

# NEWS

## Pig organ transplantation brought one step closer

Rival teams of scientists announced last week that they had succeeded in cloning “knockout” pigs, which lack one copy of a gene that prompts the human immune system to reject transplanted pig organs. The researchers say this is the first step towards creating pig organs that are suitable for transplantation into human beings.

Researchers removed the gene for  $\alpha$ -1,3 galactosyl transferase, an enzyme that puts a sugar molecule on the cell surface of pig cells. The presence or the sugar molecule triggers “hyperacute rejection” and has been the biggest hurdle in pig-to-human transplantation.

PPL Therapeutics (Edinburgh, UK) announced on Jan 2 that five piglets without the  $\alpha$ -1,3 galactosyl transferase gene had been born on Christmas day at its US laboratory in Virginia. Meanwhile, scientists at the University of Missouri, in collaboration with Immerge BioTherapeutics, a joint venture between Novartis and BioTransplant Incorporated, announced the following day in *Science* that in September and October, 2001, they had created four cloned pigs also lacking the gene ([www.sciencexpress.org](http://www.sciencexpress.org)).

“This was really the step we believed was technically the most difficult and clinically most important”, David Ayares, vice president of research at PPL, told *The Lancet*. “Until we get over the hyperacute rejection step we won’t be able to see what additional changes we believe we are going to have to add.” Ayares thinks they will also have to add complement inhibitor genes and genes involved in restoring normal coagulation to prevent long-term organ rejection.

Some experts are concerned,

however, that viruses present in pig tissue could be passed on to humans, such as the porcine endogenous retrovirus. According to Jonathan Allan (Southwest Foundation for Biomedical Research, San Antonio, TX, USA), human beings and primates are protected from other animal viruses by antibodies that neutralise the viruses. But Allan says that removing the gene that causes hyperacute rejection will also take away the body’s natural defence mechanism against porcine viruses.



Litter of cloned “knockout” pigs

“When the retrovirus buds from the cell surface as it replicates, it takes a piece of the cell membrane with it, which happens to have the  $\alpha$ -gal on it”, Allan explains. “Once you take away  $\alpha$ -gal, the antibodies are not going to neutralise the pig virus, so you’ve taken away one of the most important means of self-defence. Anything you do to blunt the immune system will also improve the chances of a viral infection.”

Alix Fano, director of the Campaign for Responsible Transplantation (New York, NY, USA), a group opposed to xenotransplantation, believes there are alternatives. “If all the private and public money that has been poured into xenotransplantation—over

\$1 billion—had been poured into disease prevention and increasing the pool of human organs for transplantation, we would have reduced the number of people on transplant waiting lists by now.” Fano also believes that legal measures, such as presumed consent laws, passed in countries such as Singapore, France, Belgium, and Italy, could increase the number of human organs available for transplantation.

“In my opinion, xenotransplantation is about profits—it’s about making money”, adds Fano. “It’s not about altruism or caring for human health because if we did care we would be doing things that are more therapeutically effective, less expensive, and less dangerous.”

Analysts estimate the xenotransplantation market is worth US\$5 billion, and competition is intense among the rival biotechnology companies. PPL was criticised by some scientists for trying to get “one up” on its rivals, by announcing its results the day before Immerge BioTherapeutics was due to publish its results in a peer-reviewed journal. “I think it’s shameful to do that”, comments Allan. PPL scientists have now submitted their findings to a peer-reviewed journal.

Ayares admits they had “an inkling” that other groups were “nipping at their heels”, but he says that Immerge BioTherapeutics’ results had no effect on the timing of their announcement. “As we’re a publicly traded company, we’re legally bound to release any stock-sensitive information as soon as we have it.” Indeed, following the announcement, shares in PPL on the London Stock Exchange soared by 40%. These were to fall by 15% the following day, when it was revealed that Dolly the sheep, the first mammal to be cloned from differentiated adult cells, had developed arthritis (see panel).

The future of xenotransplantation is still uncertain, and PPL, despite being one of the most successful companies in this field, has only limited funding. It is therefore seeking \$15 million in investment to fund its xenotransplantation research.

Helen Frankish

### Dolly the sheep develops arthritis

Dolly the sheep, the first mammal to be cloned from adult cells, has developed arthritis at the comparatively young age of five and a half, Ian Wilmut (Roslin Institute, Edinburgh, UK), one of her creators has revealed. Arthritis is not unknown in sheep, whose average lifespan is 12–14 years, but Dolly has developed it at an unusually young age, and in two joints not normally affected. However Wilmut said it was not known whether Dolly had developed arthritis as a result of the cloning process, or whether it was “an unfortunate accident”.

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PA Photos

## Transcription factor shown to have a role in triggering asthma

**A**sthma could be triggered by the loss of a transcription factor involved in regulating the immune system, according to a report by US scientists this week.

