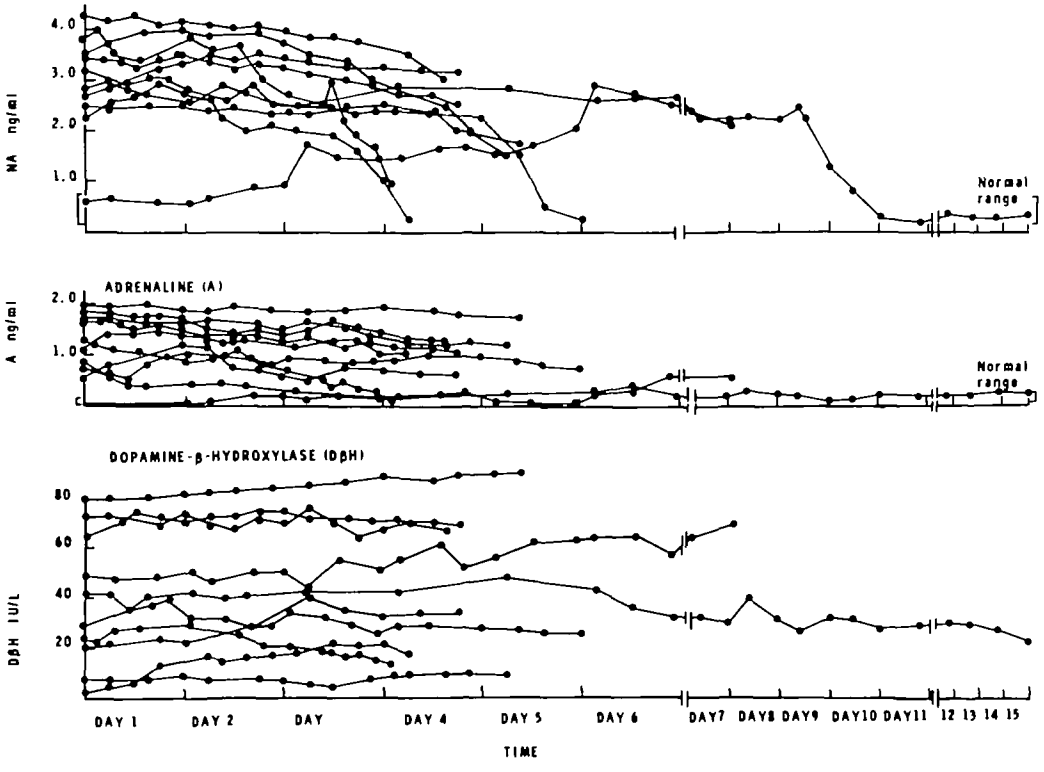

FIG. 2. Plasma noradrenaline, adrenaline and dopamine-β-hydroxylase levels in patients with septicaemic shock.

the normal range although one patient had a very high noradrenaline concentration which rapidly declined after treatment was instituted. Over the entire period of study plasma noradrenaline concentrations showed a progressive decrease and had returned to within the normal range in all patients by 36 hours. The plasma noradrenaline concentrations in patients with septicaemic shock at the time of admission to the intensive care unit were significantly increased (2·94 ± 0·32 ng/ml) when compared with the concentrations present in patients with septicaemia without shock ($p < 0.001$). Those increased concentrations remained significantly elevated compared with the concentrations in patients with septicaemia without shock. A striking observation in many patients was that plasma noradrenaline concentrations declined, sometimes steeply one to two days before death (Fig. 2).

Plasma DβH activities

Plasma DβH activities in patients with septicaemia with and without shock did not show a significant variation during the period of study and remained within the normal range. There was no difference in activities between the two groups.

Blood pressure and heart rate

There was no significant variation in blood pressure in patients with septicaemia without shock and the tachycardia present at the time of diagnosis of septicaemia

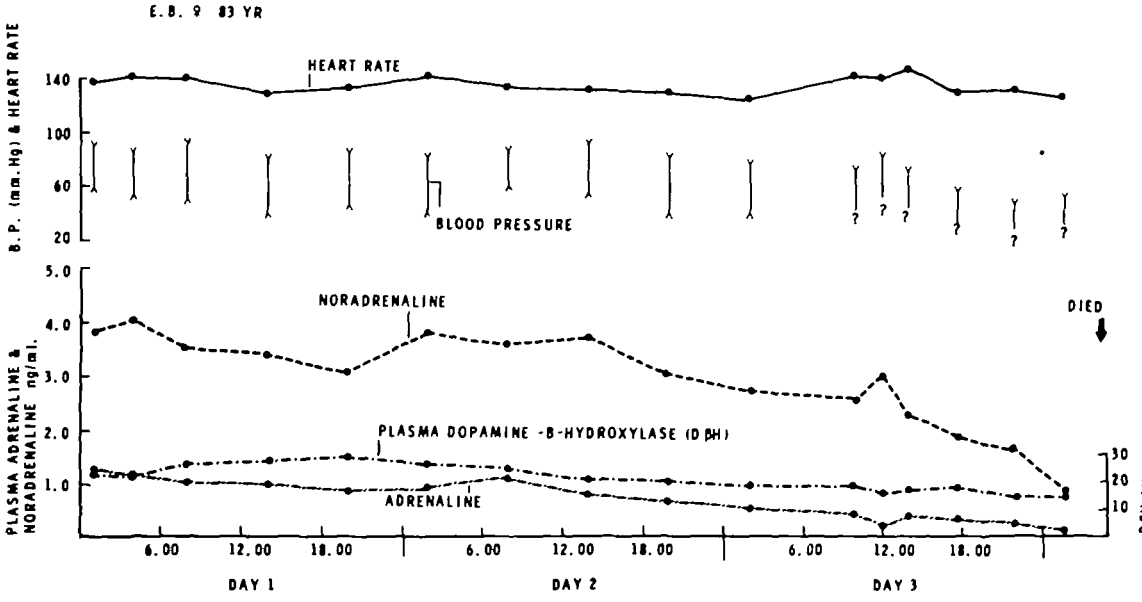

FIG. 3. Plasma noradrenaline, adrenaline, dopamine-β-hydroxylase, heart rate and blood pressure in a patient with septicaemic shock.

