and tremor would also suggest a diagnosis of Kennedy's syndrome, which can be confirmed by detecting an abnormal trinucleotide repeat (CAG) in the first exon of the androgen receptor gene.⁵

Multifocal motor neuropathy with conduction block, as defined electrophysiologically, can also mimic motor neurone disease. This is a disorder of the motor axon rather than motor nerve cell body and presents with patchy, asymmetrical wasting and weakness principally of the upper limbs.⁶ Fasciculation and preserved reflexes are also features. This condition may be associated with antiganglioside antibodies and may respond to immunosuppression. The cramp-fasciculation syndrome⁷ is one of several conditions characterised by peripheral nerve hyperexcitability. Normal muscle strength differentiates this benign and treatable condition from motor neurone disease. Finally, a significant minority of patients in the Scottish study were labelled as having "motor neurone disease plus"; they had clinical features compatible with motor neurone disease but also displayed additional neurological abnormalities, most notably dementia, as has been previously described.⁸

Nerve conduction studies and electromyography help to localise the pathological process and document the extent of denervation. The diagnosis of motor neurone disease requires clinical or electrophysiological evidence of widespread denervation of anterior horn cell origin. Detailed diagnostic criteria have recently been published.⁹ These probably have a good correlation with pathological findings² and will help to standardise research practice and allow recruitment of like patients into clinical trials.

In the management of patients with motor neurone disease, physicians' skills rest as much in their ability to convey information in an appropriate and timely fashion as in their

ability to differentiate subgroups of the disease from mimic syndromes. Sixteen years ago in a personal view in the *BMJ*, a patient with motor neurone disease described the demeaning nature of the disease and diagnostic process.¹⁰ Scientific progress may have only made things more difficult. In the words of the Boston neurologist Louis Caplan, "the increased complexity of technology and diagnostic and treatment options makes even more critical the physician's skill in managing illness and the art of communicating with patients and their loved ones. There but for the grace of God go we all, for all of us and our families are or will eventually become patients."¹¹

ANDREW M CHANCELLOR
Neurologist

Western Bay Health,
Tauranga,
New Zealand

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Transplanting porcine hearts to humans

Understanding the mechanisms gives cause for optimism

See p 657

The proposal to use transgenic swine hearts, which express a human gene, as donor organs for humans has sparked new interest in xenotransplantation (transplanting tissues from one species to another). A normal pig heart transplanted to an untreated primate is destroyed by hyperacute rejection within hours or minutes. Primates have pre-existing xenoreactive natural antibodies, which attach to the endothelial cells lining the vessels of the donor organ as soon as blood flow is established after transplantation. Recipient complement is activated, and the organ is rejected.^{1,2} Despite this overwhelmingly strong rejection reaction, many researchers remain optimistic that clinical xenotransplantation will become a reality.

Such optimism is based on several factors. The emergence of molecular genetics has provided tools to allow a detailed understanding of the mechanisms of rejection and permitted genetic engineering of donor animals. In addition, endothelial cells in the donor organ, which may contribute to rejection when activated,^{1,3,4} provide us with an important target for genetic engineering. Endothelial cell activation leads to thrombosis and inflammation,⁵ both of which are evident in a rejected discordant xenograft.

As an approach to treating hyperacute rejection, Agustin Dalmaso and I suggested several years ago that one could create transgenic pig donors that express in their endothelial

cells human genes encoding regulators of complement activation.^{3,6} We showed in vitro that human regulators of complement activation block the action of human complement on porcine endothelial cells.^{3,6} Transgenic pigs have now been created, and the first data support the concept that primate complement can be blocked by this approach and hyperacute rejection averted.

Some investigators believe that use of transgenic hearts expressing the human regulators of complement activation will allow the long term survival of a porcine heart in a human by use of immunosuppressive agents administered to the recipient. Others, including myself, do not believe that this will be possible without undue toxicity, and thus are focusing on developing additional forms of treatment, in many cases involving genetic engineering. Three examples are illustrative. First, there is the attempt to block synthesis of the gal(α1-3)gal sugar that is normally present on the surface of porcine endothelial cells and that is the prime target epitope recognised by human xenoreactive antibodies.⁷ Synthesis of this sugar can be suppressed by introducing a gene into the endothelial cells that encodes an enzyme that diverts the biosynthetic cascade.⁸ This will reduce binding of human xenoreactive natural antibodies to the porcine endothelial cells. Second, and addressing our hypothesis that endothelial cell activation underlies much of the thrombosis

and inflammation seen in a rejecting xenograft, we are expressing genes in porcine endothelial cells that inhibit a key transcriptional factor (NF- κ B) that is needed to up-regulate the genes that cause thrombosis and inflammation.^{1,9,10} Third, genetic engineering is being seen as a possible way of creating tolerance to porcine antigens that would incite a T cell response in a human host.¹¹ A multifactorial approach to treatment might involve genetic engineering with a few selected genes plus use of selected therapeutic and immunosuppressive drugs. Such an approach should balance toxicity to the patient with the ability to prevent rejection.

