

# NEWS

## Further clues emerge for strategies to attack HIV

In three new papers, US researchers report findings that may lead to new ways to combat HIV infection.

In the first study, Steven Dowdy (St Louis, MO, USA) and co-workers created a protein that causes HIV-infected cells to commit suicide by apoptosis (*Nat Med* 1999; 5: 29–33). The protein is a fusion protein composed of the TAT protein from HIV and a modified human zymogen, caspase-3 (Casp3). TAT has an unusual ability to pass through cell membranes and can be used to introduce other proteins into cells. This property has nothing to do with TAT's usual function in HIV, Dowdy says.

The second protein, Casp3, is a zymogen which, when activated by proteolytic cleavage, triggers programmed cell death. To make their Casp3 deadly to HIV-infected cells but harmless to other cells, Dowdy and co-workers substituted its activation cleavage sites with site sequences targeted by HIV proteases.

In cell cultures, the researchers report, TAT-Casp3 protein efficiently enters T cells and triggers apoptosis in HIV-infected cells while remaining inactive in uninfected cells. Dowdy

says similar "Trojan horse" molecules could be used to treat hepatitis C, cytomegalovirus, malaria, and some cancers.

In the second study, Scott Brodie (Seattle, WA) and co-workers appeared to settle the debate over the role of HIV-specific CD8 cytotoxic T lymphocytes (CTLs) in HIV infection.

Some researchers argued that CTLs cannot play an important part in containing HIV infection because they tend to concentrate in the blood rather than the lymphnodes, which harbour the virus. Others argued that CTLs do more harm than good, destroying useful CD4 cells and damaging "bystander" cells of the lung, brain, and other tissues.

In the new study, Brodie and his co-workers cultured CTL specific for HIV *gag* protein from three HIV-infected patients, generating billions of clones. Then, in series of infusions, the cultured cells were returned to the patients in doses ranging from 1–3 billion cells/m<sup>2</sup>. After each infusion, there was striking, transient decline in concentrations of CD4- infected cells, the researchers report (*Nat Med* 1999; 5: 34–41). Lymphnode biopsy samples showed that the infused cells do

indeed concentrate in lymphnodes where they cluster around HIV-infected cells. The findings suggest that CTL infusions might be effective in patients with very low viral loads, Brodie says.

In the third paper, Marc Hellerstein (San Francisco, CA) and co-workers report that HIV may reduce CD4 T-cell counts by inhibiting their production. The finding challenges the commonly held view that HIV infection causes a massive destruction of CD4 T cells (10<sup>9</sup> cells/day) that is initially matched by an equally large increase in CD4 T-cell production. In this scenario, CD4 counts fall when the competition exhausts the immune system's regenerative abilities.

In a cell-kinetics study Hellerstein and co-workers found that in untreated HIV-infected patients the half-life of CD4 T cells was about a third shorter than normal, not enough to explain the depletion of CD4 T cells seen in AIDS. The reason why CD4 counts fall, seems to be a failure of the immune system to increase CD4 T-cell production to match these fairly moderate losses, the researchers report (*Nat Med* 1999; 5: 83–89). The findings suggest that treatments to stimulate CD4 T-cell renewal might be effective in preventing AIDS.

Michael McCarthy

## No clinical trials sanctioned for South Africa's controversial HIV drug

The saga of the controversial anti-AIDS drug Virodene seems to have ended with the South African Medicines Control Council again refusing to sanction clinical trials of the drug.

The council resolution states that "no acceptable evidence" of efficacy on preclinical or clinical data was presented to it in the previous 22 months. The application contained "duplications", "incorrect figures", and "omissions", the statement says.

The sponsors of the drug—which contains the industrial solvent dimethylformamide—said the fight to get Virodene accepted "was just beginning".

The South African Cabinet supported research into the drug, ignoring pleas for caution by medical scientists. They warned that the drug had no antiretroviral effect and that certain compounds in it had been shown in culture to stimulate replication of HIV.

