Two surgeons are accused of ignoring high death rates

Clare Dyer, legal correspondent, *BMJ*

Two senior consultant surgeons persisted in carrying out heart surgery on babies and toddlers even though half their patients died, the General Medical Council (GMC) was told this week at the start of a marathon disciplinary hearing.

James Wisheart and Janardan Dhasmana disregarded warnings by colleagues that the death rates for their operations for congenital heart defects at Bristol Royal Infirmary were too high, the professional conduct committee heard. Mr Wisheart, former medical director of the United Bristol Healthcare Trust, Mr Dhasmana, consultant cardiothoracic surgeon, and Dr John Roylance, former chief executive officer of the trust, face charges of serious professional misconduct for either operating or allowing operations to go ahead between 1990 and 1995, despite much higher mortality than the national average.

A list before the GMC details operations on 53 children, 29 of whom died. The two surgeons are accused of carrying out operations beyond their technical competence, and Mr Wisheart is

also accused of misleading parents by understating the risks of the operation in his hands. All three deny serious professional misconduct. The hearings are expected to last into the new year, and the case is seen as so important that the government has announced a public inquiry, set for March. This could lead to changes in the way surgeons are audited and regulated.

Roger Henderson, QC for the GMC, said that Mr Wisheart should have realised by 1993 that the mortality of up to 54% associated with the operations that he carried out to correct atrioventricular septal defects—compared with the national average of 13.9%—was “comparatively disastrous.” Mr Dhasmana started carrying out arterial switch operations on babies under 4 weeks old in 1992. Out of 13 operations, nine babies died and one was left with severe brain damage. The national average survival rate was nine out of 10. He stopped operating on neo-nates but continued operating on older babies. The last three such operations ended in deaths.

The Department of Health had warned that the last operation should not go ahead. Concern was originally raised by a consultant anaesthetist, Stephen Bolsin, who wrote to Dr Roylance in the summer of 1990 and subsequently contacted the health department. Mr Henderson said that Dr Roylance had “abrogated his duties and failed to do what he should have done.” One mother whose son

died a week after an operation by Mr Wisheart wrote to the GMC saying that he had told her the boy had a 90% chance of recovery. That was five times higher than the rate for babies being operated on by Mr Wisheart, said Mr Henderson. The surgeon was said to have played down the risk of brain damage to the parents of another baby, who is now grossly brain damaged and paraplegic. □

SOUTH WEST NEWS SERVICE

James Wisheart faces a charge of serious professional misconduct

Cancer charity takes stand against tobacco industry

Jacqui Wise, *BMJ*

The Cancer Research Campaign has said that it will no longer provide research support to any faculty or comparable unit that receives funding from the tobacco industry.

The charity's new draft code of practice aims to ensure that future scientific grants are not tainted with tobacco money. The code was drawn up after the announcement last year that British American Tobacco was to

give £1.5m (\$2.4m) to Cambridge University to fund a chair of international relations (27 July 1996, p 186).

Professor Gordon McVie, the charity's director general, said: “The tobacco industry has a long history of gaining respectability by funding research and facilities in our centres of academic excellence. Now it's only a matter of time before the practice stops and we break that addic-

tion to tobacco funding.”

The charity also revealed the results of a MORI poll of almost 2000 adults throughout Britain which found that the overwhelming majority do not have confidence in the projects and findings of scientists who work for the tobacco industry. The survey found that the tobacco industry was the most unpopular source of sponsorship, more so than the nuclear and arms industries.

The charity said that accepting funding from the tobacco industry can lead to delays in decision making, a distortion of the research agenda, and gives respectability to the tobacco industry. It also said that funding

inevitably creates conflicts of interest for recipient institutions if they have one department funded by the tobacco industry and another researching the harmful effects of tobacco. The code of practice will now be sent to all university vice chancellors and a wide range of medical and ethical organisations for comment to determine the final wording.

Tessa Jowell, minister for public health, congratulated the charity on producing the document. “This initiative is consistent with the government's commitment to ban tobacco advertising and to develop a tobacco control strategy,” she said. □

In brief

Antidrug chief announced:

Keith Hellawell, chief constable of West Yorkshire, is to be Britain's "drug czar," heading all government action against drugs, with a salary of £102 000 (\$163 000). His deputy will be Michael Trace, director of the Rehabilitation of Addicted Prisoners Trust.