resolved once treatment with antibiotics was started and the fever subsided. In contrast patients with septicaemic shock had a systolic blood pressure of less than 90 mmHg and a heart rate of over 120 per minute which persisted up to the time shortly before death.

Case 1 (Fig. 3)

E.B., an 83-year-old woman, was transferred from the surgical ward to the intensive care unit for management of septicaemic shock. She had undergone intestinal resection for Crohn's disease a week before transfer and two days before she had developed fever with rigors, sweating and tachycardia. The abdomen had become rigid and distended. On the day of transfer she was confused and oliguric; blood pressure was 95/60 mmHg and heart rate 136 per minute. Her extremities were pale and cold with slight cyanosis. Central venous pressure was one cm of water. Arterial blood gas measurements were: PaO_2 86 mmHg, pH 7·30; $PaCO_2$

25 mmHg. White blood cell count was 34 600 per c.mm. Blood culture grew *E. coli*, sensitive to gentamicin which had been started 24 hours before admission to the unit.

Intravenous fluids, plasma and one litre of whole blood were given to improve the central venous pressure and the acidosis was corrected with 1 M sodium

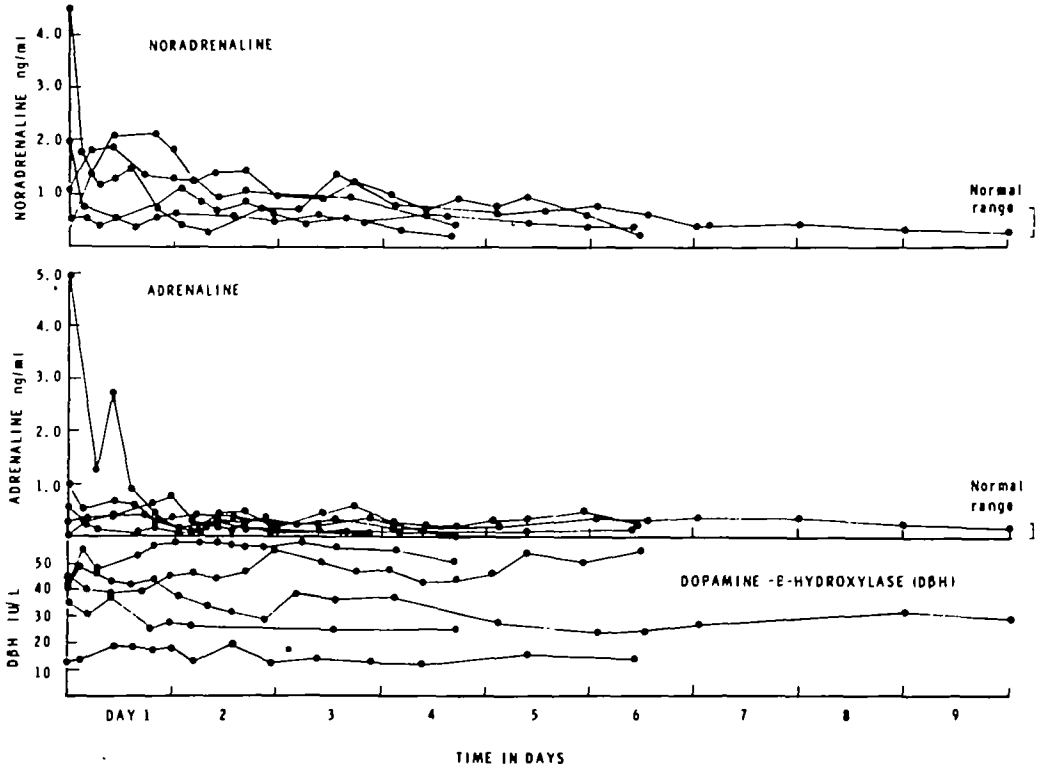

FIG. 4. Plasma noradrenaline, adrenaline and dopamine-β-hydroxylase levels in patients after traumatic shock (survivors).

bicarbonate. Her abdomen became progressively distended and bowel sound disappeared. Blood gas measurements suggested deterioration and intermittent positive pressure ventilation was started. On the third day she became anuric. Chest radiography showed severe pulmonary congestion. She remained anuric with a low blood pressure and rapid pulse of low amplitude and died on the fourth day.

Plasma adrenaline and noradrenaline concentrations and DβH activities are shown in Fig. 3. Both the adrenaline and noradrenaline concentrations were elevated at the time of admission and remained so until the third day when there was a gradual decline. There was a similar small decline in plasma DβH activity. This patient had persistent hypotension and tachycardia despite treatment. It was interesting that on the fourth day the patient's extremities were not cold or cyanosed despite the general worsening of the clinical condition in contrast to the previous days when there was marked peripheral vasoconstriction suggesting that the peripheral vasoconstriction was caused by an increase in activity of the sympathetic nervous system and adrenal medulla.