Laurie Glimcher (Harvard School of Public Health and Harvard Medical School, Boston, MA, USA) and colleagues report that people with asthma have less T-bet, a transcription factor that activates *IFN- $\gamma$*  in T-helper-1 cells (Th-1), in their lungs than non-asthmatic people. Furthermore, mice lacking the *T-bet* gene spontaneously developed signs of the disease. "These data show that T-bet regulates immune response in vivo and controls the Th-1/Th-2 cell balance, which is known to be important in asthma", Glimcher told *The Lancet*.

The researchers stained lung tissue sections from healthy people and seven patients with allergic asthma with a monoclonal antibody to T-bet and found lower levels of the protein in asthmatic patients.

The result led the group to test whether lack of T-bet could trigger asthma. They looked for signs of the disease such as airway hyper-responsiveness (AHR), inflammation, and remodelling in mice with targeted deletions of the *T-bet* gene.

Deletion mice showed increased AHR in response to challenge with the bronchial constrictor methacholine compared with normal mice. The T-bet deficient mice had also undergone airway remodelling and airway inflammation (*Science* 2002; 295: 336–38).

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Robert Harding

A new target for asthma drugs?

Glimcher cautions that findings in mice might not apply to people. "There is always the question of how much any mouse model resembles human disease." But she adds "in this model the response is spontaneous rather than produced by an external antigen, thus, it mimics human asthma more closely than models that use external antigens".

Patrick Holt (TVW Telethon Institute for Child Health Research, Perth, Australia) comments that

"these findings provide a new line of evidence suggesting that an imbalance between Th-1 and Th-2 cytokines is a central feature of asthma pathogenesis".

However, Michael Holtzman (Washington University School of Medicine, St Louis, MO, USA) asks "do the decreases in T-bet levels in asthma just reflect a decrease in the number of Th-1 cells or do they represent a more fundamental down-regulation of this factor in the Th-1 population?" He also wonders whether further study of T-bet can provide additional mechanisms for asthma. "It will be interesting to see direct comparisons of T-bet with other Th-1 components. These types of comparison will help show whether T-bet provides different information from what others have suggested before—ie, that down-regulation of Th-1 responses leads to upregulation of Th-2 responses."

Glimcher hopes that T-bet will prove a new target for the development of asthma drugs. "If you could increase T-bet activity, especially locally in the lung, you would predict that this would form an effective treatment for asthma", she says.

Sarah Venis

## Stem-cell transplantation hope for Parkinson's disease treatment?

**R**esearchers have taken a step forward in the development of stem-cell transplantation for treating neurodegenerative disorders such as Parkinson's disease.

According to a new study, mouse embryonic stem (ES) cells develop into functional dopaminergic neurons when transplanted into the damaged host brain. "This is to our knowledge the first report showing efficient in-vivo expansion of embryonic stem cells into dopamine neurons with functional effects in an animal model of Parkinson's", Ole Isacson, one of the investigators, told *The Lancet*.

Isacson and co-workers (Harvard Medical School/McLean Hospital, Belmont, MA, USA) transplanted mouse ES cells into the striatum of rats previously injected in one side of the brain with a neurotoxin that destroys dopaminergic neurons. Rats with these brain lesions turn towards the damaged side of the brain when they are given the dopamine-releasing drug amphetamine—an

effect which can be reduced, or even abolished, by a successful transplant.

To assess the function of the ES cells after grafting, the investigators measured turning behaviour after 5, 7, and 9 weeks (*PNAS* 2001; www.pnas.org; early edition). After 12–14 weeks, they looked for the presence of dopaminergic neurons histologically by staining brain slices for specific dopaminergic markers.

The team identified dopaminergic neurons in the striatum of transplanted rats, suggesting that the grafted ES cells had successfully differentiated into adult dopaminergic neurons within 14–16 weeks. They also found that amphetamine-induced turning was significantly reduced at 7 and 9 weeks, indicating that the grafted ES cells had not only differentiated, but had also integrated into the brain and were releasing dopamine in response to amphetamine. To confirm these results, the researchers also used imaging techniques (PET and MRI) to demonstrate the presence of func-

tioning dopaminergic neurons in the grafted striatum.

Transplantation as a treatment for Parkinson's disease is not a new concept, but due to ethical and practical considerations surrounding use of aborted fetal tissue, an alternative source of dopaminergic neurons needs to be found. If, as shown in this study, grafted ES cells can differentiate, integrate, and restore normal function, they could represent an ideal cell source as they are self-renewing and sustainable. However, other aspects also need to be carefully considered.

"While this important study is very encouraging, a small number of animals developed teratoma-like tumors and had to be excluded from the study", comments Clive Svendsen (University of Wisconsin-Madison, WI, USA). "This elegantly reveals both the excitement and necessary caution that needs to be exerted before taking ES cells to the clinic".