When the council rejected clinical

trials of the drug, Health Minister Nkosazana Zuma accused it of being biased. Heads rolled and new members were appointed, but the rejection has been upheld. Rejection of the application was based on questions of science and public safety, the council says, who add that it "was at all times mindful of the urgent need to develop safe effective and affordable medication for the treatment of HIV".

Adele Baleta

## How drugs might damage developing brains

Researchers may have discovered one way in which prenatal and postnatal exposure to drugs may result in human neurodevelopmental disorders. Chrysanthy Ikonomidou (Humboldt University, Berlin, Germany) and colleagues report that blockade of N-methyl-D-aspartate (NMDA) glutamate receptors for a few hours in late prenatal or early postnatal life causes widespread apoptotic neurodegeneration in the developing rat brain. This result, they say, may explain why children born to mothers who used drugs or drank heavily during late pregnancy can have neurodevelopmental problems.

Glutamate is involved in many aspects of neuronal development and NMDA-receptor activation promotes survival of specific neurons *in vivo*. Further, in rats, during the first 2 postnatal weeks, neurons carrying NMDA receptors are very sensitive to excitotoxic degeneration. But, write the authors, "evidence that even transient inactivation of NMDA receptors can be lethal for many neurons has not been described".

The researchers gave neonatal and prenatal rats one of several NMDA

antagonists. When examined 24 hours later, there was an increase in the number of apoptotic neurons in brains treated with NMDA antagonists when compared with brains of rats treated with vehicle.

The size of the increase and brain areas affected depended on the animal's age at the time of receptor blockade. The apoptosis-inducing action of NMDA antagonists was not reproduced by antagonists of non-NMDA glutamate, cholinergic, muscarinic, or dopamine receptors, or by calcium-channel blockers (*Science* 1999; 283: 70-74).

In human beings, NMDA-receptor expression peaks in weeks 20-22 of gestation—the beginning of the brain growth spurt which continues into early postnatal life. Extrapolating from their results in rats, the researchers suggest that the "window of vulnerability for humans [to NMDA antagonists] would include the entire third trimester of pregnancy. Our results may have relevance in a human context of drug abuse, where fetuses may be exposed *in utero* to agents such as PCP (angel dust), ketamine (special K) and ethanol".

Jane Bradbury

## US cardiovascular disease rates double

The American Heart Association's (AHA) latest statistics seem to show that the rate of cardiovascular disease in the USA overnight has doubled overnight.

The AHA publishes annual statistical reports on cardiovascular disease. Until this year's publication of the *1999 Heart and Stroke Statistical Update*, all figures were age-adjusted based on data from the year 1940. Starting this year, the figures are age-adjusted for the year 2000. Because the elderly form a much larger percentage of the population today than in 1940, and far more likely to have cardiovascular disease, the rates now seem to be much higher. The rate of myocardial infarction in 1996, for example, increased from 86.7 per 100 000 with the 1940 figures to 187.1 per 100 000 with the new figures.

"The good news is that the new year brings a new formula for compiling death rates for cardiovascular disease", said Valentin Fuster, the president of the AHA. "The bad news is that it only reinforces how immense the burden of heart disease and stroke is on the public."

The new statistics show that each year about 400 000 Americans developed congestive heart failure.

Larry Husten

## Non-invasive technique keeps track of coronary artery disease

Electron beam computed tomography (EBCT) non-invasively detects coronary artery disease (CAD) and tracks its progression, according to reports in last week's *New England Journal of Medicine*. "The promise is two-fold", says Tracy Callister (Electron Beam Tomography Research Foundation, Hendersonville, TN, USA). EBCT could be used as a "cheaper and non-invasive" alternative to angiograms for assessing treatment efficacy in CAD drug trials, and to monitor the effects of "aggressive prevention" strategies in patients at risk for CAD.