Blood given by patients with CJD to be traced:

The British government confirmed that one patient suspected of having new variant Creutzfeldt-Jakob disease and three patients confirmed as having the disease have given blood. Although there is no epidemiological evidence to suggest that classic CJD has been transmitted between humans through blood transfusions, it is not known whether this will be true for the new variant form of the disease. The National CJD Surveillance Unit is following this up.

Xenotransplants carry risk of infection: British scientists have identified two different classes of endogenous proviruses from a kidney cell line of a pig. Endogenous proviruses are passed on in the germ line as proviruses and so are very difficult to remove when producing organs for transplants. The researchers found that the surface glycoproteins of the resulting viruses would allow them to infect human cells (*Nature* 1997;389:681-2).

Landmine campaigners win Nobel peace prize:

The Norwegian Nobel committee said the £600 000 (\$960 000) award would go in equal parts to the International Campaign to Ban Landmines and to Jody Williams, the campaign's coordinator.

Calman to step down: Sir Kenneth Calman, chief medical officer at the Department of Health, will leave next year to become vice chancellor and warden of Durham University.

Dissatisfaction with the NHS has risen: A survey by the King's Fund found that the number of people who were either quite or very dissatisfied with the NHS has risen by 55% since 1992.

US flight attendants win settlement over passive smoking

Deborah Josefson, *San Francisco*

In a landmark trial on second hand smoke 60 000 flight attendants have wrested a historic settlement from five major tobacco companies.

The flight attendants had filed a class action suit charging that they had suffered smoking related illnesses from being subjected to high concentrations of environmental smoke and seeking \$5bn (£8bn) in damages. The companies on trial were Philip Morris, R J Reynolds, Brown and Williamson, the Liggett Group, and the Lorillard Group. Also named in the suit were two lobbying groups funded by the tobacco industry—the Tobacco Institute and the Council for Tobacco Research.

Under the terms of the settle-

ment, the tobacco industry agreed to establish a \$300m research institute for the study, prevention, and treatment of tobacco related illnesses. The research institute will be named after Norma Broin, a non-smoking flight attendant who contracted lung cancer and initiated the suit against the tobacco companies.

Under the agreement, the individual plaintiffs received no money and the tobacco industry made no admission of guilt. The attendants are now free to seek individual damages, however, and the terms of the settlement may make it easier for them to win such suits. The burden of proof has been shifted from the plaintiffs to the defendants, so it

Norma Broin (second from left) and fellow plaintiffs celebrate

is now up to the tobacco companies to disprove that an illness was caused by passive smoking rather than the plaintiff having to prove that it was. Also, the cigarette manufacturers agreed to waive the statute of limitations requiring that an affected person sue within four years of discovering an illness, thus allowing many more people to claim damages.

In a statement the tobacco industry said: "The agreement was a common sense approach to resolving the class action aspects of the suit in a way which is consistent with the much broader legislation resolution now pending in Congress." The statement referred to the \$368.5bn proposed national settlement pending congressional and presidential approval (28 June, p 1849). The tobacco industry is expected to try to shield itself from further lawsuits under the terms of the national settlement.

However, Lawrence Gostin, a law professor at Georgetown University in Washington, DC, said: "This might well open the door to a lot of other lawsuits by other workers who are coerced up—those in factories, restaurants, theatres, and casinos—who have consumed a steady diet of second hand smoke."

The plaintiffs' case was strengthened by the testimony of numerous medical experts, including two former surgeon generals, who detailed the deleterious effects of passive smoke. (See pp 961, 973, 980.) □

Report calls for shake up for public health

Jacqui Wise, *BMJ*

Public health directors should be given clear responsibility for tackling health inequalities, according to a report from the Institute for Public Policy Research.

The study, *Reporting the Public Health*, finds that the annual reports produced by directors of public health are too varied in scope and quality and are a sadly wasted resource. Anne Davies, author of the report, argues that this is due to the confused status

and unfocused role of the directors and the fact that there is no clear guidance or coordination of health reports at a national level.