Rebecca Love

## Study surveys brain-death guidelines in 80 nations

The concept of brain death has gained acceptance worldwide, according to a new study. But at the same time, the criteria for determining whether a patient is brain dead can vary considerably from country to country, the study finds.

Elco Wijdicks, a specialist in critical care neurology at the Mayo Medical Center (Rochester, MN, USA), surveyed the brain death guidelines for adults of 80 nations. Of those countries surveyed, 70 (88%) have adopted guidelines allowing the diagnosis of brain death, he reports (*Neurology* 2002; **58**: 20–25).

In those countries with guidelines, the definition of brain death is relatively uniform from country to country. The definitions typically require that the patient be in an irreversible coma, show no motor response to painful stimuli, and lack all brainstem reflexes. The patient should also have no other condition that might be responsible for their unresponsiveness, such as drug intoxication,

hypothermia, or a severe metabolic derangement.

But Wijdicks also found that the requirements for making the diagnosis of brain death were markedly different in many countries, even in different jurisdictions of the same country. In the USA, for example, federal law defines brain death but allows the individual states to draw up the requirements for making the diagnosis. In most states, one physician can make the determination alone, in others a second physician must confirm the diagnosis independently, but in two states a nurse can declare a patient dead provided there is subsequent certification by a physician within 24 h.

In Turkey, on the other hand, an organ-harvesting law requires that a cardiologist, a neurosurgeon, a neurologist, and an anaesthesiologist examine the patient. Japan's guidelines in addition to neurological examination require that CT scan show "irreparable lesions"; that if the coma was the

result of a cardiac arrest, the cause of the cardiac arrest be determined; and that an apnoea test, which determines whether a patient can breathe spontaneously, be performed after loss of seven specified brainstem reflexes and after an isoelectric EEG.

Of particular concern to Wijdicks were variations in guidelines for apnoea testing, which indicate that in many countries these tests are not being done uniformly. The findings suggest, Wijdicks concludes, that perhaps there is a need for either individual national or international taskforces to work on standardising guidelines for brain death determination. These taskforces could address the most important inconsistencies in guidelines, in particular, develop uniform criteria for apnoea testing and, overall, simplify the process of diagnosis, which Wijdicks feels, has become unnecessarily complicated in many countries.

Michael McCarthy

## Maternal genotype alters effect of smoking on infant birthweight

Variations in genes that help metabolise the by-products of cigarette smoke are associated with reduced birthweight among infants born to mothers who smoke, US researchers report this week.

"Our data show that a subgroup of pregnant women with certain metabolic genotypes appeared to be particularly susceptible to the adverse effect of cigarette smoke, suggesting an interaction between metabolic genes and cigarette smoking", the researchers state.

To better understand genetic susceptibility to cigarette smoking in relation to adverse outcomes of pregnancy, Xiaobin Wang and colleagues studied metabolic genes in 741 mothers who gave birth at Boston Medical Center, MA, USA. 174 women had smoked at some point during pregnancy and 567 had not.

The researchers concentrated on *CYP1A1* and *GSTT1*, genes that can vary in levels of expression and are involved in metabolising chemicals in cigarette smoke.

The study indicates that, irrespective of genotype, smoking adversely affects the health of an unborn infant. However, maternal *GSTT1* and *CYP1A1* genotypes can, to some extent, alter the effect of cigarette smoking on infant birthweight. For

*CYP1A1*, mothers who smoked and who had the Aa or aa genotype had a 3.2 times increased risk of having a low birthweight baby compared with 1.3 in mothers with the AA genotype. For *GSTT1*, the absent and present genotypes carried a 3.5 and 1.7 times increased risk, respectively, of having a low birthweight child (*JAMA* 2002; **287**: 195–202).

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**Worse for some babies than others?**

Wang cautions that the results should not yet lead to prenatal screening of women for these genes. "Our study is the first step in investigating how genetic susceptibility interacts with environmental exposures to effect infant birthweight. Low birthweight is a complex entity and many environment and genetic factors may be involved. Therefore, much work remains to be done." She adds, "Our hope is that this work will open up new

areas of research that will lead to better understanding of the causes of low birthweight and ultimately to a reduction in the number of tragic cases of low birthweight and infant mortality."

George Vogler and Lynn Kozlowski, who wrote an accompanying commentary (*JAMA* 2002; **287**: 241–42), told *The Lancet* that, "while prevention of all maternal smoking would be the ideal outcome of any intervention, the ability to identify individuals at particularly high risk of an adverse outcome in response to smoking is intriguing. The complexity of genetic and environmental influences on low birthweight makes genetic screening impractical. However, enhanced ability to predict individual differences in response to intervention in other contexts could improve the effectiveness of individually tailored therapeutic programmes."