Callister and co-workers retrospectively studied 149 patients who underwent two EBCT scans, 12-15 months apart; 105 patients were being treated with lipid-lowering drugs and 44 were not. Untreated patients showed significant increases in calcium volume in the second

scan, and only treated patients who had low-density-lipoprotein concentrations of less than 3.1 mmol/L showed a net reduction in calcium volume. "The bottom line is, it looks like this tool can be used to track disease", says Callister.

Separately, German researchers used EBCT to detect coronary artery stenosis and occlusions in patients after intravenous injection of a contrast agent. 25% of 500 images were unusable because of "technical problems", and no vessels could be evaluated in 15% of patients. But in evaluable patients, EBCT compared favorably with angiography (*N Engl J Med* 1998; 339: 1964-71, 1972-8).

"The pictures are remarkably good, but you can't always get the image or area you want", notes Callister, whose group reported similar findings for EBCT angiography at the recent American Heart

Association meeting. For example, scans are limited to the proximal coronary arteries, and patients who are overweight or move between scans are not good candidates. Other obstacles must also be overcome. "Until recently, we've had tools that only found disease very late, and now we're jumping to tools that show disease so early, it's hard to know who to screen when, and what to do if small amounts of calcification are detected", observes Callister.

An editorial warns that before EBCT can be used routinely for CAD screening, studies are needed to define calcium's role in plaque progression and the impact of EBCT scanning on clinical outcomes. Such studies are underway, says Callister, and preliminary results are expected in 1-2 years.

Marilynn Larkin

## Two new genes implicated in development of ovarian cancer

A gene that encodes a subunit of phosphatidylinositol 3-kinase (PI3-kinase), a cell-signalling protein, has been implicated as an oncogene in ovarian cancer. "A broad range of cancer-related functions have been associated with PI3-kinase mediated cell signalling", say Joe Gray (University of California, San Francisco, CA, USA) and colleagues. Inhibitors of PI3-kinase or downstream effectors could "become interesting as possible therapeutic agents against this devastating disease", they add. Ovarian cancer is the fourth leading cause of cancer mortality in the USA, causing 14 500 deaths there in 1998.

*PIK3CA*, on chromosome 3q26, is amplified in 40% of ovarian and other cancers. In ovarian cancer cell lines Gray and colleagues found that an increase in *PIK3CA* copy number was mirrored by an equivalent increase in *PIK3CA* transcription. Expression of p110a, the *PIK3CA*-

encoded catalytic subunit of PI3-kinase, was higher in three ovarian cancer cell lines with increased *PIK3CA* copy number than in two cell lines (normal ovarian epithelium and one ovarian cancer cell line) with normal *PIK3CA* copy number. By contrast, p85, the regulatory subunit of PI3-kinase, was expressed equally in all cells. Although most p85 was not associated with p110a, p110a was always associated with p85, so that in cells in which p110a was overexpressed the p110a-p85 heterodimer was also overexpressed, leading to enhanced PI3-kinase activity (*Nature Genet* 1998; **21**: 99–102).

Blocking PI3-kinase activity in *PIK3CA*-amplified cell lines with a specific PI3-kinase inhibitor, LY294002, reduced cell proliferation and increased apoptosis. The authors conclude that "Our observations suggest *PIK3CA* is an oncogene that has an important role in ovarian cancer".

Another, maternally imprinted,

gene is also implicated in ovarian cancer. Robert Bast (University of Texas M D Anderson Cancer Center, Houston, TX, USA) and colleagues have identified *NOEY2* (chromosome 1p31) as a putative tumour suppressor that is expressed consistently in normal ovarian and breast epithelial cells but not in ovarian and breast cancers (*Proc Natl Acad Sci USA* 1999; **96**: 214–19). Re-expression of *NOEY2* by transfection suppressed the growth of transformed cells. Loss of heterozygosity (most often loss of the functional, non-imprinted allele) was detected in about 40% of tumours. The authors suggest that *NOEY2*, a member of the ras superfamily of genes, which have an important role in regulating cell growth and differentiation, might control cell growth by regulating expression of cyclins and cyclin-dependent kinase inhibitors.