The Institute for Public Policy Research, a left leaning "think tank," says that public health directors should coordinate their reports to produce data for comparison with other similar areas and contribute to a national health audit. The reports should also be produced in full less often (every two to three years), with short annual updates, to make more efficient use of resources.

The report also calls for a new public health infrastructure, with a distinct pyramid and clear lines of accountability, that is outside the NHS Executive and answerable to the minister for public health. It says that direc-

tors should receive separate funding from the minister for public health for production and dissemination of their reports in order to affirm their independence from health authorities and to safeguard their integrity.

Ms Davies said: "It is important to have a strong independent voice—an advocate—for the public health, able to speak freely and where necessary to criticise health authorities, local councils, and other agencies whose policies have an impact on public health." □

Reporting the Public Health is published by the Institute for Public Policy Research, 30-32 Southampton Street, London WC2E 7RA, price £6.50 (plus 50p postage and packing).

Hormone replacement therapy increases risk of breast cancer

Jacqui Wise, *BMJ*

The risk of breast cancer increases slightly in women using hormone replacement therapy (HRT), and this risk increases the longer the treatment is used, according to a thorough reanalysis of data on more than 160 000 women.

Many individual studies of the effects of HRT on the risk of breast cancer have been published, but because results differ it has not been clear until now how great the increased risk might be and even if a risk existed at all.

Professor Valerie Beral, director of the Imperial Cancer Research Fund's Cancer Epidemiology Unit in Oxford, and her collaborators collated and analysed data on 52 705 women

with breast cancer and 108 411 women without breast cancer from 51 studies in 21 countries (*Lancet* 1997;350:1047-59). More than 900 of the women in the analysis had been taking HRT for 15 years or more.

The relative risk of having breast cancer diagnosed increased by a factor of 1.023 for each year of use among current users of HRT or those who had stopped using it in the previous four years. The relative risk was 1.35 for women who had used HRT for five years or longer.

The background incidence of breast cancer in women aged between 50 and 70 is 45 cases per 1000. Use of HRT for five years translates to about two extra breast cancers being diagnosed by the age of 70. Use of HRT for 10 years would mean an extra six cases per 1000 women and for 20 years, an extra 12 cases. Professor Beral said: "The increased risk with use of HRT is very similar to that seen if the menopause is delayed naturally."

The increased risk is reduced after stopping HRT and largely, if not wholly, disappears after about five years. Also the cancers diagnosed in women who had ever used HRT tend to be more localised and less advanced clinically than those diagnosed in never users. It is not clear, how-

Breast cancers associated with use of HRT

The *Lancet* has strongly criticised the Imperial Cancer Research Fund (ICRF) over the leaking to the press of a draft of the research paper linking hormone replacement therapy (HRT) and breast cancer.

Richard Horton, writing in the *Lancet*, said: "ICRF staff have pitted themselves against one another, decisions have been driven by greed for publicity, and the fundraising image of the ICRF seems to have become the charity's overriding priority."

The *Lancet* had agreed to publish the research on 18 October, but the article was leaked to the *Sunday Times*, which published a front page story on 5 October. As a result, the *Lancet* had to move the publication date forward to 11 October.

The report in the *Sunday Times* included a major error: "Among some groups of women receiving HRT, the risk of developing breast cancer is 2.3 times higher, or more than double that of non-users." In fact, the relative risk was 1.023, not 2.3—a 100-fold error.

Dr Horton asks why the ICRF has done nothing to investigate which researcher leaked a draft version of the HRT paper, thus jeopardising its accurate reporting and the health of thousands of women. He also criticises the fact that the communications department has recently been subsumed within the ICRF's fundraising work, and says that there needs to be an urgent independent inquiry, perhaps by the UK Charity Commissioners, into the workings of the organisation. "The blurring of publicity with fundraising risks a serious conflict of interest. The danger is that messages projected from ICRF research will be determined not by the scientific evidence but by the need to have a pristine fundraising image."

Ardi Kollah, head of communications at the ICRF, said: "This week's comment from Richard Horton in the *Lancet* regarding the paper on HRT and breast cancer is intemperate and draws inaccurate conclusions. We will be communicating with the *Lancet* in due course."