(*2*) *Plasma adrenaline and noradrenaline concentrations and DβH activities in patients with traumatic shock after road-traffic accidents* (see Figs. 4 and 5)

Of the nine patients in this group four died between the fourth and eighth days after admission to the unit and five recovered. There was no significant difference in age between the two groups. The time interval between the road-traffic accident

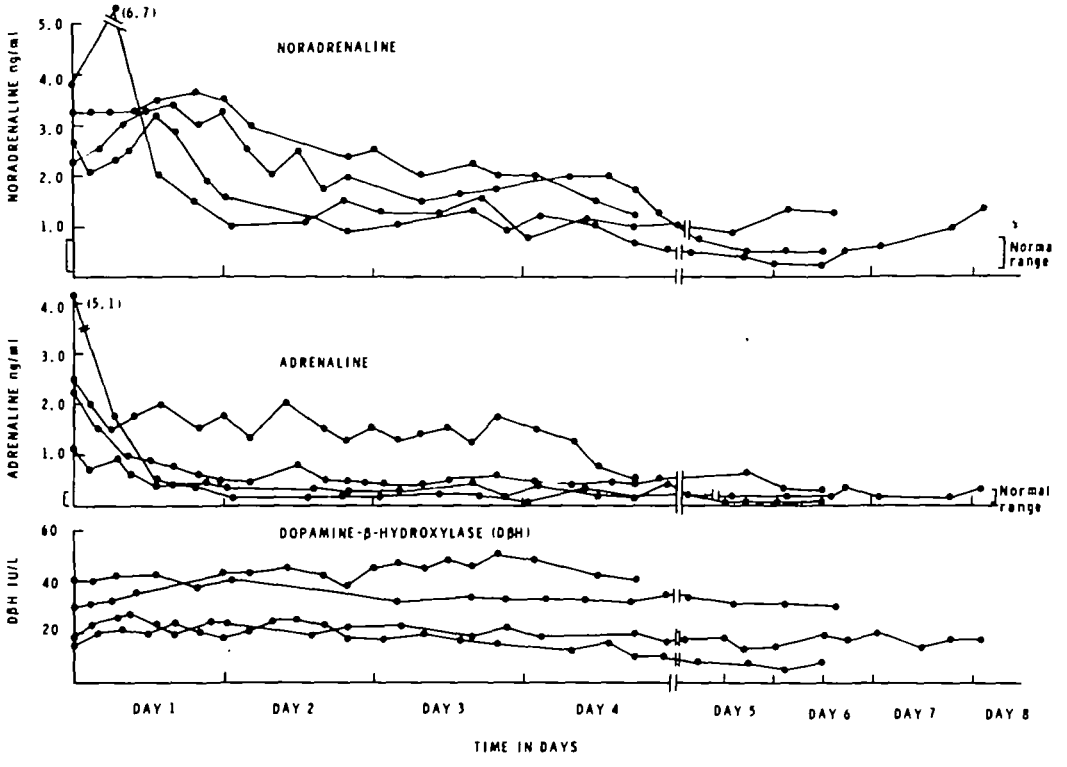

FIG. 5. Plasma noradrenaline, adrenaline and dopamine-β-hydroxylase levels in patients after traumatic shock (non-survivors).

and collection of the first blood sample was not significantly different between the two groups of patients.

Plasma adrenaline concentrations

In patients who survived, at the time of admission the plasma adrenaline concentrations were significantly increased above the normal range. Those increased concentrations decreased rapidly and 48 hours later were within the normal range. In non-survivors the plasma adrenaline concentrations were higher than in survivors but not statistically significantly so. Plasma adrenaline concentrations in non-survivors also declined after admission to the unit and were similar to the concentrations in patients who survived.

Plasma noradrenaline concentrations

The plasma noradrenaline concentrations in patients who survived were increased on admission but by the end of the third day had returned to within the

normal range. In non-survivors the mean concentrations present at the time of admission were higher when compared with the survivors but not significantly so. However, six hours after admission plasma noradrenaline concentrations in survivors showed a decline but in non-survivors it increased even further. Although the high concentration in non-survivors declined during the period of study they did not reach normal and remained significantly different from the corresponding values in survivors.

Plasma DβH activities

The changes in plasma DβH activities in both groups were very small and not statistically significant.

Blood pressure and heart rate

At the time of admission to the unit all the patients with traumatic shock were hypotensive and had a tachycardia (Table 5). In survivors, within six hours systolic blood pressure returned to normal while in non-survivors systolic blood pressure remained low. In both survivors and non-survivors a tachycardia was present at the time of admission. In survivors the heart rate declined rapidly while in non-survivors tachycardia persisted to the time shortly before death. Peripheral signs of vasoconstriction were present in all patients and usually persisted in non-survivors while in survivors the peripheral circulation improved within a few hours.