Dorothy Bonn

### News in brief

#### No rise in violence by mentally ill

Analysis of data extracted from Home Office criminal statistics for England and Wales (1957–95) shows little change in the number of homicides committed by people with mental illness (*Br J Psychiatry* 1999; **174**: 9–14). In fact, despite media and public perceptions, there has been a steady annual decline in such homicides of about 3%. Authors Pamela Taylor and John Gunn conclude that these data do not support the argument that the "care in the community" policy is a dangerous experiment that should be reversed. However, "There appears to be some case for specially focused improvement of services for people with a personality disorder and/or substance misuse."

#### Dietary supplements database

On Jan 6, the Office of Dietary Supplements at the US National Institutes of Health announced the launch of its new International Bibliographic Information on Dietary Supplements (IBIDS) database. The database contains international scientific work on food supplements and is available free on the internet via the Office of Dietary Supplements home page (<http://dietary-supplements.info.nih.gov>).

## Peptide provides toothsome restraint of *S mutans*

A small trial has shown that a synthetic peptide that mimics the adhesion epitope of streptococcal adhesin antigen III can prevent oral recolonisation by *Streptococcus mutans*, the main aetiological agent of dental caries.

Charles Kelly (Guy's and St Thomas' Hospital, London, UK) and colleagues used p1025, which corresponds to residues 1025–1044 of the cell-surface adhesin in a double-blind trial. 11 volunteers were treated for 9 days with chlorhexidine to deplete oral flora. On day 10, peptide (10mg/mL solution) or saline was applied directly to the teeth; the volunteers had two applications per week for 3 weeks. The volunteers were also asked to use a mouthwash with peptide at 1 mg/mL or saline, daily for the first 2 weeks. Samples of dental plaque and saliva were collected at monthly intervals for 4 months.

*S mutans* was detected in plaque samples from controls as early as day 21. Six of seven controls had recolonisation by *S mutans* by day

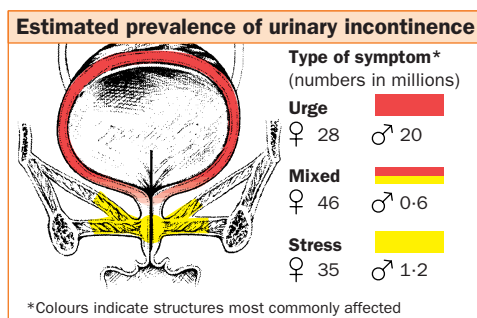
120. Encouragingly, *S mutans* was not found in any of the experimental volunteers 88 days after the start of the study and only one had recolonisation by day 120. Recolonisation by an *Actinomyces* spp occurred by day 21 in both groups, confirming the specificity of the peptide (*Nat Biotechnol* 1999; **17**: 42–47).

Kelly suggests that "the peptide initially inhibits adhesion of *S mutans* but subsequent long-term prevention of recolonisation is probably mediated by competition from other plaque bacteria". The group plans to conduct a larger study in people that could lead to a phase I trial if the technique continues to show promise. "Bacteria play a role in periodontal disease but it is not clear which species are most active. Selectively removing bacteria using peptides specific for individual bacterial adhesins might tell us", says Kelly. He concludes that "the technique could also prove more broadly applicable to other infections at other mucosal surfaces".

Kathryn Senior

## Tackling the taboo of urinary incontinence

With impotence out in the open, urinary incontinence is one of the last social taboos. More than 200 million people worldwide have bladder-control problems, but few seek treatment, explains Paul Abrams, chair of the first WHO-sponsored International Consultation on Incontinence, held in June, 1998. This may explain why at least US\$4.5 billion is spent on incontinence pads each year. Yet with current treatments, "patients can definitely be helped substantially and in most cases cured", says Rodney Appell of the Cleveland Clinic, OH, USA.



