SIR,—The dangers of intravenous thrombolysis treatment have been comprehensively reviewed by Dr M C Petch.¹ We report a case of haemorrhage induced by streptokinase successfully treated with intravenous tranexamic acid. Tranexamic acid inhibits plasminogen activation and thrombus fibrinolysis and is referred to in the *British National Formulary* for use in streptokinase overdosage.

A 58 year old man with severe ischaemic heart disease presented with chest pain and electrocardiographic changes characteristic of myocardial infarction. One hour after receiving streptokinase he developed haemoptysis, haematuria, and progressive focal neurological signs suggesting right cerebral haemorrhage. He was treated with intravenous tranexamic acid (1 g by slow intravenous infusion six hourly). The haemorrhage ceased after the first infusion, and his neurological signs resolved over two days.

Aprotinin and fresh frozen plasma are useful in reversing the coagulopathy subsequent to giving streptokinase,² and tranexamic acid should be evaluated as an immediate antidote to streptokinase. These agents may be of great value used in conjunction when streptokinase has been given inappropriately or dangerous bleeding has occurred.

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- 1 Petch MC. Dangers of thrombolysis. *Br Med J* 1990;300:483-4. (24 February.)
- 2 Butler J, Davies AH, Westaby S. Streptokinase in acute aortic dissection. *Br Med J* 1990;300:517-9. (24 February.)

SIR,—Few would argue with Dr M C Petch's main conclusions,¹ but one aspect of the dangers of streptokinase deserves further emphasis. The increasing use of streptokinase has been associated with a proliferation of reports of a serum sickness type of reaction to the drug.^{2,9} Many of the reported patients had cutaneous vasculitis or impairment of renal function, or both, so these reactions cannot be dismissed as "mild." There are close antigenic similarities between group A streptococci, which includes the major human pathogen *S pyogenes*, and group C streptococci, from which streptokinase is produced.¹⁰ A recent study of patients receiving streptokinase showed that plasma taken before treatment contained low levels of neutralising capacity for the drug, suggesting the presence of pre-existing antibodies.¹¹ Streptococcal infections are common, and there is likely to be a large reservoir of sensitised people in the community; as the use of streptokinase increases the serum sickness type of reactions are likely to be increasingly recognised. Consideration of cost is obviously important in choice of thrombolytic agent, but infusing large amounts of a highly antigenic bacterial protein into sensitised patients is likely to generate many more cases like those discussed above.

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SIR,—In his editorial Dr M C Petch describes the now well defined contraindications to thrombolytic treatment and reminds us that the benefits of this treatment outweigh the risks. We suggest that recent pancreatitis is included in the list of cautions.

A 47 year old man was admitted to the coronary care unit with a four hour history of severe retrosternal chest pain and electrocardiographic changes of an acute inferolateral myocardial infarction. He was included in a randomised study of thrombolytic agents and was treated with anistreplase (APSAC). The patient was known to have had alcohol related acute pancreatitis. A recent abdominal ultrasound examination had shown a 5 cm pseudocyst within the body of the gland, but this information was not immediately available to the admitting doctors.

Two hours after admission he developed severe central abdominal pain and became progressively more shocked, having been normotensive on admission. A Swan-Ganz catheter was inserted for haemodynamic monitoring, and the pulmonary arterial wedge pressure confirmed hypovolaemia with a pressure measurement of less than 5 mm Hg. Serum amylase was raised at 960 U/l (normal range <200 U/l), strongly suggesting a diagnosis of acute pancreatitis. Despite attempted resuscitation with fresh frozen plasma and 5 litres of intravenous colloid he remained hypotensive and anuric and died 15 hours after admission.

Postmortem examination showed changes of a recent myocardial infarction in association with multivessel coronary atheroma. No intracoronary thrombosis was detected, and there was interstitial infarct haemorrhage in keeping with reperfusion due to thrombolysis. The peritoneal cavity contained 3.5 litres of blood, and there was an extensive retroperitoneal haematoma constituting the contents of a pseudocyst of the body of the pancreas. The residual pancreas was not enlarged but had flecks of fat necrosis around its head. Although no specific site for the haemorrhage could be identified within the pseudocyst, this was considered to be the source of the intraperitoneal bleeding.

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SIR,—Given the expertise in, and commitment to, the management of cardiothoracic emergencies that Mr S Westaby and his colleagues are known for, one is loathe to criticise their recent paper.¹

There is one point, however, that as a radiologist I feel merits comment. They say in their paper that "aortic dissection should have been considered on the basis of the chest x ray appearance in all four cases." There are severe limitations to the chest x ray in the diagnosis of aortic dissection. Ectatic great vessels, "unfolded aortic arch," mediastinal fat, patient rotation or scoliosis, poor inspiratory effort by the patient, an x ray taken with the patient

supine—all can give a true or spurious impression of mediastinal widening. The vast majority of patients with a wide mediastinum or chest x ray will not have aortic dissection. Other chest radiological signs in favour of aortic dissection are often not present. I agree that serial chest x rays or review with previous comparable films, or both, are useful. A measure of the difficulty in interpreting chest x ray films in patients suspected of acute aortic dissection can be gauged from the very modest widening of the mediastinum seen in figure 2 in the paper—it is of a degree often seen in a "reporting pile."