Cancers in women who use HRT tend to be more localised

ever, if this is due to a biological effect of hormonal treatment or the earlier diagnosis of breast cancer in these women.

The analysis also found that the excess risk of breast cancer is more obvious in women who are thin. Thinner women have a lower risk than fatter women of developing breast cancer, and so taking HRT brings them up to the level of risk of a fatter person, explained Professor Beral.

Professor Sir Richard Doll, a coauthor of the study, said: "Delaying the menopause by using HRT has advantages but it

also has disadvantages. There are obvious benefits—for example, in relieving the symptoms associated with the menopause and preventing osteoporosis and probably reducing the risk of coronary heart disease. But it does have the disadvantage of increasing the risk of breast cancer slightly. It is difficult to assess at this stage the overall balance of benefits and risks."

Professor Andrea LaCroix and Dr Wylie Burke, from the Fred Hutchinson Cancer Research Center and the Women's Health Care Center at the University of Washington, comment in an accompanying editorial that the report has many strengths, including the consideration of numerous confounding factors and the use of conservative 99% confidence intervals for all but the main comparisons. But they warn that despite the large numbers of women included in the analysis, only 12% of hormone users had been exposed to progestogens so the study may not truly reflect modern practice.

They said: "Because the data are based on observation of women rather than controlled experimental trials, the excess risk should be viewed as a possibility but not a certainty." But they said that the findings create an ethical responsibility for doctors to advise women of the increased risk of breast cancer with HRT. □

Hong Kong issues guidelines to prevent further medical blunders

Joanne McManus, *Hong Kong*

Hong Kong's Hospital Authority has issued a series of guidelines to improve the quality of clinical care in the public hospital system after a spate of medical blunders in public hospitals, some of which have led to deaths. Senior doctors in Hong Kong's 42 public hospitals have been advised to spend more time supervising and training and less time on paperwork.

Recent well publicised mistakes include the severing of a woman's right fallopian tube during an appendectomy; the removal of a section of a 4 year old's fallopian tube because the surgeon thought that it was her appendix; a junior nurse pumping milk instead of blood into a patient; a patient being given the wrong type of blood; an overdose of antibiotics being given to a patient with heart disease; and an operating room attendant pumping air into an elderly patient's bloodstream instead of into her pillow. Lack of experience among surgeons and nurses was largely to blame for the mistakes.

Sixty per cent of doctors providing hospital related services in Hong Kong work for the Hospital Authority, which provides 93% of hospital based services.

The authority is calling for a two tier system of supervision in all clinical units to ensure that junior doctors are directly supervised and trained by senior doctors.

The chief executive of the Hospital Authority, Dr Yeoh Eng Kiong, said: "The system ensures that a junior doctor will call for assistance and advice from a senior doctor when complex or difficult situations are encountered. Both will be held

responsible for the wellbeing of the patient treated." The guidelines also state that chiefs of service and ward managers should spend at least three quarters of their time in clinical duties and patient services; the target for consultants and nursing officers should be 90%.

Dr Poon Tak Lun, the president of the Public Doctors' Association, said: "The recommendations, when looked at one by one, are all correct and have to be done to improve care. But they also mean a larger workload for senior doctors. If additional resources are not provided then they can't be fully enforced." □

All junior doctors in Hong Kong will receive more supervision

AMA moves to tackle medical errors

Janice Hopkins Tanne, *New York*

The American Medical Association (AMA) has set up the National Patient Safety Foundation to try to reduce the number of mistakes happening in medicine.

A person faces a 1 in 200 risk of error in a hospital compared with a 1 in two million risk on an airplane, said Dr Lucian Leape of Harvard University's School of Public Health at a briefing held by the association last week.

To tackle the problem the AMA, several drug companies, the Department of Veterans Affairs (which operates the largest healthcare system in the United States), the Kaiser Permanente health maintenance organisation, and malpractice insurance companies have provided three years of funding to establish the National Patient Safety Foundation. The foundation, which will be based at the AMA's office in Chicago, will draw on expertise in the aviation, military, and nuclear power industries to fund research into identifying and preventing human and organisational error.

