Cardiac sequelae of acute head injury

ANDREW A McLEOD,* GLEN NEIL-DWYER, CARL H A MEYER, PETER L RICHARDSON, JOHN CRUICKSHANK, JOHN BARTLETT

From the Cardiac Department, King's College Hospital, Denmark Hill, London; and the Neurosurgical Unit, Brook General Hospital, Shooters Hill, London

SUMMARY An intensive 72 hour study of the cardiovascular effects of severe diffuse brain injury was made in seven patients. No other major injury was present. Patients received optimal care very rapidly after injury and intracranial pressure, which was continuously monitored, was maintained at or just above normal by elective positive pressure ventilation techniques. Three patients showed evidence of progressive myocardial ischaemia on continuous electrocardiographic monitoring. Two of these patients died. Ventricular arrhythmias were uncommon but one of the patients with ischaemia developed ventricular tachycardia. Heart rate patterns were very abnormal but did not predict complications. Blood pressure did not vary greatly and cardiac outputs were usually normal. Pronounced excesses of urinary catecholamines and serum creatine kinase 2 isoenzyme (CK MB) as well as total creatine kinase were found. Histological evidence of myocardial damage could be shown at necropsy in the one case whose heart was available for study.

This study shows that the cardiac effects of isolated diffuse cerebral injury may be harmful and even fatal despite correction of secondary factors such as anoxia and raised intracranial pressure. The findings suggest that evaluation of the potential benefits of sympathetic blockade is warranted. Cardiac complications of cerebral damage deserve wider recognition by intensive care personnel, neurologists, and neurosurgeons.

Electrocardiographic abnormalities and myocardial damage are recognised accompaniments of subarachnoid haemorrhage.¹⁻⁴ The subsequent clinical course of these patients may be complicated by rebleeding, investigation and surgery, and occasional diffuse cerebral ischaemia. Intervention designed to protect the heart may therefore have no effect on the overall prognosis. Myocardial damage after cerebral trauma has received less attention, and no systematic attempt has been made to examine potential cardiac sequelae of head injury alone. All such patients, except those with acute haematomata, show a neurological deficit that is maximal initially, but can be expected to improve steadily with appropriate clinical care. Many of these patients can make an excellent neurological recovery. A group of young subjects with no prior history of cardiac disease who had sustained an isolated severe head injury in road accidents was therefore studied to determine whether any serious cardiac sequelae resulted.

Patients and methods

We studied seven patients with severe head injuries from road accidents. Their ages ranged from 11 to 39 (mean = 22). All had been apparently in perfect health before their accident. None was overtly obese or in any other way abnormal, with the exception of their presenting injury. Questioning of relatives disclosed no evidence of prior cardiac disorder, hypertension, or other significant disease. The presence of any other injury excluded patients from the study.

Computerised axial tomographic scans of the brain were obtained in all cases. The presence of a focal lesion or haematoma also excluded patients from the study. All patients were deeply unconscious and showed either no response to pain or purposeless or decerebrate response. Pupils were dilated and fixed to light in all but two. All were admitted immediately to our unit from the scene of the accident. This was usually within the hour but was in all cases less than four hours. Each patient was then studied intensively for 72 hours.

Patients were admitted to the intensive care unit, intubated electively, and ventilated to maintain Pco₂

*Present address: British Heart Foundation Research Fellow, Division of Cardiology, Duke University, Durham, NC, USA.

in the range 3 to 4 kPa (23 to 30 mmHg). Subdural pressure transducers (Gaeltec Ltd.) were inserted through a burr hole. Continuous recording of the electrocardiogram was made with an Oxford-Medilog recorder and was analysed using an Oxford analysis system and a Reynolds Pathfinder. Recordings were continued for 72 hours. A thermodilution cardiac output catheter was sited in the pulmonary artery and used for pressure monitoring and regular measurements of cardiac output. Routine pulse and blood pressure measurements were made by the nursing staff. Daily assays of creatine kinase (CK) and its myocardial isoenzyme (CK MB) were made from serum samples. Care was taken to avoid possible enzyme degradation^{5,6} and isoenzyme separation was then achieved by electrophoresis on agarose gel. A fluorimetric technique was used to measure enzyme activity.^{7,8} Twenty-four hour urine samples were collected for assay of free catecholamines and their metabolites.⁹⁻¹¹ On each of the first three days in hospital, the P_{CO_2} was allowed briefly to rise to normal and cerebral blood flow to both hemispheres was measured using a ^{133}Xe rebreathing method.^{12,13} No parasympatholytic drugs were used in management. The maintenance of a satisfactory intracranial pressure by ventilatory techniques meant that none of these patients received corticosteroids or hyperosmolar fluids. Paralysis for ventilation was achieved with pancuronium alone, other drugs being unnecessary by virtue of the patient's deeply unconscious state.