Maternal cigarette smoking has been identified as the single largest modifiable risk factor affecting the growth of unborn babies in developed countries. However, not all women who smoke during pregnancy have low birthweight children. This work should help to target more effectively individuals at highest risk for adverse outcomes.

Abigail Pound



## Common drugs and the pursuit of a good night's sleep

Sleep is an essential part of our lives. Yet, we know relatively little about how sleep is regulated or what disrupts it. There are more than 90 recognised sleep disorders, many of which are very common. For example, a recent report estimated an 11.9% prevalence for insomnia in Norway (*Sleep* 2001; 24: 771–79). Many sleep disorders are associated with medical or psychiatric conditions, but for each disorder some cases—no-one is sure how many—are induced by commonly prescribed drugs. Little research is being done on these side-effects, says Merrill Mitler (Scripps Research Institute, La Jolla, CA, USA), who lists methylxanthines, ethanol, non-sedating antidepressants, and anti-Parkinson's drugs among those that can disrupt sleep. "This does not mean patients should stop their medication. Instead, doctors must learn to adjust medications and their timing to minimise these undesirable side-effects", he stresses.

"We know a lot about what happens in our brains when we are asleep and awake but we know much less about the control of these events", explains Joan Hendricks (University of Pennsylvania, Philadelphia, PA, USA). "If we could get at these basic mechanisms we would be better able to help people with sleep disorders." Hendricks studies sleep in fruit flies. "In these insects, which sleep for 8 h a day, we have discovered that cAMP response-element binding protein [CREB] promotes wakefulness. Sleep also promotes wakefulness, so maybe it acts through the same signalling system", she suggests (*Nat Neurosci* 2001; 4: 1108–15). No prescription drugs directly target CREB but, says Hendricks, "any drug that increases neural activity will upregulate CREB" and could promote waking.

While CREB is a prime candidate for the body's wake-up call, adenosine is the front-runner for a sleep-inducing signal. Accumulation of extracellular adenosine in the brain seems to promote the onset of sleepiness after prolonged wakefulness, explains Mitler. "Drugs containing methylxanthines, for example some of the asthma drugs, probably cause sleep disturbances through this pathway." And everyone knows about the sleep-disrupting effects of the methylxanthine caffeine.

What about other prescription drugs that disrupt sleep? "Many neurotransmitters are involved in initiating and maintaining sleep", says Timothy Roehrs (Henry Ford

Hospital, Detroit, MI, USA), "so any drug that disrupts normal neurotransmitter functioning can have sleep-disrupting effects." Roehrs' recent interest is in ethanol which, at high doses, can disturb sleep. However, ethanol can also be sedating. Among

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### More sleep research needed

its effects on neurotransmitters, ethanol works synergistically with  $\gamma$ -amino butyric acid (GABA) to hold open the GABA receptor ion channel, thus facilitating an inhibitory transmitter. Roehrs has found that low doses of ethanol lengthen stage III/IV sleep in insomniacs but have no effect in normal sleepers. Stage III/IV sleep is considered deep, restorative sleep and people with insomnia tend to have less stage III/IV sleep than normal sleepers so maybe this is why insomniacs will self-administer alcohol if given the chance. Old hypnotics, such as benzodiazepines, suppress stage III/IV sleep but newer hypnotics do not. However, says Roehrs, "if you compare old and new hypnotics, even though the patient gets more III/IV sleep with the latter, they typically report no subjective difference in the morning".

The complexity of the relation between sleep laboratory data and subjective reports is a recurring theme in sleep research. Antidepressant drugs provide another example and also illustrate the complex interplay between illness-induced sleep disruptions and those caused by the cure. "The effects on sleep of depression versus those of antidepressants are hard to tease apart", says Karl Doghramji (Thomas Jefferson University, Philadelphia, PA, USA). "Also, two medications with similar effects on depression can have very different effects on sleep architecture." Doghramji describes a study in which the selective serotonin reuptake inhibitor (SSRI) fluoxetine decreased sleep quality whereas the non-SSRI antidepressant nefazodone improved sleep quality according to lab measurements. "Depression decreased equally with both drugs and both sets

of patients reported sleep improvements", says Doghramji. "Similarly, the suppression of rapid eye movement sleep [REM] by tricyclic antidepressants has been correlated with efficacy. Many of the newer antidepressants also decrease REM sleep but there is little known correlation between this objective sleep measure and subjective responses. Our understanding of the implications of these data is in a state of infancy, but as a clinician I would tend to choose those drugs that improve sleep, particularly for patients who have a pre-existing sleep problem." This counts out most SSRIs, which probably cause sleeplessness by stimulating the 5HT<sub>2</sub> postsynaptic receptor.