Dr Leape estimates that three million medical accidents occur in hospitals in the United States each year, with costs as high as \$200bn (£125bn). "The main reason we haven't addressed this problem is that we punish people for mistakes. Punishment gives the incentive to hide," he said. He said that when an error occurs, it is often a problem of the system, not the individual who takes the blame.

John Santell from the American Society of Health System Pharmacists said that hospitals can be protected against drug errors by the unit dose system used in 90% of US hospitals. Each patient's drug treatment is made up as a single dose in the pharmacy, individually labelled, and then sent to the person administering the dose, rather than having a nurse at the ward make up the dose from a larger container. However, Dr Leape warned that some managed care organisations are going back to making up the dose from a larger container to economise. □

Conflict over South African attempts to cut drug costs

Pat Sidley, *Cape Town*

Controversy continues to dog the South African ministry of health's attempts to introduce a change to the way in which drugs reach the market in South Africa. A third attempt to introduce a parliamentary bill that is designed to ensure drug prices are reduced looks set to end in conflict.

The Medicines and Related Substances Control Bill has pitted the large multinational drug companies against the government. One of the most contentious clauses in the bill would allow for parallel importing of drugs so that brand name drugs can be bought more cheaply. The drug companies claim that this will break their patent protection and

threaten international treaties.

The drafting of the legislation has also managed to create conflict between the controversial minister for health, Dr Nkosazana Dlamini-Zuma, and the Medicines Control Council—previously a staunch ally. A clause would allow the minister to override a decision of the regulatory authority if she deems it is in the public interest. She says that she hopes never to have to use the clause, but it may be necessary in certain circumstances—for example, if there is an outbreak of a rare infectious disease. The cochairman of the council, Professor Peter Folb, has warned of dire consequences of such a move and

said that even if the present minister has no intention of using the clause, others may not have the same reservations.

The bill—which is in a discussion process before formally being put to parliament in two weeks—also seeks to regulate the behaviour of dispensing doctors and drug companies. Current arrangements ensure a steady flow of cheap drugs to dispensing doctors, who are given many incentives to prescribe them. The doctors are also in open rebellion against the minister.

The fight between the multinational pharmaceutical companies and the government has taken on international dimensions. The United States government has made known its displeasure at what it claims is a breach of international trading regulations. Several pharmaceutical companies have threatened to withdraw from South Africa. □

Government injects cash to reduce winter crisis in NHS

John Warden, *London*

The British government is preparing to inject an extra £300m (\$480m) into the NHS for this winter in a tacit admission that patient care will deteriorate at current funding levels.

Existing resources have already been diverted to ease winter pressures (30 August, p 501), but ministers have concluded that more is needed. Previously they had said that no additional money would be released until the new financial year next April.

Chancellor of the Exchequer Gordon Brown now says that "careful and prudent" management has made it possible to transfer £300m to patient care during the winter. "We are re-allocating our priorities," he said.

The extra money is at the expense of the defence and trade budgets and assumes economies in the NHS in addition to the £100m savings in bureaucracy already in force. The new money includes £30m to be found from efficiency savings in the NHS. Health secretary Frank Dobson said the extra money is not just

an Elastoplast for the winter, but to modernise the NHS long term and break down the "Berlin Wall" between health and social services by funding increased home care. The government now can claim that it is almost meeting the BMA's estimate that £500m is needed for winter emergencies.

The about turn, however, opened the Labour government to the charge of crisis management and of departing from its election pledge to work within departmental spending ceilings already set by the Conservatives. This has proved to be incompatible with Labour's pledge to "save the NHS." The Conservatives are forecasting a further shortfall of £500m in NHS funding for 1998-9, for which the Chancellor allocated an extra £1.2bn.

Meanwhile, the Treasury's fundamental review of spending will search for new ways of financing the NHS. The long term problem may, in the end, have to be referred to a royal commission. The last time a government conceded a mid-year

British ministers have signalled broad support for plans for a new Europe-wide drink-drive limit of 50 mg per 100 ml proposed by Neil Kinnock, the transport commissioner. The prime minister Tony Blair signalled his support for road safety schemes by praising the former transport minister, Barbara Castle, who introduced the breathalyser to Britain 30 years ago.

subvention to the NHS was £100m in the winter of 1987-8, which led to the internal market reforms.