Written consent could not be obtained for this plan of management and investigation but the objectives of such intensive care and monitoring were discussed with the relatives in all cases and approval was obtained for each patient. The 11-year-old child was not, however, exposed to ^{133}Xe or subjected to Swan-Ganz catheter insertion.

Results

NEUROLOGICAL FINDINGS

All patients had severe diffuse brain injury without any focal lesion as evidenced by computerised axial tomographic scanning. In consequence cerebral blood flow was low bilaterally in all cases but rose steadily throughout the 72 hour period of observation, from a mean value of 33.4 ml/100 g tissue per min to 40.8 ml/100 g per min ($p < 0.001$ by paired t test; normal value for this group of patients 51.5 ml/100 g brain tissue per min¹³). Intracranial pressure on day 1 varied from a mean minimum pressure of 21.6 cm H_2O to a mean maximum pressure of 26.4 cm H_2O . No significant change occurred on the subsequent days of study (upper limit of normal 18 to 20 cm H_2O). The absolute range was 18 to 30 cm H_2O and

no intervention was deemed necessary to reduce pressure apart from reduction of P_{CO_2} by ventilation.

CARDIOVASCULAR FINDINGS

Blood pressure in the adult patients varied between 110/70 and 205/110 mmHg (lowest recorded in the 11 year old child 60/40 mmHg). Typically, values were normal or slightly raised. Mean cardiac outputs were slightly above normal (6.2 l/min on day 1, with no significant change on days 2 or 3). These were influenced, however, by one patient who consistently showed outputs above 10 l/min.

12 lead electrocardiograms showed features associated with intracerebral lesions.¹⁴ Peaked P waves and T waves were seen, with short PR intervals in two cases. Definite ischaemic change of the ST segment was only present, however, in one case on routine electrocardiogram (inferior lead ST depression) and this resolved in later tracings.

Continuous tape recording of the electrocardiogram disclosed very abnormal patterns. A normal heart rate trend recording in a resting subject is shown in Fig. 1. By contrast, the typical pattern in our patients was of a pronounced sinus tachycardia without any beat to beat variation (Fig. 2). This was present in five cases on day 1. Heart rate pattern generally became more normal, but one case showed sudden accelerations of heart rate on day 2, with dramatic variation in sinus rate from around 75/min to 160/min (Fig. 3).

Continuous electrocardiographic monitoring disclosed evidence suggestive of significant myocardial ischaemia (ST segment depression of 3 mm, 5 mm, and 13 mm) in three cases. One patient showed steadily increasing depression of the ST segment with concomitant increase in heart rate (Fig. 4). Peak heart rate of 190/min and ST depression of 13 mm were seen. Despite treatment with beta-blocking agents during the later hours after admission, lethal cardiac arrhythmias supervened (Fig. 5). Another patient had salvos of ventricular tachycardia on day 1 and had developed 5 mm ST depression on day 3. This patient died suddenly on day 5 after making apparently satisfactory neurological progress. Histological study of the heart showed focal myocardial necrosis. Study of the brain and other organs did not show a clear cause for death. With the exception of the patient with ventricular tachycardia, ventricular arrhythmias were infrequent. Isolated ventricular premature beats occurred in an unpredictable fashion, were generally fewer than 30/hour, and were transient.

BIOCHEMICAL FINDINGS

Twenty-four hour urinary catecholamines were raised in all cases (Table 1). Metabolites were frequently raised but to a lesser degree. CK levels showed pronounced variation but were frequently grossly high.

Fig. 1 One hour heart rate trend in normal adult, obtained by plotting electrocardiogram R-R interval from a continuous 24 hour recording. Ordinate: instantaneous heart rate. Abscissa: time; time marker indicates 10 minute period. One hour where the subject is resting in bed is shown. The subject falls asleep after about half an hour. At arrow, first episode of rapid eye movement sleep occurs. Compare Fig. 2 and 3 (see text).

Fig. 2 Case 2. One hour heart rate trend on first day after acute head injury. Scale as in Fig. 1. Note unvarying sinus tachycardia, mean rate 158/min.