TABLE 5. *Systolic blood pressure (SBP) and heart rate (HR) in patients with traumatic shock after road traffic accidents (mean ± S.D.)*

Time* (hours)	SBP (mmHg)		HR (beats/min)	
	Survivors	Non-survivors	Survivors	Non-survivors
0	81·0 ± 12·4	70·0 ± 18·6	124·6 ± 17·3	125·7 ± 22·2
6	121·6 ± 11·0	94·0 ± 15·7	112·6 ± 14·7	128·0 ± 21·2
12	123·8 ± 17·0	89·6 ± 14·3	110·2 ± 6·4	132·2 ± 20·6
18	136·0 ± 16·0	86·2 ± 13·8	112·4 ± 9·6	134·6 ± 21·4
24	133·0 ± 17·9	98·6 ± 15·0	107·0 ± 12·8	139·4 ± 19·0
36	144·0 ± 20·4	100·7 ± 22·0	100·4 ± 12·6	132·6 ± 16·2
48	144·0 ± 19·5	95·4 ± 23·2	96·4 ± 12·7	134·8 ± 16·4
60	134·0 ± 18·2	99·7 ± 21·5	95·6 ± 8·4	134·3 ± 16·9
72	137·0 ± 26·4	101·3 ± 21·4	95·4 ± 14·1	124·6 ± 25·0
84	135·0 ± 25·2	103·6 ± 20·6	93·6 ± 15·1	120·8 ± 19·6
96	134·7 ± 22·4	100·4 ± 23·2	94·8 ± 16·7	110·7 ± 24·2
1–3 hr before death	—	89·4 ± 14·7	—	89·9 ± 20·3

* Time interval after admission to intensive care unit.

Case 2 (Fig. 6)

N.G., a 17-year-old man, was admitted to the hospital about two hours after a road-traffic accident. Blood pressure was unrecordable, pulse was rapid and thready at 164 per minute and he had marked peripheral vasoconstriction and

cyanosis. He had difficulty in breathing and his abdomen was markedly distended and rigid. A rapid blood transfusion was started and he was taken to the operating theatre for splenectomy and repair of a torn left renal vein. A drain was inserted to release a right-sided haemopneumothorax and he was transferred to the intensive care unit for further management. At the time of admission to the unit he looked shocked but blood pressure was 90/65 mmHg. Blood transfusion was continued and he received altogether 10 litres of blood. Blood gases were satisfactory. Urine output improved following a mannitol (20 per cent) infusion. Ten days after admission he was transferred to a general surgical ward.

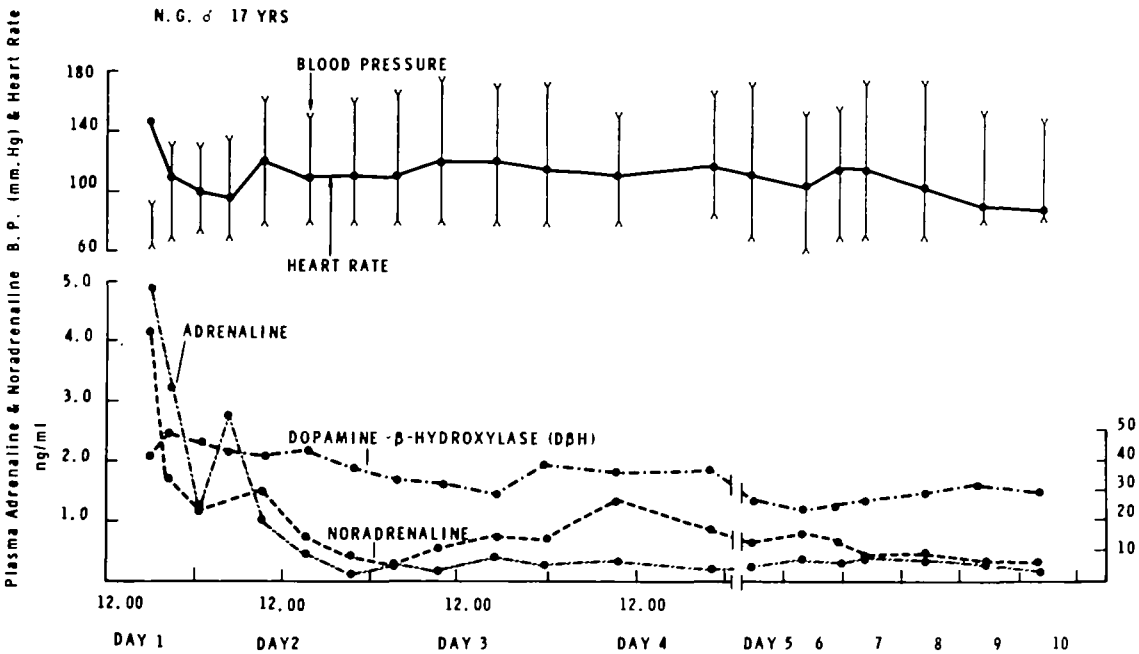

FIG. 6. Plasma noradrenaline, adrenaline, dopamine-β-hydroxylase, heart rate and blood pressure in a patient with traumatic shock who recovered.

Plasma adrenaline and noradrenaline concentrations and DβH activities measured in this patient are shown in Fig. 6. Both plasma adrenaline and noradrenaline concentrations were increased at the time of admission. However, those high concentrations rapidly fell towards the normal range within 24 hours. This rapid fall was accompanied by a decrease in heart rate and a steady improvement in blood pressure. Thereafter all those variables remained more or less steady. Plasma DβH activities tended to show a slow, small decline during the period of study.