Many factors contribute to the undertreatment. First, urinary incontinence is not classified as a disease under the International Classification of Diseases, so patients and doctors may believe that incontinence is a normal consequence of childbirth and aging. Also, patients often remain silent because of embarrassment and a misconception that incontinence cannot be treated, says the American Urological Association (AUA). "You Are Not Alone"—an initiative launched on Dec 10 by AUA and the American Foundation for Urologic Disease—aims to break this silence (<http://www.drylife.org>). Finally, doctors add to undertreatment by not raising the topic with their patients, or by not initiating appropriate therapy.

One difficulty the non-specialist faces when a patient presents with incontinence is that symptoms do not always correlate with the underlying problem. Thus, symptoms of urge incontinence often, but not always, result from an overactive bladder. And genuine stress incontinence—sphincter weakness or incompetence—does not exclusively present with stress incontinence symptoms.

Behavioural therapies can help many individuals by focussing on control of the bladder and pelvic muscle responses that mediate continence. "Most patients can be

improved considerably", says Jerry Blaivas (Cornell University School of Medicine, NY, USA). Linda Cardozo (King's College Hospital, London, UK) adds that "about 25% of women with genuine stress incontinence are cured with intensive pelvic floor exercises" and the problem is lessened in a even greater proportion of women. Addition of biofeedback techniques—eg, using bladder and bowel electrodes—can help patients identify when the appropriate muscles are being used. A recent study showed that a biofeedback-assisted behavioural strategy was more effective and acceptable to women with urge or mixed incontinence than oxybutinin treatment (*JAMA* 1998; **280**: 1995–2000). But though behavioural strategies could be safe and effective first-line treatments, there are not enough suitably trained behavioural therapists to provide this care currently, warns Blaivas.

An overactive bladder is most often treated with drugs that reduce smooth muscle excitability, such as anticholinergics. But few new agents have been launched in the past two decades. Those that have, such as propiverine and tolterodine, act in a similar way to older drugs, and may be superior only in their side-effect profiles. Drugs that affect other aspects of the complex neural pathway that maintains continence are now under development. For example, capsaicin, which targets the sensory input from the bladder, is effective when instilled every few months into the hyper-reflexic bladders of patients with multiple sclerosis. Capsaicin analogues and other drugs that act on sensory afferent nerve fibres are now being tested.

Centrally acting drugs may also affect continence. Duloxetine, a serotonin and norepinephrine reuptake inhibitor, is in clinical trials, and may improve sphincter function as well as reduce bladder contractions. But Scott Litwiller of the University of Texas Southwestern Medical Center (UTSMC; Dallas, TX, USA) notes that most patients stop drug therapy, often because of side-effects.

An alternative way to treat an overactive bladder is electrical suppression of bladder contractions. This is usually a last-resort procedure because implantation of sacral nerve stimulators is invasive and costly. However, a few years ago, experts at

the University of California found that bladder contractions are reduced by percutaneous stimulation of the tibial nerve near the ankle, perhaps by causing neurotransmitter changes in the spinal cord. This technique is very promising, says Litwiller, who is involved in a multicentre trial of the device. A permanent subcutaneous device stimulated by a radiofrequency transducer held over the ankle is also being developed.

Genuine stress incontinence is usually treated surgically, with suspension or sling procedures that support the bladder neck and urethra. But the most effective operations have the highest complication rates so experts are looking for less invasive procedures. One way to improve sphincter function is periurethral injection of substances such as collagen and autologous fat. The procedure usually improves rather than cures, but Gary Lemack of UTSMC speculates that newer injectables, including microballoons and cultured myoblasts, may have a role in the future. Another day-case procedure is the insertion under local anaesthesia of tension-free vaginal tape to support the mid-urethra. In a recent uncontrolled trial, 91% of women treated had no postoperative voiding difficulties or urinary leakage, notes Ulf Ulmsten (Uppsala University Hospital, Sweden). This cure rate seems to be maintained for 5 years, he adds.