The new money was welcomed by health professionals as a necessary lifeline. Mr James

Johnson, chairman of the BMA's consultants committee, said that it would make it possible to open wards that had been closed, but until the NHS was properly financed it would be fire fighting every winter. (See p 1024.) □

Surgical training for overseas doctors to end

Jacqui Wise, *BMJ*

The council of the British Association of Plastic Surgeons voted last week to discontinue the overseas trainees diploma scheme after they failed to get funding for it to continue.

Brian Morgan, president of the association, said: "We are very disappointed. Obviously countries abroad are going to suffer, but also Britain will suffer because of a lack of people to carry out the service commitments."

Since 1988, when the scheme started, 93 trainees have taken part. The 32 trainees who are currently on the scheme will be able to finish training, but no more trainees will be taken on. In all, 23 countries have participated in the scheme, which

involved three years' training in two different units—one year at senior house officer level and two at registrar level.

The association approached the Department of Health and the British Council for funding to allow the scheme to continue but had no success. Mr Morgan said that he envisaged that training schemes carried out in other specialties may also be under threat because of similar problems.

Mr Morgan said the main reason that the scheme has been brought into jeopardy was the "Calmanisation" of training, which has led to an inflexible description of posts available to trainees and increased competition for these posts.

Dr Surendra Kumar, chairman of the Overseas Doctors Association, said that he was very upset that the scheme had to come to an end purely because of a lack of funding. "It's a sad day for developing countries and also for Britain." □

Patient's charter will emphasise patients' responsibilities

Jacqui Wise, *BMJ*

The British government announced last week that it will replace the patient's charter with a new NHS charter emphasising patients' responsibilities to the health service.

Greg Dyke, chairman and chief executive of Pearson television (but perhaps best known for bringing Roland Rat to British television screens), is to lead the project to modernise the charter. It will be published next July to coincide with the 50th anniversary of the NHS.

The health secretary, Frank Dobson, said: "The old patient's charter focused too much on patients' rights and on easily measured administrative targets. It encouraged consumerism, but made health professionals defensive and led to wasteful

reactions like appointing 'hello nurses' in accident and emergency departments."

The new charter will include not only targets on waiting times but also more information about quality of care so that people can make informed choices about their health.

Mr Dobson said that there had been a growth in the number of assaults, both physical and verbal, in accident and emergency departments, partly because of a crude misunderstanding of a patient's rights under the patient's charter.

The new charter would emphasise patients' responsibilities to the health service—for example, in keeping appointments and in treating NHS staff with respect. □

The prion hypothesis is finally accepted by the establishment

Professor Stanley Prusiner has won this year's Nobel prize for medicine for his pioneering work on prions. Deborah Josefson examines his groundbreaking and frequently controversial research

Stanley Prusiner, professor of neurology and biochemistry at the University of California, San Francisco, has won the 1997 Nobel prize for medicine for his work on prions. This new class of infectious agents are thought to underlie a variety of sporadic, transmissible, and hereditary neurodegenerative disorders including kuru, Gerstmann-Sträussler-Scheinker disease, fatal familial insomnia, Creutzfeldt-Jakob disease (CJD), scrapie, and bovine spongiform encephalopathy (BSE).

Professor Prusiner's work has long been controversial because it challenges conventional biomedical dogma which holds that an infectious agent must contain nucleic acid. The Nobel prize winner's revolutionary concept was that a deformed protein could serve as an infectious particle and propagate in the absence of genetic material. Professor Prusiner dubbed these proteins "prions"—short for proteinaceous infectious particles.

The Karolinska Institute, which bestowed the prize, said: "Stanley Prusiner has added prions to the list of well known infectious agents including bacteria, viruses, fungi, and parasites. Stanley Prusiner's discovery provides important insights that may furnish the basis of understanding the biological mechanisms underlying other types of dementia related illnesses—for example, Alzheimer's disease—and establishes a foundation for drug development and medical treatment strategies."