(*3*) *Plasma adrenaline and noradrenaline concentrations and DβH activities in patients with haemorrhagic shock* (Fig. 7)

Plasma adrenaline concentrations

Of the six patients investigated four died and on admission to the unit all four had strikingly high plasma adrenaline concentrations (Fig. 7) compared with the

two survivors who had comparatively low concentrations of 1·30 and 0·84 ng/ml. In the non-survivors there was a rapid fall in the high circulating plasma adrenaline concentration although the concentration remained elevated 36 or more hours after admission. In contrast the concentration was below 0·4 ng/ml in survivors within four hours of admission.

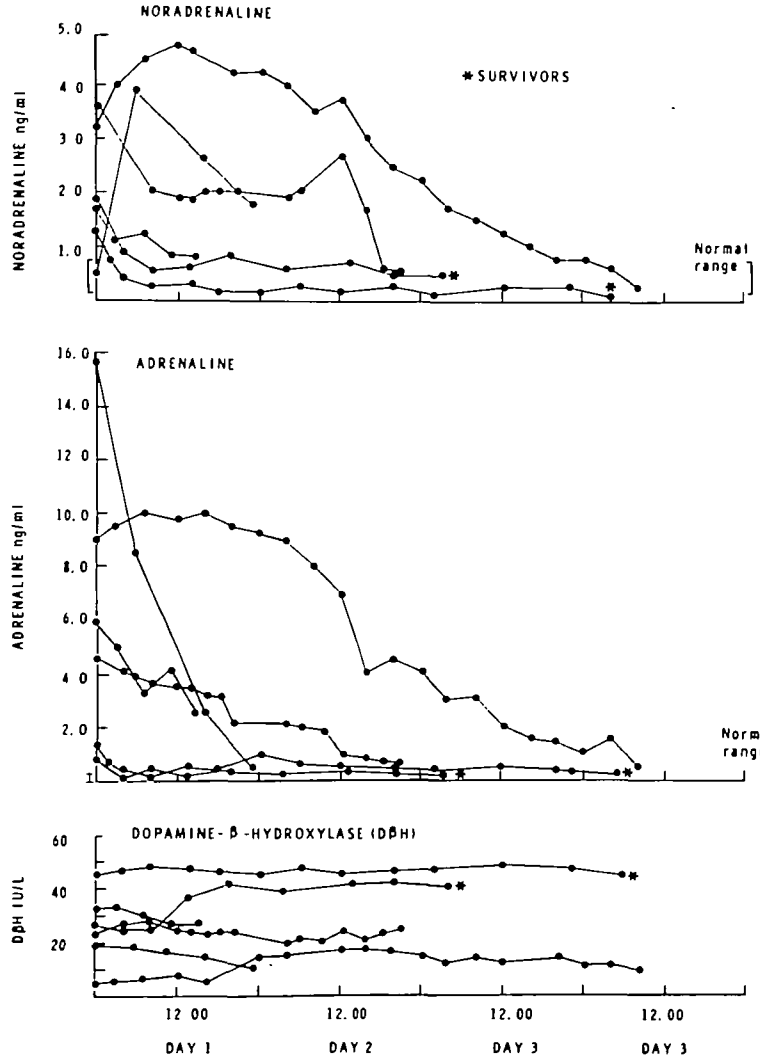

FIG. 7. Plasma noradrenaline, adrenaline and dopamine-β-hydroxylase levels in patients with haemorrhagic shock.

Plasma noradrenaline concentrations

Although the plasma noradrenaline concentration in patients who died was high (2·28 ± 0·74 ng/ml) it was less than the concentration of adrenaline (8·79 ± 2·48 mg/ml). Plasma noradrenaline concentrations in the two patients who survived (1·24 and 1·91 ng/ml) rapidly fell towards the normal range within eight hours while in non-survivors they remained elevated until the patients died. In three out of

four patients there was considerable fall in plasma noradrenaline concentration just before death. Plasma DβH activities remained within normal range.

Blood pressure and heart rate

In patients who did not survive systolic blood pressure remained persistently below 100 mmHg and heart rate over 130 beats per minute. In patients who survived, the systolic blood pressure improved gradually and heart rate fell. All the patients on admission to the unit had peripheral vasoconstriction and were sweating. In survivors the peripheral vasoconstriction gradually resolved whereas in non-survivors it persisted until death.

Case 3 (Fig. 8)

M.N., a 67-year-old woman, while awaiting surgery for carcinoma of the sigmoid colon suddenly developed lower abdominal pain and became shocked. Blood pressure was unrecordable and pulse rate was 152 per minute. Her abdomen was slightly distended and rigid and bowel sounds were absent. A rapid blood transfusion was started and she underwent laparotomy within two hours. A blood clot in the pelvic cavity was cleared, an eroded blood vessel ligated and hemicolectomy was carried out. The patient was transferred to the intensive care unit but was still hypotensive with a heart rate of 132 per minute. To maintain satisfactory blood gases she was ventilated using a volume pre-set ventilator. Sodium bicarbonate (50 mls of a 1 M solution) was given to correct the acidosis and blood transfusion was continued. Despite these measures and the administration of frusemide and mannitol (20 per cent) by infusion she developed acute renal failure. Although her blood pressure improved the tachycardia and vasoconstriction persisted. She died 24 hours after operation.

The plasma adrenaline and noradrenaline concentrations and DβH activities measured in this patient are shown in Fig. 8. Initially plasma adrenaline concentrations were very high but declined towards normal before she died. Plasma noradrenaline concentrations were normal initially but then increased and gradually fell until death occurred. Plasma DβH activity was within normal range but showed a slow decline. These changes in plasma catecholamines were not related to alterations in heart rate or blood pressure but the peripheral vasoconstriction persisted until death.