With such an array of treatments, experts are divided over who should receive which treatment. Few comparative data exist, so doctors have to rely on their own experience, and may be swayed by the latest industry fashion. Though a surgeon's individual experience is obviously important, recommendations from the International Consultation, expected in a few weeks, may offer a more systematic approach. But, a lack of consensus in several areas, including terminology and appropriate outcome measures, is hampering further research. "If we cannot even agree on how to determine success, we will be unable to devise a treatment to attain that goal", warns Lemack.

Ultimately, treatment should be "based on the aims and expectations of the individual patient" as well as local expertise, says Cardozo. Then, concludes Blaivas, "the vast majority of patients can achieve a satisfactory treatment outcome".

Kelly Morris

## LONDON **A difficult new year for the National Health Service**

Frank Dobson, England's roly-poly Health Secretary, has a Sisphean problem. Just as he rolls one boulder up the hill, another starts rolling down. For most of last year his biggest political boulder was the rise in hospital waiting lists, which was all the more embarrassing because his government arrived in office 18 months ago with an imprudent "early pledge" to reduce hospital queues by 100 000. Far from reducing, they rose a further 100 000 during the government's first 9 months to a record 1.3 million as elective surgery took second place in ministers' priorities to ensuring there were no interruptions to emergency care in the government's first winter in office.

Last spring, ministers launched a new assault on waiting lists with each hospital trust set "local targets" with "rewards for those who hit their targets and sanctions for those who do not". Extra money was handed out, much of it earmarked towards helping people avoid going to hospital through more minor surgery in clinics or at family-doctor premises as well as streamlining hospital services, particularly day surgery, through better booking systems.

The political investment worked with the Health Secretary becoming increasingly buoyant about his falling hospital queues. But now another boulder has ominously slipped down the hill: a winter emergency-care crisis caused by an influenza outbreak in the midlands and North of England compounded by a critical shortage of nursing staff. Winter has always been a crucial time for the National Health Service (NHS). Last year it survived because of low temperatures and low levels of 'flu. This year the Health Secretary has not been as lucky.

The bad news began on New Year's Eve with the release of new figures showing the cost to the NHS of a record exit of nursing staff—2700 in 1 year, many of them taking new jobs as agency nurses where they receive higher pay and more flexible hours. The exit, along with a record 15% drop in students enrolled on training courses, forced the government to make increasing use of agency nurses pushing up the agency staff bill to £200 million—double the figure of 5 years ago.

New Year opened with even worse news for ministers: front-page stories of hospitals with no available beds in

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### **"The team found emergency-bed occupancy was 95% last winter"**

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their emergency wards, patients waiting hours on trolleys, long-planned operations cancelled in a move to create more emergency beds.

The 'flu outbreak began in the north but spread down to the midlands with some ambulance services reporting double the number of normal winter calls. The Health Secretary conceded that staff in many areas were "working their guts out trying to cope" and apologised for the difficulties in some parts of the country where "some people's treatment is being delayed". A British Medical Association spokeswoman warned: "If the 'flu epidemic in the midlands spreads to the rest of the country then we will be in trouble. There are shortages of doctors and shortages of nurses."

Yet only 8 weeks ago, the Health Secretary believed he had cracked the winter problem. He announced a £250 million winter package,

declared last winter's £300 million fund had enabled the NHS to avoid a crisis, and insisted that "the NHS today is better able to cope with winter than ever before."

In reality, as the Emergency Services Action Team set up by the government to monitor and advise on winter pressures noted in a report in September, the NHS only survived last winter because of the mild weather and low level of 'flu. It warned ministers that the NHS could not continue on a crisis-management basis. The team found emergency-bed occupancy was 95% last winter.

Experts are still divided on how to respond. The Audit Commission suggested closing smaller accident and emergency departments in 1996 on the grounds that larger departments delivered better care. But other research by the Health Department pointed in the opposite direction. Some observers believe the last government's plan to introduce "high dependency" beds to fill the gap between general and intensive care would help. All are agreed the nursing shortage must be addressed. Serious pay negotiations begin this month.