Parkinson's disease is another illness in which both the disorder and therapeutic drugs affect sleep. "There is a swamp of contradictions in the literature about anti-Parkinson's medications and effects on sleep", says Mitler. "We don't even have a good database on L-dopa. Some reports say it is alerting; others say it sedates. We have to make clinical decisions about which drug to prescribe in an information vacuum." Mitler hopes to remedy this, at least in part, in his studies on L-dopa and sleep patterns.

No-one doubts, however, that dopamine agonists cause nightmares, says James Pagel (University of Colorado Medical School, Denver, CO, USA). "How many nightmares are associated with prescription drug use is not clear but nightmare occurrence has been reported in the past 10 years for 36 different drugs. Most are medications that affect neurotransmitter levels", he explains, "but some other drugs also cause nightmares, for example, ciprofloxacin. Until recently clinical trials did not ask about dreaming as a side-effect. With standardised trial reports, at last we are getting real data about the impact of medications on dreams. It's kind of delightful to have that and it's going to shake up the whole field."

Others are less optimistic about progress in understanding how common drugs affect sleep. "Drug manufacturers are not particularly interested in showing the shortcomings of their medications", says Mitler. In the end, concludes Hendricks, "we will probably need to unravel the molecular basis of sleep regulation before we can understand how drugs alter sleep to both good and bad effect".

Jane Bradbury

## LONDON National health service to face a difficult year

One thing seems certain about 2002: it will be a year of change in the National Health Service (NHS). There are three separate fronts. Two involve block contracts of patients travelling to hospitals with spare capacity around the UK or the continent. The third involves an increasing number of NHS patients being treated in private hospitals also to reduce waiting times.

Compared with the first two changes, the third idea involves much more risk—or “calculated risk” as the health secretary prefers to refer to it—with the transfer of 75% of the NHS’s £50 billion plus budget to 400 untried and untested primary care trusts. This is billed as proof of a new spirit of devolution in Labour’s control and command management structure, but in reality it is merely transferring funds from one local system of administration—the current 90 health authorities—to another.

It is easy to predict some developments. Two types of stories are likely to emerge from the new contracts with continental hospitals, which will be mostly in Germany, Belgium, and France, and neither will help the government. The first will be full of praise for the efficiency and expertise of the foreign clinical teams compared with the UK’s clinicians—with reminders that France once topped the WHO league table of effective health systems compared with the UK’s lowly 18th position. The second category of story will involve continental errors and report the misinterpretation or misunderstanding of patients’ wishes. Tabloid editorials will condemn ministers for approving the exodus of patients.

A similar double-edged view of the increased use of private hospitals is likely to emerge. The NHS has already signed its first contract with a private hospital to work fulltime on reducing NHS waiting lists. Several of the new 20 fast-track 24-h surgery units are being earmarked for private sector innovation. But, like the relief being provided by continental hospitals, there will be two categories of news story about private sector NHS operations and neither angle will help the government. Success stories where the comfort and care of the private sector is described in detail will be contrasted with the thread-

bare conditions in some NHS hospitals. And reports about private hospital mistakes will prompt public-service union protests on their use and angry resolutions at Labour’s annual conference.

Both sectors together are unlikely to treat more than 250 000 patients,

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### No more long waits?

which is tiny compared with the NHS caseload: eight million hospital admissions a year, 14 million accident and emergency attendances, and 45 million outpatient visits. But in spite of the marginal nature of this work, acres of news stories will concentrate on it.

The move to 400 primary care trusts is regarded by many as a step taken too early. It has distracted

**“The Wanless report in November calculated a staggering £267 billion shortfall when compared with the average EU investment during the past 26 years”**

managers from the host of other reforms currently being pushed through under Labour’s 10-year plan. It has meant the abolition of the existing 90 health authorities (plus most of the regional offices), requiring these managers to search for new posts in the new 30 strategic health authorities or 400 primary care trusts. It is not quite as big a step as it looks because most of the commissioning for the new financial year that starts in April will already have been done by existing health authorities.

The first new item to emerge in this new year will be the government’s response to the Kennedy

inquiry into medical standards. Ministers are expected to link their response to this massive report with their response to the proposal for a strict new revalidation process. This strategy has been proposed by the General Medical Council, which provides all medical practitioners with their licence to practise. Under this proposal, all doctors would face a systematic reassessment of their competence to practise every 5 years before being relicensed.

Finance will remain high on the agenda. Gordon Brown, the chancellor of the exchequer, in his prebudget speech in November made it clear that health will be enjoying even further increases to the current record spending programme. The government’s third comprehensive 3-year spending review will be released in July.

The Tories are currently touring the continent looking for new ideas. They are already insisting on the promotion of more private medicine on the grounds that this would relieve the pressure on the NHS. They have also broken with tradition by saying the party would put public services before tax cuts. But they have not yet signalled any readiness to support an increase in taxation, which will surely be needed if the serious under-investment in the NHS is to be repaired. The Wanless report in November (see *Lancet* 2001; 358: 1971) calculated a staggering £267 billion shortfall when compared with the average EU investment during the past 26 years.