The decision to undertake computed tomography out of hours is likely to result in a delay of one hour and possibly longer, which may well diminish the potential benefit of streptokinase if the patient actually has had a myocardial infarction and not an aortic dissection. Moreover, were computed tomograms done in many patients with acute chest pain simply because of a "wide" mediastinum, not only would some suffer from delayed administration or non-administration of streptokinase but the computed tomography department would be overrun with requests for a condition which the Pittsburgh University's *Manual of Diagnostic Imaging* estimates occurs in one in 10 000 hospital admissions.²

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- 1 Butler J, Davies AH, Westaby S. Streptokinase in acute aortic dissection. *Br Med J* 1990;300:517-9. (24 February.)
- 2 Straub WH, ed. *Manual of diagnostic imaging: a clinician's guide to problem solving*. 2nd ed. Boston: Little, Brown, 1989:103.

Benefits of animal research and the doctor's responsibility

SIR,—Having spent a great part of my career doing animal experiments, I am dismayed by the number of my distinguished colleagues who refuse to acknowledge that such use of animals is subject to any moral reservations. Sir Michael Drury and his seven colleagues¹ suggest that patients should, when they receive their prescriptions, be persuaded that animal experiments are justified by the medical advantages they are getting the benefit of, and that these blessings would not be available to them if such experiments had been disallowed. The first proposition instances the moral defection implied in "ends justify means"; the second proposition is logically unsustainable.

Contrary to the absurd propaganda of strict antivivisectionists, it is undeniable that animal experiments have played a very large part in the development of many modern therapeutic resources. But it underrates the ingenuity of researchers to assert that medical progress would have been seriously impeded had animal experiments been illegal, although a different strategy would have been required. It is the skill of the scientist to find a way round the intellectual, technical, and ethical limitations to investigation. No one complains, surely, that we have been denied the benefit of potential advances by prohibiting experiments on unsuspecting patients, criminals, or idiots or that embryo research will be brought to a standstill by application of the 14 day rule.

Your earlier correspondent on this topic, Sir Walter Bodmer, decries "speciesism" as an "extraordinary concept" and a "peculiar philosophy."² Speciesism is, in fact, a perfectly valid moral indictment that is in the reforming spirit of the times, which is to extend more widely the respect and protection deserved by previously exploited creatures, human or animal. All moral innovators have been impolitely branded as cranks in their time.

I am no renegade from animal experimentation, if only because I believe that quite enough can be achieved by it without resort to manifestly painful or distressing procedures. The pity is that the recent Animals (Scientific Procedures) Act 1986 does no more than tighten the regulation of permissiveness. Essentially, the act requires only that the severity of procedures permitted be commensurate with the perceived necessity or importance of the information sought. It imposes no absolute limit either on the purposes for which experiments may be done or on the degree of severity permitted. Yet the observance of any moral principle supposes some real sacrifice of advantage or convenience.

Parroting of the uninspired and iterative propaganda of the Research Defence Society by doctors does not assist the achievement of sympathetic understanding and fair compromise between well meaning pragmatists and well meaning idealists.

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1 Drury M, Wade O, Kuenssberg E, *et al.* Benefits of animal research and the doctor's responsibility. *Br Med J* 1990; 300:538. (24 February.)

2 Bodmer W. Experiments on animals. *Br Med J* 1989;299:1524. (16 December.)

Identification of the cystic fibrosis gene

SIR,—The gene deletion $\Delta F508$ on chromosome 7 has been found in approximately 70% of gene carriers for cystic fibrosis and provides an opportunity to offer detection of carrier state both to members of the general population and to members of families in whom cystic fibrosis has been diagnosed.¹ The clinical implications of the screening test require careful consideration.

Screening for carriers of cystic fibrosis is not a simple test to distinguish those who are carriers from those who are not. For unscreened members of the northern European population the chance of being a carrier is one in 20. Finding the deletion indicates that the person is a carrier. Out of 1000 members of the general population screened 50 will be carriers for cystic fibrosis. Of the 50 carriers, 35 can be told that the deletion $\Delta F508$ has been found and that they are carriers, but 15 carriers will be undetected. The 965 not found to be carriers of the mutation can be told their risk has been reduced from one in 20 to one in 45. For relatives of affected patients a negative screen at present will only halve the chance of a first cousin being a carrier and change the chance of a brother or sister being a carrier from two in three to one in two.

The importance of a negative result on screening is affected by the accuracy of the information about the proportion of carriers detected by finding a deletion. If the proportion of carriers detected by the test changed from 70% to 80% the chance for members of the northern European population with a negative result on screening of being a carrier would be reduced from one in 45 to one in 83 and for siblings of affected patients from one in two to one in three (table 1).