Given our increased understanding of mechanisms, the treatments being developed, and the preliminary data that are accumulating in pig to primate transplants, there is cause for optimism. But practical problems and ethical controversies remain. Possible transmission of disease from a donor animal to the recipient is emphasised in a report recently published by the Nuffield Council of Bioethics in London¹² and was also raised at the recent conference of the Institute of Medicine in Washington, DC, from which a report will be published. Even if we can overcome all the vascular, immunological, and other factors that contribute to rejection, we shall have to assess whether recipient factors that are critical for the function of the donor organ will perform across the species barrier.

Research into xenotransplantation presents exciting prospects for treating organ failure. It also offers insights into issues common to medicine as a whole. From tackling the

problem of thrombosis and inflammation in rejecting grafts, for example, we are likely to be able to introduce genes into a patient's endothelial cells via the blood to treat a segment of diseased vessel or other tissues. The results of xenotransplantation research should provide broad benefits in treating human disease.

FRITZ H BACH
Lewis Thomas professor

Harvard Medical School,
New England Deaconess Hospital,
Boston, MA 02215, USA

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Global commissioning by general practitioners

Affects attitudes and culture more than service delivery

The purchaser-provider split was introduced to allow "money to follow patients"¹ and to move control away from hospital providers towards those making the purchasing decisions. General practitioner referrals were seen as being at the core of those decisions, and general practitioner fundholding aimed to bring the decision making directly into the consulting room. The range of services purchased by fundholders has grown steadily and will cover virtually all elective services from April 1996.² Conceptually, it makes sense to test the idea of general practitioner purchasing to the limit by applying it to the purchasing of all services, and various models are being explored. Some involve the direct purchasing of secondary care services. Others aspire to more strategic commissioning for larger populations and longer time scales. But all involve general practitioners on the "purchaser" side of the purchaser-provider split. How are these experiments shaping up to evaluation and what can they tell us about the future shape of healthcare in Britain?

Existing models of general practitioner purchasing range from the four current "pioneer" total purchasing projects (in Berkshire, Bromsgrove, Runcorn, and Worth Valley and the 50 or so sites planned for the "second wave" of total purchasing³; through the gamut of different locality projects (exemplified by Newcastle and North Tyneside's locality commissioning, North Derbyshire's practice sensitive purchasing, Doncaster's Project 2000, and the Bromley general practitioner clinical commissioning board model) and general practitioner led projects (including Nottingham's non-fundholders' group and the Birmingham multi-fund covering a population of over 250 000 people); to models that encompass other agencies, such as depart-

ments of social services (as in County Durham and Wiltshire).

The most intensive evaluation of total purchasing is currently being carried out on the four "pioneer" sites—in Berkshire by the Health Services Management Centre, University of Birmingham; at Bromsgrove by St Mary's Medical School, London; at Runcorn by the University of Liverpool; and in the Worth Valley by the Nuffield Institute of Health, University of Leeds—with a broader national evaluation (by a consortium of seven research institutions, coordinated by King's Fund Institute) for the second wave of total purchasing projects. Elsewhere, levels of evaluation range from none to extra assessments funded by the local health authority. From these evaluations, several clear messages are beginning to emerge.

The first message is that change is happening but that we need the right eyes to see it. Most pilot projects have been created with the aim of changing services and showing number driven outcomes to satisfy economists and politicians. The reality is that sustainable changes in service cannot occur until the professional culture is ripe. In all the experiments with general practitioner commissioning, a consistent finding is that general practitioners' attitudes are changing. Fundholders or not, general practitioners are moving from short term "gung ho" purchasing towards more thoughtful, longer term relationships with their providers and health authorities.

The second message to emerge from the evaluations concerns the ambiguous relationship between health authorities and their commissioning general practitioners: most health authorities have not worked out whether they are working in partnership with their general practitioners, or as their bosses and overseers. Some authorities seem to take a