Meanwhile central interference, alas, will continue. Just as health ministers belatedly recognised they had set too many targets for the NHS and thus reduced them to 20, along came the chancellor and the prime minister with many extra targets of their own. Just as health ministers can be indicted for their micromanagement of the NHS, so the prime minister and chancellor can be condemned for micromanaging health ministers. Worse still, far from being united, the two top ministers are in open competition with each other, both having commissioned independent reports on the future of health. It seems the NHS will continue to be never far from heated political dispute.

Malcolm Dean

## Argentina's economic collapse creates serious problems for health services

Argentina's economic collapse has had a drastic impact on the health-care system, according to reports from hospitals, doctors, pharmacists, and the drug industry.

The scale of the crisis became apparent when Argentina's President, Eduardo Duhalde, was forced to appeal to the government of neighbouring Brazil for emergency supplies of insulin after drug firms cut the manufacture and supply of many essential drugs. However on Jan 8 the national ombudsman, Eduardo Mondino, secured an order from a federal court that required the pharmaceutical industry to resume supplies at prices used on Dec 3—before the country's currency crisis.

Hospitals in Buenos Aires province, which is home to more than a third of the population, have reported severe shortages of other essential drugs and medical supplies. For accident and emergency work, hospitals have been forced to use reserve stocks of antibiotics. All minor operations have been postponed, as hospital administrators and general practitioners confront the pressing problem of drug shortages.

Exactly who is to blame for the drug shortages has prompted claims and counter-claims. Drug manufacturers and suppliers decreased production and withheld deliveries unless they were paid in US dollars, rather than the Argentine peso

which has slumped in value since the newly elected president ended the one to one parity between the two currencies.

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### Patients may face hard times ahead

Pharmacists faced severe cash problems because health insurers were no longer able to reimburse prescription charges due to their own financial problems. In response pharmacists have demanded full payment in cash from all patients, including pensioners. Drug manufacturers have blamed the shortage of drugs on retailers for over-ordering and hoarding supplies, in the expectation of price increases.

Duhalde convened a meeting on Jan 5 with pharmaceutical industry leaders and representatives of retail pharmacists who agreed to resume normal operations. They also promised drug price stability—despite effective devaluation of the peso—in return for a commitment

from Duhalde that he would not introduce price controls and that the federal government will be prepared to contribute US\$100 million of the US\$600 million owed by the national pensions fund. Retailers insist that they need this money to finance restocking.

Spokesman for the professional chamber representing pharmacists in the federal capital (Colegio de Farmacéuticos y Bioquímicos de la Capital Federal) Oscar Oviedo said: "The rules are not clear. Some drug companies are only making limited deliveries. Some pharmacists are over-ordering. But prices are also being forced up because a few retailers will pay any price to acquire stocks."

On Jan 7 Duhalde announced a preliminary response to the crisis, which included the amalgamation of the ministries responsible for health, social development, and social security. At the time of going to press, he had yet to name the minister in charge of this new operation.

Meanwhile it has emerged that Duhalde's wife Hilda—also known as Chiche—will coordinate assistance programmes in which federal payments are made to alleviate problems associated with poverty—recalling the work of an earlier, charismatic 'first lady' Eva Peron.

Graciela Iglesias-Rogers

## Rival independent doctors group emerges in Kenya

A split could emerge among Kenya's medical professionals following an announcement that a new professional body is to be launched. Fears are being expressed that the proposal to form the Kenya Association of General Practitioners would weaken the Kenya Medical Association (KMA), which has supported doctors' rights for many years.

It all started last December when an advertisement in the *Daily Nation* newspaper announced the proposal to form a Kenya Association of General Practitioners, which would improve the health care of the people of Kenya. According to the notice, the group will re-install the speciality of general practice/family medicine to its rightful place as the bedrock of good medical care in Kenya. The association will "represent the interests of general practitioners in all aspects of their work", continued the announcement.

The announcement, which was signed by the chairman of the group's steering committee but whose name was not mentioned, gave the impression that the medical profession was in a mess and that reform and a new doctor's organisation was needed.

The concerns are not unwarranted: KMA has had problems in negotiating doctors' salaries and stamping out allegations of corruption. The KMA and the government has also had to face the exodus of doctors from Kenya.

Kenyan doctors have also called for a stronger Medical Practitioners and Dentists Board. On Sept 2, the Western Kenya region's board chairman Samson Ndege called for the transformation of the board. He said: "The board is like a toothless bulldog as all its activities are controlled by the government."

He said the government should

withdraw from running the board. The board should be given responsibility to punish errant members and promote the interests of medical professionals. The East African country's government has appointed seven out of ten officials of the board.