DISCUSSION

(1) Septicaemic shock

Studies reporting sequential changes in plasma adrenaline and noradrenaline concentrations and DβH activities in patients with septicaemic shock have not previously been published although Hanquet, Cession–Fossion, and Lecomte (1970) reported significantly increased plasma adrenaline and noradrenaline concentrations in a single patient.

The present study indicates that in patients with septicaemic shock plasma adrenaline and noradrenaline concentrations are both increased with minimal changes in plasma DβH activities. All the patients had tachycardia and peripheral

signs of vasoconstriction, features which are clinically associated with sympathetic nervous system and adrenal medullary overactivity. They were hypotensive. Therefore this study confirms that patients with septicaemic shock with clinical evidence of sympathetic nervous system and adrenal medullary overactivity have increased plasma adrenaline and noradrenaline concentrations. In contrast there were

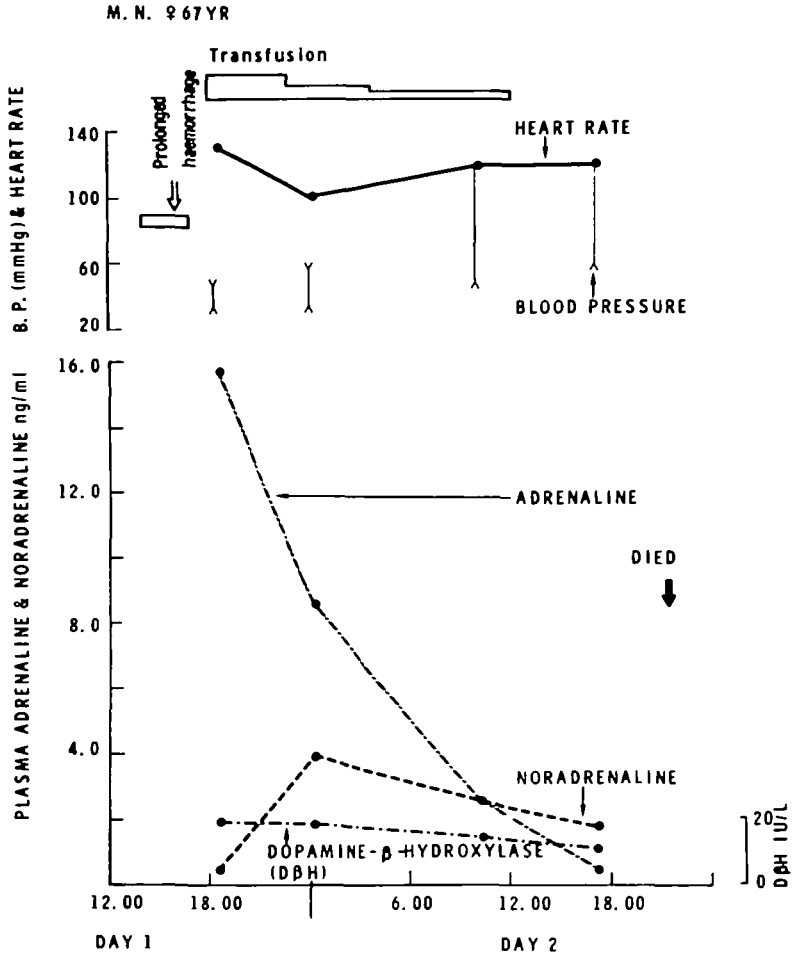

FIG. 8. Plasma noradrenaline, adrenaline, dopamine-β-hydroxylase, heart rate and blood pressure in a patient with haemorrhagic shock.

minimal changes in plasma DβH levels implying that this may be a poor indicator of sympathetic nervous system activity.

Another explanation for the high plasma adrenaline and noradrenaline concentrations could be some component of the septicaemic process itself which might enhance the release of adrenaline and noradrenaline or decrease their reuptake by sympathetic neurones or peripheral removal by tissues. This is unlikely, because patients with septicaemia but without shock have lower concentrations of plasma adrenaline and noradrenaline. Metabolic acidosis might be a factor as the

patients studied arterial blood pH ranged from 7·06 to 7·28. Nahas, Ligou, and Mehlman (1960) demonstrated that in dogs a decrease in blood pH without hypoxia caused an increase in circulating adrenaline concentrations. Therefore, although acidosis may account partly for the initially increased plasma adrenaline and noradrenaline concentration this is not the whole explanation as the high levels of noradrenaline persisted after the acidosis had been corrected. The most likely explanation is hypotension which persisted despite treatment. Lillehei *et al.* (1964), Rosenberg *et al.* (1961) and Spink *et al.* (1966) showed that following the administration of endotoxin to dogs there was a marked decrease in blood pressure associated with an increase in the plasma concentration of catecholamine. Although septicaemic shock in man and endotoxic shock in animals are different this observation is in keeping with the above hypothesis.

(2) *Traumatic shock*

Attempts made in the past to measure plasma adrenaline and noradrenaline concentrations in plasma after trauma have yielded equivocal results (Johnston, 1972). However Jäättelä in 1972 demonstrated that in traumatic shock plasma adrenaline and noradrenaline concentrations were increased. In our study there was significant elevation in plasma adrenaline and noradrenaline concentrations in all the patients in agreement with Jäättelä, Alho, Avikainen, Karaharju, Kataja, Lahdensuu, Lepisto, Rokkanen, and Tervo (1975). Haemorrhage can cause an increase in plasma adrenaline and noradrenaline concentrations (see below) and it may be argued that the elevation in plasma adrenaline and noradrenaline concentrations in this series was due to severe injuries with haemorrhage. However Young and Gray (1956) found that trauma alone produced an increase in plasma adrenaline and noradrenaline concentrations in the rat. It is likely that in injured patients the increase in plasma adrenaline and noradrenaline concentrations was due to a combination of trauma and haemorrhage.