Fig. 3 One hour heart rate trend on second day in patient who initially showed cardiac rhythm similar to the case in Fig. 2. Note abrupt and extreme accelerations in heart rate.

CK MB levels were also raised (Table 2). CK MB is not detectable in normal subjects in our laboratory, but there is controversy over methodology in this field. Conditions which have provoked rises in total CK have produced small increases in CK MB. Significant rises in CK MB have been observed in cardiac injury only (*vide infra*).

Discussion

Little or no mention of cardiac sequelae after head injury is made in current neurosurgical texts. This study provides evidence that young and healthy subjects who suffer an isolated severe head injury are at risk from secondary myocardial damage, despite optimal conventional management. Our study differs in several important respects from previous reports

Fig. 4 Extracts taken from 24 hour electrocardiogram in the case whose heart rate trend is shown in Fig. 2. Each extract is taken at the end of the hour indicated. Heart rate increases from 150/min to 190/min. ST segment becomes depressed in hour 9 and reaches 13 mm below isoelectric line in hour 17.

suggesting myocardial injury in these circumstances^{15 16}. Firstly, patients studied were all admitted directly to a neurosurgical unit immediately after their injury. No patient underwent inter-hospital transfer. Very early direct admission under neurosurgical care is unusual in the United Kingdom¹⁷ and these patients received optimal treatment very rapidly. Intensive care and controlled hyperventilation were instituted on admission, thus minimising secondary effects of anoxia and raised intracranial pressure. Intracranial pressure monitoring was used to establish the efficacy of this treatment. In addition, care was taken to exclude from the study any patients with possible pre-existing cardiac disease, and computerised axial tomography

Fig. 5 Terminal arrhythmias during hour 18 in patient discussed in Fig. 2 and 4.

scanning was used in all cases to exclude patients with focal lesions such as haematomata. Patients with additional major injury were also excluded. The effects studied were thus those which were caused by diffuse cerebral injury itself.

The evidence for cardiac morbidity and mortality in these patients rests on several investigative methods. Firstly two patients died, and neither from any apparent intracranial cause. In the one heart which was

available to us for study, focal myocardial necrosis was found. We have observed similar changes after subarachnoid haemorrhage¹⁸ and several studies suggest that catecholamines are the major determinant of such lesions.¹⁹⁻²² Similar findings can be observed after catecholamine infusion and in pheochromocytoma.²³ The harmful effects may further be potentiated by corticosteroids.²⁴

There is controversy over two of the other study methods used in the investigation of these patients: namely, the findings on continuous electrocardiographic recordings, and the results of total CK and isoenzyme CK MB assays. Poorly understood electrocardiographic changes are common in cerebral injury²⁵ but the findings of ST segment depression to the extent shown here—3 mm, 5 mm, and 13 mm are less well recognised. The second and third patient both showed very high catecholamine levels. Such extreme sympathetic stimulation may produce gross changes in regional myocardial perfusion²⁶ and result in myocardial damage. This is probably partly because of vasoconstriction since angiotensin under appropriate conditions may also provoke such changes.²⁷ The additional metabolic energy demand produced by sympathomimetic amines may, however, have its own deleterious effect. The inotropic action of these agents may be mediated secondarily by enhanced delivery of intracellular calcium and this accumulation may increase ischaemic damage.²⁸ The resultant effects on the electrocardiogram are less well understood. Emotion, stress, and sudden pressure loading may all provoke electrocardiographic abnormalities in subjects whose coronary arteries are normal.²⁹⁻³¹ Some of these effects may be duplicated by catecholamine infusions and can be returned to normal by beta-blockade. There is evidence to support both a cellular electrophysiological effect,³² or an action on blood flow redistribution²⁶ as a mechanism for this observation. The very gross changes seen in case 2, however, in the presence of entirely satisfac-

Table 1 Levels of catecholamines and their metabolites in 24 hour urine collections; presence of pronounced sinus tachycardia and ST segment depression is also noted