The chairman of the KMA, James Nyikal, shrugged off the threat saying the new organisation is welcome and "can not affect us at all". It is meant for general practitioners, he said, and there would be no harm to the KMA—the KMA encompasses various specialists including gynaecologists, physicians, and dentists.

However Douglas Ontomwa, a private doctor, said that the launch of the new group could be an effort to derail the bargaining power of the KMA on salary negotiations with the government.

Samuel Siringi



## French general practitioners strike for higher fees

About 80% of France's 55 000 general practitioners (GPs) went on strike for higher salaries from Christmas eve until New Year's day, which left patients no choice but to call emergency ambulance services or be forced to wait for hours for treatment in hospitals.

Since mid-November, 2001, most GPs have refused to visit patients between 8 pm and 8 am if the patient's health insurer will not pay their increased consultation and home visit fees. In December, doctors decided to extend their "night strike" with a "weekend and holiday strike", which affected all health services during the end of year holidays.

In France, most patients are used to calling their GPs outside normal business hours, and can easily reach a doctor if their regular physician is not available at night or at weekends. But the strike forced patients to change their habits and public emergency services were not always equipped to

face the sudden increase in patients. From Dec 22–26 and Dec 28 to Jan 2, emergency ambulance services received up to another four calls per hour on top of the normal call out rate.

Exhausted emergency doctors were forced to ask people not to call if they had minor illnesses or injuries. However many patients went directly to hospitals' emergency units but had to wait hours before receiving treatment.

Talks between trade unions, health insurers, and the government were to resume on Jan 3, but doctors have already threatened to hold another weekend strike in January until they satisfactory salaries. They have asked for an increase on their normal consultation fee from US\$15 to \$18 and a

30% increase on their home visit fees, which should rise from \$18 to \$27.

Doctors consider that the French health insurance scheme could finance the request without difficulty but the insurers says they cannot afford such new expenses. Trade unions recall that, since 1995, 10% of all GPs have closed their practice or started a new job because of their poor working conditions and low income, and that the number of young doctors wishing to become a GP is dramatically decreasing.

They warned that doctors cannot continue to offer a high quality service without appropriate remuneration.

*Denis Durand de Bousingen*

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Interns strike in Dec, 2001

## Mixed reactions to approval of human ova imports into Israel

Israel's Health Minister, Nissim Dahan, approved an unprecedented amendment to regulations for in-vitro fertilisation (IVF) on Dec 24, that will enforce supervision of imported fertilised human ova and authorises the use of commercially purchased human organs or tissues.

The move is seen as a major advance by most IVF experts. But critics have called the revision another impediment to passing comprehensive IVF legislation, which could ensure that Israel's donor population fulfils the needs of the 3000 infertile women waiting for IVF treatment.

The demand for an interim solution arose about 5 months ago when two leading fertility experts issued a formal complaint to the Health Ministry and warned that ova from donors in Eastern Europe were at risk of being infected by HIV and other sexually transmitted diseases. In response "the [Health] Minister moved immediately to halt this process, concerned for the health of the women involved", said Mordechai Halperin, the Health Ministry's chief officer of medical ethics.

However 100 Israeli women who had started IVF treatment and were about to receive fertilised eggs from gynaecologist Ilya Barr (American

Medical Center, Rishone Letzion) petitioned the Israel's Supreme Court. The Health Ministry reconsidered and appeared in court with new interim regulations, which authorised imported egg donation.

Head legal counsel to the Health Ministry, Mira Hibner-Harel, said the new regulations, which will come into effect on Feb 5—are a bridge to comprehensive legislation that "will probably become law within 6 months" and would expand the donor population to satisfy demand. Later this month, Hibner-Harel will lead a delegation to Romania to set up procedures "in close coordination with the Health Ministry" assuring that all ova would be handled "under strict medical and safety conditions equivalent to those in Israel". Only these officially accredited centres would be legally recognised and supported by the government, she added.

The comprehensive legislation is a "mixed marriage" of proposals by veteran Labour MK Yael Dayan and the Health Ministry approved recommendations from the professional public committee to investigate ovum donation. Dayan, who chairs the Knesset Committee for the advancement of the status of women said "ultimately all women must be

assured their right to motherhood".

However a fierce opponent to importing eggs is IVF pioneer, Neri Laufer (Hadassah Medical Center, Jerusalem), who said "this whole thing smells of exploitation". Although he conceded that the new regulations could help fulfill the demand for IVF treatment, he noted "the danger that this will become part of the solution itself instead of organising Israeli medicine to take care of Israeli women".