TABLE 1—*Chance of being a carrier of cystic fibrosis who has deletion $\Delta F508$*

	Prior probability	Proportion of carriers with deletion	
		70%	80%
Northern Europeans	1 in 20	1 in 45	1 in 83
First cousin affected	1 in 8	1 in 20	1 in 50
Uncle or aunt affected	1 in 4	1 in 8	1 in 13
Sibling of affected person	2 in 3	1 in 2	1 in 3
Sibling of known carrier	1 in 2	1 in 3.3	1 in 5

If members of the public are to be alerted to the risks of being a carrier for cystic fibrosis they need to understand the implications of a reduction in the chance of being a carrier. Table II shows the chance of offspring being affected for various matings of probable carriers.

TABLE II—*Chance of having affected offspring for different carrier states of parents*

Parents	Carrier state	Chance of having affected offspring
Population; unscreened	1 in 20	1 in 1600
Population; unscreened	1 in 20	
Population; negative screen	1 in 45	1 in 3600
Population; unscreened	1 in 20	
Population; negative screen	1 in 45	1 in 6100
Population; negative screen	1 in 45	
Sibling of affected patient; unscreened	2 in 3	1 in 120
Population; unscreened	1 in 20	
Sibling of affected patient; negative screen	1 in 2	1 in 360
Population; negative screen	1 in 45	
Known carrier		1 in 80
Population; unscreened	1 in 20	
Known carrier		1 in 180
Population; negative screen	1 in 45	

The most efficient use of the test can be made only if the deletion has been shown in the index patient or another carrier in the family. It seems to us very important that the implications of the test should be understood by those who are to be offered screening so that they can accept or decline the test, knowing that the results may be indecisive. The acceptability of this for the public needs evaluation before a massive screening programme is offered to the general population.

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1 Knight RA, Hodson ME. Identification of the cystic fibrosis gene: practical implications for patients and their families. *Br Med J* 1990;300:345-6. (10 February.)

Clinical directorates

SIR,—J N Johnson's editorial¹ was a disappointingly negative, ill informed, and rather paranoid treatment of what is a very complex and significant change in management practice within our hospitals. The most glaring omission was the complete lack of any recognition of those wider organisational themes (well understood in other contexts) that point towards this particular form of self management for the profession.

The National Health Service is not immune from influences acting in a much wider context, although it often lags several years in recognising and accommodating them. Many recent changes owe their genesis to these influences rather than being the manifestation of some purely political whim of the government. Generally speaking, in Western economies major organisations are becoming less hierarchical and more decentralised at the same time as growing larger.

The reason for this apparent paradox lies within the improved information and communications systems that often cover every aspect of the prime business being undertaken. These systems foster changed management behaviour by way of precise

setting of objectives and comprehensive performance monitoring at all levels. These two management processes inevitably lead to devolution of responsibility and to flatter organisational structures. Consequently, the managerial performance of those people who must work close to the principal activities of the organisation must become stronger and better.

Mr Johnson has failed to notice that this is now happening even within the NHS. Just as the Eastern bloc is disintegrating because of better communication, so too the monolithic structures of the NHS are melting under the influence of better, more timely information. Powerful forces indeed are at work. Hospital information support systems, which record every aspect of patient care; resource management; and clinical directorates are all concepts that fit comfortably within this general trend.

Far from this being a cynical attempt by lay managers to entrap doctors within the decision making process, the profession has perhaps the best opportunity for many years to control its own future. Logically, doctors are the only group who really determine the resource usage by patients. Other professional groups make their input within a context set by the patient's medical condition. This means that doctors must inevitably make those decisions in the light of available resources. Until recently, reliable information with which to do this has been lacking.

The alternative is responsibility without power, indeed a recipe for continuing frustration. By taking on the direct management of the delivery of care to patients in a positive fashion, clinical directors can establish properly what is really needed and articulate this to those who fix resource levels. By pricing clinical activities they can conduct the dialogue with government in terms of the work for patients which is to be done, not what health service workers should be paid.

At present we are unable to do that; instead we wave shrouds at insensitive politicians and become sidetracked into discussing our incomes as though these were in some way prejudicial to patient care. It is no wonder that we achieve so little if the debate is always constrained. By contrast, the evidence over four years in my own district shows that clinical directors take better, more sensitive decisions than lay managers and that they can overcome the restrictive practices between different professional groups that so often lie unresolved.

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1 Johnson JN. Clinical directorates. *Br Med J* 1990;300:488. (24 February.)

SIR,—Mr J N Johnson's discussion of clinical directorates is rather negative regarding the participation of clinicians in management, if not about the Guy's Hospital management system.¹ It is important to recognise that the Guy's system was not brought in by management to control doctors; it was brought in by doctors to take control of the problems for which they have a responsibility. It has decentralised to the appropriate level the management of those areas in which doctors and nurses are the prime movers. In the process managers have learnt much about clinical problems and the thought processes of doctors and nurses. Doctors have learnt to value the contributions made by their managerial colleagues, and it is some time since statements to the effect that there are too many managers were heard at Guy's. Perhaps more than most hospitals we have had to cope with stringent financial discipline, with our revenue being reduced by over £8m per annum over five years; but in spite of this we have been able to maintain patient throughput and are more or less in financial balance, and there is a deter-