Case No.	Age (y)	Sex	ST depression	Heart rate >150 at any time	Day 1				Day 2				Day 3			
					Adr	Nor	HMMA	META	Adr	Nor	HMMA	META	Adr	Nor	HMMA	META
1*	39	F	Yes	Yes	330	3340	71	3.6	670	1050	68	2.1	630	1670	63.5	3.6
2†	22	M	Yes	Yes	2080	5070	59.5	5.2	—	—	—	—	—	—	—	—
3	11	M	No	Yes	260	1305	44.5	3.5	625	2040	44	4.6	—	—	—	—
4	27	M	Yes	No	—	—	—	—	1500	2025	69	5.2	955	3540	73	6.2
5	21	M	No	No	780	500	33	1.7	1790	495	45	3.2	1500	490	54	5.5
6	16	M	No	No	1120	2170	52	6.8	1065	845	48	5.6	1290	1460	40	5.1
7	19	M	No	Yes	1225	1370	18.5	1.4	1815	9030	44.5	3.7	1700	3850	35.5	3.8

Adr, adrenaline, nmol, normal range 0 to 275 nmol/24 h; Nor, noradrenaline, nmol, normal range 110 to 1100 nmol/24 h; HMMA, 4-hydroxy-3-methoxy-mandelic acid, μ mol, normal range 10 to 35 μ mol/24 h; META, combined metanephrines, μ mol, normal range 0 to 4 μ mol/24 h.

*Patient died on fifth day.

†Patient died on first day.

Cardiac sequelae of acute head injury

Table 2 Levels of creatine kinase; values of total CK given in IU/l (normal < 130); isoenzyme CK MB given in % of total CK (normally undetectable)

Case No.	Day 1		Day 2		Day 3	
	Total CK	MB%	Total CK	MB%	Total CK	MB%
1*	8750	4	8950	3.1	1070	1.2
2†	—	—	—	—	—	—
3	60	1.6	290	2.0	—	—
4	—	—	1050	4.0	3100	4.0
5	500	2.7	780	3.2	360	2.6
6	1720	4.7	1110	6.5	—	—
7	430	3.6	490	3.4	530	4.4

*Patient died on fifth day.

†Patient died on first day.

tory blood gases, plasma electrolytes, and intracranial pressure, together with an extreme and unwavering sinus tachycardia suggest that real and lethal cardiac ischaemia was present until terminal arrhythmias developed. In case 1 a lesser degree of ST segment depression was seen, but ventricular tachycardia during tape recordings and sudden death on the fifth day after admission, combined with necropsy evidence of focal myocardial necrosis all indicate that ischaemic cardiac damage occurred.

The heart rate trend recordings in our patients suggest that sympathetic overactivity is common early after severe brain injury, and this accords with the measured urinary catecholamines and their metabolites. The two patients who died had the highest levels. Overactivity may not be constant, however, and bizarre cyclical discharges as seen in Fig. 3 may occur. We have attempted to correlate these findings with the release of CK MB isoenzyme of CK. As yet no perfect method for fractionation of CK isoenzymes exists^{33 34} and this has confused the published reports on this subject. Some authors have considered CK MB as "cardiospecific"³⁵⁻³⁷ but low levels which may reach 2% total CK have been found in normal subjects and in a variety of non-cardiac disorders.³⁸ Recently evidence has been presented for differing lability of the isoenzymes, and modifications in collection methods which we have adopted have been suggested to avoid oxidative changes which may alter electrophoretic mobility.^{5 39} Further study on subsequent head injury cases has shown the presence of "brain specific" isoenzyme (CK BB) in a number of patients, and satisfactory separation between this and CK MB has been achieved. We have attempted to rule out the effects of skeletal trauma as a cause of enzyme rises in our subjects by studying separately a series of 10 patients undergoing major orthopaedic surgery. In these patients total CK did not exceed 600 IU/l and CK MB remained at 2% or less. Thus, though there is some overlap, there is apparently release of myocardial CK in our patients. Kaste and his colleagues have

provided evidence that this occurs¹⁵ and may worsen prognosis. Some of their cases included purely intracranial catastrophes where there could be no question of skeletal muscle injury.

The results of our study, and of other attempts to investigate the damaging effect of brain lesions on the heart,¹⁵ suggest that attention to the cardiovascular system may be important in neurosurgical practice. Further investigation is needed to explore the possibility that the heart can be protected against the damage induced by intense sympathoadrenal stimulation. A second study has therefore been initiated to investigate the possible protective effects of cardioselective beta-blockade. Non-selective beta-blockade is theoretically unattractive by virtue of a potentially unopposed alpha-vasoconstrictor action in resistance vessels resulting in systemic hypertension. Preliminary studies suggest that accurate titration may be difficult to achieve, however; plasma adrenaline and noradrenaline levels have been found in excess of 18 times the upper limit of normal values by the present authors (unpublished observations).