*Rachelle HB Fishman*

### Israelis adopting more children

The failures of IVF legislation and treatments are leading increasing numbers of Israelis to adopt children especially from Eastern Europe and South America. The cost of adopting a child is about US\$20 000. Romania is about to allow 14 adoptions after 18 months of negotiations by parents and Romanian adoption agencies. The process had been suspended in light of recent grave suspicions that two Israeli associations had forged authorisation papers to offer babies who had not been approved for adoption. *Rachelle HB Fishman*

## UN agency concerned by exploitation of poor nations' fish stocks

The United Nations Environment Programme (UNEP) has expressed serious concern over the depletion of fish stocks in several developing countries, including Senegal, and Argentina, as a result of fishing by foreign fleets operating under international trade agreements.

"Unless strict safeguards are in place, this [agreement] can be a costly mistake", warned UNEP executive director Klaus Toepfer. His concerns come after two studies on the effects of trade liberalisation and other trade-related policies on fisheries in Senegal and Argentina highlighted the "over-exploitation" of fish stocks by foreign fleets. "Many local people rely on fish for their livelihoods and as a key source [of] protein needed for health and well-being", said Toepfer. "Overexploitation by foreign fleets can drive these people into ever greater poverty", he added.

Srinath Reddy from the Initiative for Cardiovascular Health Research in

the Developing Countries (New Delhi, India) warned that the "depletion of fish from the diet... would

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Panos Pictures

### Local fisherman cannot compete

contribute to an increased risk of cardiovascular diseases by depriving people in the developing countries of essential protective fats available in fish".

Fish stocks in Argentina have "fallen dramatically" since 1997 and revenues from catches have dropped by 14% from 1997-99. The UNEP studies strongly link overfishing and

the depletion of fish stocks to "subsidies from developed countries for fishing overseas". Similarly trade liberalisation in Senegal "has had a devastating effect" on the stocks of several species (see editorial page 91).

Hussein Abaza, a spokesperson for UNEP told *The Lancet* that the number of affected developing countries will increase as more embargoes are placed on fishing in the waters of developed countries and with the economic slowdown forcing many developing countries to generate revenue by allowing access to their waters.

The UNEP has called for a "worldwide independent assessment" of current practices, policies, and agreements affecting fisheries and recommends the introduction of quotas and higher prices for foreign fishing fleets, and a suspension of agreements if fish stocks become seriously depleted.

Khabir Ahmad

## Spain investigates four cancer cases diagnosed in children in one school

The emergence of haematological malignancies in four children at a school in the Spanish city of Valladolid during a 12-month period forced the regional government of Castilla y León to close the school on Jan 2 so that experts could try to identify the cause of the cluster of cases.

On Dec 21, before the fourth case was identified, a judge ordered the owners of 36 nearby telephone aeri- als to switch them off, after repeated complaints by parents. The aeri- als were on the roof of a building, which was 46 metres from the school. However, before the fourth case of acute lymphoblastic leukaemia (ALL) was diagnosed, an epidemiological study by the regional authorities found no relation between the aeri- als and the first three cases.

The study confirmed that from December, 2000, to September, 2001, two 5-year-old girls and a 9-year-old boy at the school had developed ALL and Hodgkin's disease respectively and noted that the aeri- als were erected in November, 2000. Although the expected incidence rate of leukaemia and lymphoma in the school was significantly higher than the national average incidence rate—4.3 cases per 100 000 person-

years in the 0-14-year-old age group)—the study found no link to the aeri- als and could not offer any explanation for the three cases.

The study also concluded that the electromagnetic exposure levels from the aeri- als were within the normal range and that the school was not affected by direct emission of radiation from the masts. The study also noted that the time between the placement of the aeri- als and the emergence of the cases was too short to justify the development of the malignancies. The study concluded that "it has not been possible to demonstrate a cause for the cluster of cancer cases in the children from the Garcia Quintana school. The report's authors suggested close surveillance measures should be set up to unravel the source of the cases.

However, the emergence of the fourth case at the end of December prompted the regional authorities to close the school for 455 children as a "health and safety" measure. A new team of experts, commissioned by the health ministry, have been asked to do another epidemiological study. The team will comprise experts from the Instituto Carlos III and the National Institute of Cancer, both at the ministry, and independent epi-

demiologists, oncologists, paediatricians, and haematologists.

Juan José Represa, a researcher at the Higher Research Council, considered the most sensible approach from now on was to investigate whether the malignancies may be related to other causes such as a high-dose exposure to chemical agents in the school or materials used to construct the school. The new study will include an examination of all sources of ionising and non-ionising radiation and will include an analysis of the school's water supply. All children and school staff will have a medical examination. A representative from the school will be invited to all the meetings of the public-health team.

On Jan 3, parents of children at the school filed a lawsuit against the local authorities because they had been prevented from entering the school without a legal order. The director of the school was also prevented from entering the school by the police. Luis Martín, a spokesman for the parents association, said that the closure, and move of the children to another school, was an attempt to put the aeri- als back into service.

Xavier Bosch