At the time of admission the non-survivors did not have significantly different plasma adrenaline and noradrenaline concentrations from survivors. However, six hours after admission, plasma noradrenaline concentrations increased significantly and remained so in those who died. This suggests that there is persistently increased sympathetic nervous system activity in non-survivors despite the fact that in both the groups hypovolaemia, hypoxia and acidosis had been adequately treated and pain had been relieved by analgesics. Haemorrhage is a potent stimulus for the release of adrenaline from adrenal medulla and less so for the release of noradrenaline. Thus when hypovolaemia was corrected in patients with traumatic shock by blood transfusion, plasma adrenaline concentrations showed a marked decline in both survivors and non-survivors and there was no significant difference between the two groups.

Plasma DβH activities in these patients remained within the normal range despite the marked increases in plasma noradrenaline concentration. Nor were the sequential changes significant. This indicates that unlike plasma noradrenaline concentrations plasma DβH activities reflect poorly the changes in sympathetic nervous activity.

(3) Haemorrhagic shock

Some of the patients in this group had the highest plasma adrenaline concentrations recorded. Studies reporting sequential changes in plasma adrenaline and noradrenaline concentrations have not been published previously. Hanquet *et al.* (1970) made single plasma adrenaline and noradrenaline concentration measurement in patients with haemorrhagic shock and showed an increase above the normal range. There is considerable animal experimental evidence to indicate that plasma adrenaline and noradrenaline concentrations are increased after haemorrhage (Abel and Kessler, 1973; Avakian and Shirinian, 1976; Greever and Watts, 1959; Millar and Benfey, 1958; Rosenberg *et al.*, 1961; Walton *et al.*, 1959; Watts and Bragg, 1957). Furthermore Watts (1965) found a relationship between increased plasma adrenaline concentrations, severity of haemorrhage and arterial pressure. Other workers have shown that following haemorrhage adrenaline and noradrenaline concentrations in adrenal venous blood increase and the adrenaline to noradrenaline ratio alters from approximately 3 : 1 to 6 : 1 or more indicating that more adrenaline than noradrenaline is released by the adrenal medulla following haemorrhage (Zileli, Gedik, Adalar, and Cağlar, 1974). It appears that in haemorrhagic shock in man the increase in plasma adrenaline is frequently greater than the rise in plasma noradrenaline, an interesting point distinguishing haemorrhagic shock from septicaemic and traumatic shock.

Osborne, Rowe, Kaufman, and Johnson (1968) found that in dogs subjected to haemorrhage, animals with lower venous plasma adrenaline concentrations survived while animals with high concentrations died. This is in keeping with our finding that non-survivors had higher plasma adrenaline concentrations than survivors. Furthermore in non-survivors the plasma adrenaline concentration to plasma noradrenaline concentration ratio was greater than unity whereas in two survivors it was less than unity. When plasma adrenaline and noradrenaline concentrations were measured sequentially it was evident that in the two survivors, those concentrations rapidly reached the normal range whereas in non-survivors they remained elevated and fell just before death. Jakschik, Marshall, Kourik, and Needleman (1974) found that in dogs subjected to haemorrhage plasma levels of catecholamines increased steadily during the initial stages and if haemorrhage was prolonged and severe, there was a decline just before death. A similar decrease appears to have been present in patients who died after haemorrhagic shock.

Plasma DβH activities were within the normal range and did not show significant variation with time despite the changes in plasma noradrenaline concentrations indicating again that alterations in plasma DβH do not mirror changes in sympathetic nervous system activity.

GENERAL DISCUSSION

Irrespective of the type of shock sustained, plasma adrenaline and noradrenaline concentrations are increased above the normal range in the early phase. Clinical signs of hypotension, tachycardia and peripheral vasoconstriction indicate that there is increased sympathetic nervous system and adrenal medullary activity in

these patients. Hanquet *et al.* (1970) in a study of 14 patients with septicaemic and haemorrhagic shock found five patients with plasma adrenaline concentrations and six patients with plasma noradrenaline concentrations above the normal range.

Although at the time of admission elevated plasma adrenaline and noradrenaline concentrations were associated with hypotension tachycardia and peripheral vasoconstriction, the changes with time in plasma adrenaline and/or noradrenaline concentrations did not correspond directly with alterations in blood pressure or heart rate. However, in general, as the patients' clinical condition improved plasma adrenaline and noradrenaline concentrations decreased. When signs of shock persisted plasma catecholamines, particularly plasma noradrenaline concentrations, remained elevated.

In most of the non-survivors, irrespective of the type of shock high plasma noradrenaline and to a lesser extent adrenaline concentrations were sustained but fell rapidly just before death. Although not reported for patients with shock, Goodall and Moncrieff (1965) found that patients who suffered severe burns had increased urinary catecholamine excretion which became subnormal prior to death in most patients. Abel and Kessler (1973) reported that in monkeys subjected to prolonged haemorrhage there was a fall in plasma catecholamine levels from previously increased concentrations just before death. Similarly Greever and Watts (1969), Lillehei *et al.* (1964), Rosenberg *et al.* (1961) and Watts and Bragg (1957) showed that in experimental animals, after long periods of hypotension, the circulating catecholamine concentrations, especially those of adrenaline, tended to decrease just before death.