Our findings may also be relevant in the field of cardiac transplantation which has re-emerged as an occasional treatment for advanced cardiovascular failure in the United Kingdom. Many donor hearts are removed from victims of road accidents, and by extrapolation from our results some of these may have microscopic foci of myocardial necrosis. Even if there is no lasting impairment of cardiac function, myocardial necrotic lesions may have some effect on the immune response in the recipient.

In conclusion, in a series of patients with isolated diffuse cerebral injury who had no prior cardiac defect, who were admitted rapidly to hospital, and who were intensively monitored and treated to reduce unnecessary metabolic or respiratory insults, evidence of extreme sympathetic disturbance with deleterious cardiac sequelae was found. Our studies suggest that a large proportion of these cases may show biochemical evidence of disturbance of catecholamine mediators, and secondary release of CK and CK MB from injured tissue, some of this arising from the heart. Electrocardiographic evidence of severe disturbance may be found. Direct evidence of myocardial damage may be apparent in patients who die. Attempts must now be made to interrupt the damaging stimulus-response link in these patients. Cardiac morbidity and possible mortality deserve wider attention from those working in intensive care or neurosurgical units.

References

- Byer E, Ashman R, Toth LA. Electrocardiograms with large upright T waves and long Q-T intervals. *Am Heart J* 1947; 33: 796-806.