Professor Prusiner began his work on prions as a neurology resident in the 1970s after a patient died of CJD, a rare neurological disorder that affects one in a million people. In a review of the literature on the disease, he found that kuru (a disease of ritually cannibalistic people of Papua New Guinea, who ingested the brains of infected people), scrapie, and CJD had all been shown to be transmissible by the injection of diseased brain extracts into healthy animals. The infectious agent was thought to be a slow acting virus, yet numerous attempts to isolate this virus

Stanley Prusiner persisted with his radical theories on prions

were fruitless. Moreover, several procedures known to denature nucleic acids and inactivate viruses failed to eradicate the infectious principle in these extracts. When the extracts were exposed to protein denaturing agents, however, they were rendered uninfected.

Agent isolated

Intrigued, Dr Prusiner and his colleagues set out to isolate the infectious agent of scrapie, a disease of sheep so named because the afflicted animal incessantly scratches and scrapes off its skin. As suspected from previous work, no virus was isolated. The team did, however, find a protein, dubbed PrP, which transmitted the infection. Amino acid sequencing of this protein led to the identification of the gene specifying it. Further analysis showed that the gene was highly conserved and resided on the chromosomes of all mammals studied—from mice to men.

It seemed, then, that having a prion protein was normal. So how did it cause disease? Professor Prusiner speculated that an isoform of the protein might exist that could be responsible. Further work showed this to be the case. The prion protein was present in at least two forms—a normal form that does not cause disease (designated PrP^C) and another form that does (PrP^{Sc}). The proteins differ in their tertiary structure, with the normal protein exhibit-

ing a tightly coiled α helical configuration while the PrP^{Sc} form is in unwound β pleated sheets.

Professor Prusiner found that the prion diseases are due to abnormal protein conformations, which occur when the normal tightly coiled α helical structure unwinds to form the unwieldy, but more stable, PrP^{Sc} form. The therapeutic implication of these observations is that anything which could stabilise the native α helical structure could prevent the progression of prion diseases.

Accordingly, Professor Prusiner and his colleagues are working on developing drugs which bind to the α helical form and stabilise it. A further therapeutic avenue relies on breeding sheep and cattle that lack the prion protein. Preliminary work with transgenic "knock out" mice, in which the gene for PrP^C is entirely eliminated, have shown that these mice are resistant to contracting scrapie, even when inoculated with the prion that causes disease. Interestingly, these mice—lacking the PrP^C gene—appeared entirely normal. Thus, although it is unknown what the function of the normal prion protein is, at least in mice, it does not seem to be essential for life.

The BSE epidemic in Britain is thought to be secondary to the practice, outlawed in 1988, of supplementing cattle feed with sheep offal. The prion that causes scrapie is believed to have been

transmitted from sheep to cattle and thence to humans as new variant CJD. So far, 20 cases of new variant CJD have been identified, and they differ from conventional CJD in having a younger age of onset and shorter course. Professor Prusiner has proposed that the breeding of prion resistant domestic animals might be one way of preventing prion transmission to humans (*Science* 1997;278:245-50).

Awarding the Nobel prize to Professor Prusiner represents official acceptance of the prion hypothesis. None the less, sceptics remain. Dr Robert Rohwer, director of neurovirology at the Veterans Affairs Medical Center in Baltimore, calls prions the "cold fusion of infectious disease." Dr Laura Maneulidis of Yale University thinks that a virus will eventually be found to have caused prion-type diseases and worries that the Nobel prize will prevent further inquiry. "That's the problem with Nobel prizes. If people think that everything is decided, you can't possibly risk going against the grain," she said.

Heretical hypothesis

The irony is that Professor Prusiner did go against the grain, and he endured decades of ridicule for persisting in his notions. Dr Zachary Hall of the National Institute of Neurological Disorders and Stroke said: "It's a very, very well deserved prize. The ideas were bold and the hypothesis was heretical. But he pushed unrelentingly and was unfazed." Dr David Baltimore, himself a Nobel laureate and former director of the Whitehead Institute and Rockefeller University, said, "These are the mythological stories of science—people who have really kept their own faith for so many years and lived through a period of opprobrium and finally are discovered to be right."

In an interview after learning he had won the prize, Professor Prusiner said that scientists were right to doubt him: "I think that scientists should be very reticent to accept new ideas—99% of new ideas are wrong. We have to be very tough on our colleagues." □