A possible explanation for this is depletion of catecholamines from adrenal medulla and/or sympathetic nerve endings. Hanquet *et al.* (1970) measured the adrenaline and noradrenaline content of the medulla of adrenal glands removed from patients who had died of shock and showed a marked depletion of stores of both. Goodall and Moncrieff (1965) demonstrated in their patients with burns that the adrenaline and noradrenaline content of lumbar sympathetic axons and ganglia were diminished. This is presumably due to a combination of sustained release for a long period combined eventually with decreased synthesis which might be caused by hypoxia and acidosis. One could speak of 'exhaustion' of the sympathetic nervous system and adrenal medulla but however descriptive the term may be, it does not explain the cause.

REFERENCES

ABEL, F. L., and KESSLER, D. P., 1973. *Circulation Res.* **32**, 492.
AVAKIAN, O. M., and SHIRINIAN, E. A., 1976. In *Catecholamines and Stress* Ed. E. Usdin, R. Kvetňansky, and I. J. Kopin. Pergamon Press, Oxford, pp. 475.
AXELROD, J., 1972. *Pharmac. Rev.* **24**, 233.
BECK, L., and DONTAS, A. S., 1955. *Fedn. Proc. Fedn. Amer. Soc. exp. Biol.* **14**, 318.
BEDFORD, E. A., 1917. *Amer. J. Physiol.* **43**, 235.
GERNANDT, B., LILJESTRAND, G., and ZOTTERMAN, Y., 1946. *Acta Physiol. scand.* **11**, 231.
GOODALL, MCC., and MONCRIEFF, J. A., 1965. *Ann. Surg.* **162**, 893.
GREEVER, C. J., and WATTS, D. T., 1959. *Circulation Res.* **7**, 192.
HALL, R. C., and HODGE, R. L., 1971. *J. Physiol. (Lond.)* **213**, 69.
HANQUET, M., CESSION-FOSSION, A., and LECOMTE, J., 1970. *Canad. anaesth. soc. J.* **17**, 201.

HÖRTNAGL, H., BENEDICT, C. R., GRAHAME-SMITH, D. G., and MCGRATH, B., 1977. *Brit. J. clin. Pharmacol.* **4**, 553.

JÄÄTTELÄ, A., 1972. *Ann. Clin. Res.* **4**, 204.

—— ALHO, A., AVIKAINEN, V., KARAHARJU, E., KATAJA, J., LAHDENSUU, M., LEPISTÖ, P., ROKKANEN, P., and TERVO, T., 1975. *Brit. J. Surg.* **62**, 177.

JACOBSON, E. D., MEHLMAN, B., and KALAS, J. P., 1964. *J. clin. Invest.* **43**, 1000.

JAKSCHIK, B. A., MARSHALL, G. R., KOURIK, J. L., and NEEDLEMAN, P., 1974. *J. clin. Invest.* **54**, 842.

JOHNSTON, J. D. A., 1972. *Adv. clin. Chem.* **15**, 255.

LILLEHEI, R. C., LONGERBEAM, J. K., BLOCK, J. H., and MANAX, W. G., 1964. *Ann. Surg.* **160**, 682.

LUNDGREN, O., LUNDWALL, J., and MELLANDER, S., 1964. *Acta physiol. scand.* **62**, 380.

MILLAR, R. A., and BENFEY, B. G., 1958. *Brit. J. Anaesth.* **30**, 158.

NAGATSU, T., and UDENFRIEND, S., 1972. *Clin. Chem.* **18**, 980.

NAHAS, G. G., LIGOU, J. C., and MEHLMAN, B., 1960. *Amer. J. Physiol.* **198**, 60.

OSBORNE, M. W., ROWE, H., KAUFMAN, R., and JOHNSON, M., 1968. *Arch. int. Pharmacodyn.* **174**, 167.

PRAGER, R. L., ERNEST, L. D., and SEATON, J. F., 1975. *J. surg. Res.* **18**, 371.

RHOADS, J. E., and HOWARD, J. M., 1973. *The Chemistry of Trauma*, Thomas, Springfield, Illinois.

ROSENBERG, J. C., LILLEHEI, R. C., LONGERBEAM, J., and ZIMMERMAN, B., 1961. *Ann. Surg.* **154**, 611.

SPINK, W. W., REDDIN, J., ZAK, S. J., PETERSON, M., STARZECKI, B., and SELJESKOG, E., 1966. *J. clin. Invest.* **45**, 78.

WALTON, R. P., RICHARDSON, J. A., WALTON, R. P. JR., and THOMPSON, W. L., 1959. *Amer. J. Physiol.* **197**, 223.

WATTS, D. T., 1965. In *Shock and Hypertension*, Ed. L. C. Mills and J. H. Moyer. Grune and Stratton, New York, pp. 385.

—— and BRAGG, A. D., 1957. *Proc. Soc. exp. Biol.* **96**, 609.

—— and WERTFALL, V., 1964. *Proc. Soc. exp. Biol.* **115**, 601.

YOUNG, J. G., and GRAY, J., 1956. *Amer. J. Physiol.* **186**, 351.

ZILELI, M. S., GEDIK, O., ADALAR, N., and CAĞLAR, S., 1974. *Endocrinology* **95**, 1477.