- 2 Connor RCR. Myocardial damage secondary to brain lesions. *Am Heart J* 1969; 78: 145-8.
- 3 Greenhoot JH, Reichenbach DD. Cardiac injury and subarachnoid hemorrhage. A clinical, pathological and physiological correlation. *J Neurosurg* 1969; 30: 521-31.
- 4 Koskelo P, Punsar S, Sipilä W. Subendocardial haemorrhage and ECG changes in intracranial bleeding. *Br Med J* 1964; i: 1479-80.
- 5 Cho HW, Meltzer HY. Factors affecting stability of isozymes of creatine phosphokinase. *Am J Clin Pathol* 1979; 71: 75-82.
- 6 Morin LG. Creatine kinase; stability, inactivation, reactivation. *Clin Chem* 1977; 23: 646-52.
- 7 Oliver IT. A spectrophotometric method for the determination of creatine phosphokinase and myokinase. *Biochem J* 1955; 61: 116-22.
- 8 Rosalki SB. An improved procedure for serum creatine phosphokinase determination. *J Lab Clin Med* 1967; 69: 696-705.
- 9 Sobel C, Henry RJ. Determination of catecholamines (adrenalin and noradrenalin) in urine and tissue. *Am J Clin Pathol* 1957; 27: 240-5.
- 10 Pisano JJ. A simple analysis for normetanephrine and metanephrine in urine. *Clin Chim Acta* 1960; 5: 406-14.
- 11 Pisano JJ, Crout JR, Abraham D. Determination of 3-methoxy-4-hydroxymandelic acid in urine. *Clin Chim Acta* 1962; 7: 285-91.
- 12 Wyper DJ, Lennox GA, Rowan JO. Two minute slope inhalation technique for cerebral blood flow measurement in man. *J Neurol Neurosurg Psychiatr* 1976; 39: 141-6.
- 13 Wyper DJ, Rowan JO. The construction and use of nomograms for cerebral blood flow calculation using a ^{133}Xe inhalation technique. *Phys Med Biol* 1976; 21: 406-13.
- 14 Cruickshank JM, Neil-Dwyer G, Stott AW. Possible role of catecholamines, corticosteroids, and potassium in production of electrocardiographic abnormalities associated with subarachnoid haemorrhage. *Br Heart J* 1974; 36: 697-706.
- 15 Kaste M, Somer H, Kontinen A. Heart type creatine kinase isoenzyme (CK MB) in acute cerebral disorders. *Br Heart J* 1978; 40: 802-5.
- 16 Somer H, Kaste M, Troupp H, Kontinen A. Brain creatine kinase in blood after acute brain injury. *J Neurol Neurosurg Psychiatr* 1975; 38: 572-6.
- 17 Jennett B, Murray A, Carlin J, McKean M, MacMillan R, Strang I. Head injuries in three Scottish neurosurgical units. *Br Med J* 1979; ii: 955-8.
- 18 Doshi R, Neil-Dwyer G. Hypothalamic and myocardial lesions after subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatr* 1977; 40: 821-6.
- 19 Haft JL. Cardiovascular injury induced by sympathetic catecholamines. *Progr Cardiovasc Dis* 1974; 17: 73-86.
- 20 Szakacs JE, Mehlman B. Pathologic changes induced by 1-norepinephrine. *Am J Cardiol* 1960; 5: 619-27.
- 21 Kaye MP, McDonald RH, Randall WC. Systolic hypertension and subendocardial hemorrhages produced by electrical stimulation of the stellate ganglion. *Circ Res* 1961; 9: 1164-70.
- 22 McNair JL, Clower BR, Sanford RA. The effect of reserpine pretreatment on myocardial damage associated with simulated intracranial hemorrhage in mice. *Eur J Pharmacol* 1970; 9: 1-6.
- 23 Reichenbach DD, Benditt EP. Catecholamines and cardiomyopathy. *Hum Pathol* 1970; 1: 125-50.
- 24 Selye H. The evolution of the stress concept. *Am J Cardiol* 1970; 26: 289-99.
- 25 Marriott HJL. *Workshop in electrocardiography*. Oldsmar, Florida: Tampa Tracings, 1972: 327.
- 26 Hoffman JIE, Buckberg GD. Transmural variations in myocardial perfusion. In: Yu PN, Goodwin JF, eds. *Progress in cardiology*, 5. Philadelphia: Lea & Febiger, 1976: 37-89.
- 27 Gavras H, Kremer D, Brown JJ, et al. Angiotensin- and norepinephrine-induced myocardial lesions: experimental and clinical studies in rabbits and man. *Am Heart J* 1975; 89: 321-32.
- 28 Fleckenstein A. Myocardial fiber necrosis due to intracellular Ca overload—a new principle in cardiac pathophysiology. In: Dhalla NS, ed. *Myocardial biology* (Recent advances in studies on cardiac structure and metabolism). Baltimore: University Park Press, 1974; 4: 563-80.
- 29 Taggart P, Carruthers M, Somerville W. Emotions, catecholamines and electrocardiogram. In: Yu PN, Goodwin JF, eds. *Progress in cardiology*, 7. Philadelphia: Lea & Febiger, 1978: 103-24.
- 30 Barnard RJ, MacAlpin R, Kattus AA, Buckberg GD. Ischemic response to sudden strenuous exercise in healthy men. *Circulation* 1973; 48: 936-42.
- 31 Monroe RG, Gamble WJ, LaFarge CG, et al. The Anrep effect reconsidered. *J Clin Invest* 1972; 51: 2573-83.
- 32 Taggart P, Carruthers M, Joseph S, et al. Electrocardiographic changes resembling myocardial ischaemia in asymptomatic men with normal coronary arteriograms. *Br Heart J* 1979; 41: 214-25.
- 33 Nordlander R. Enzymes in acute myocardial infarction. Diagnosis with special reference to creatine kinase MB isoenzyme. *Acta Med Scand* 1978; suppl 623: 18-26.
- 34 Ogunro EA, Hearse DJ, Shillingford JP. Creatine kinase isoenzymes: their separation and quantitation. *Cardiovasc Res* 1977; 11: 94-102.
- 35 Roe CR, Limbird LE, Wagner GS, Nerenberg ST. Combined isoenzyme analysis in the diagnosis of myocardial injury: application of electrophoretic methods for the detection and quantitation of the creatine phosphokinase MB isoenzyme. *J Lab Clin Med* 1972; 80: 577-90.
- 36 Veen KJ van der, Willebrands AF. Isoenzymes of creatine phosphokinase in tissue extracts and in normal and pathological sera. *Clin Chim Acta* 1966; 13: 312-6.
- 37 Smith AF, Radford D, Wong CP, Oliver MF. Creatine kinase MB isoenzyme studies in diagnosis of myocardial infarction. *Br Heart J* 1976; 38: 225-32.
- 38 Mercer DW, Varat MA. Detection of cardiac-specific creatine kinase isoenzyme in sera with normal or slightly increased total creatine kinase activity. *Clin Chem* 1975; 21: 1088-92.
- 39 Sax SM, Moore JJ, Giegel JL, Welsh M. Atypical increase in serum creatine kinase activity in hospital patients. *Clin Chem* 1976; 22: 87-91.

Requests for reprints to Dr Andrew A McLeod, Cardiac Department, King's College Hospital, Denmark Hill, London SE5 9RS.