And when these problems are resolved, a new waiting-list challenge awaits ministers. The British Medical Association called last week for a move away from mere numbers on a list to a more advanced approach involving "severity tests", which would rank patients according to their individual needs and dictate how quickly they would be treated. That would bring health rationing out into the open—a practice which all British health ministers have sought to avoid.

*Malcolm Dean*

## WASHINGTON **Clinton to propose more funds to fight antibiotic resistance**

Efforts by the US Centers for Disease Control and Prevention to monitor and curb the spread of emerging infectious diseases might get a boost in the federal budget that President Clinton will send to Congress next month.

Clinton administration officials have said the president will propose an additional US\$25 million for CDC's infectious-diseases programme, an increase of nearly one-third. A major part of CDC's effort is aimed at fighting the increase in

antibiotic-resistant infections.

70% of hospital-acquired infections are resistant to at least one antibiotic. However, as CDC Director Jeffrey Koplan told a Capitol Hill briefing on antibiotic resistance in December, the agency has no coordinated national system to track or monitor resistant strains of bacteria. The sponsors of that briefing, Senator Bill Frist (Republican, Tennessee) and Edward Kennedy (Democrat, Massachusetts) said they were

working on legislation to put the force of Congress behind CDC's efforts.

If Congress approves the extra funding, at least part would be used for an education campaign. The campaign will encourage patients not to seek antibiotics for viral infections, and encourage doctors not to give in to requests for antibiotics where the physician suspects they will be of no value.

*Julie Rovner*

## Widespread horror over killing of AIDS activist in South Africa

The "barbaric" killing of a South African anti-AIDS worker who was beaten to death after going public about being HIV positive has raised fears that the disease will be driven underground. However, anti-AIDS activists insisted this week that 36-year-old Gugu Dlamini's death was not a setback and instead would add impetus to the national "disclosure and acceptance" campaign.

The two-pronged approach to the disease started by the National Association of People Living With Aids (NAPWA) encourages people to voluntarily admit to being HIV positive and educating and preparing the community to accept them.

Dlamini, of KwaMashu township in KwaZulu Natal died on Dec 17 after being assaulted by a mob who accused her of degrading her neighbourhood by revealing her HIV status. On the day of the attack (Dec 16) she was stoned, kicked, and beaten with sticks. She died of head injuries the next day. A volunteer NAPWA fieldworker, Dlamini helped to educate communities about HIV/AIDS. On World Aids Day, Dec 1, she spoke out for the first time about her HIV infection

on Zulu-language radio and on television.

According to the latest UNAIDS report, South Africa has the world's fastest-growing AIDS epidemic with 1500 people infected every day. KwaZulu Natal is the worst-hit province where an estimated 20% to 30% of people are living with the virus.

NAPWA's Pat Hlongwane said Dlamini's death sent a strong message to politicians to stop paying lip service to the disease. "We say end the preaching and expecting underfunded non-governmental organisations to do the work for you." He described Dlamini's death as "barbaric" saying KwaMashu was a political hotbed where people thought nothing of shooting their community leaders. "We are not freedom fighters with AK-47s. We are anti-AIDS workers armed only with banners and condoms. We need assistance."

NAPWA has challenged Deputy President Thabo Mbeki's R80-million "Partnership Against Aids" programme, the community, and church leaders to help end the victimisation of people who are infected with HIV.

Head of the association Peter Busse said disclosure had to be linked with acceptance. "It takes enormous courage for an individual to disclose their HIV status but acceptance is a far greater task because it means changing the attitude of entire communities."

Deputy President Thabo Mbeki, who promoted AIDS awareness in his Christmas message to the nation, said: "It is a terrible story. We have to treat people who have HIV with care and support, and not as if they have an illness that is evil."

Peter Piot, Executive Director of UNAIDS, the Joint United Nations Programme on HIV/AIDS sent a letter to Mbeki on Jan 5. He wrote of Dlamini: "She was one of the many unsung heroes of the daily struggle against HIV. Her death reminds us how stigmatising a disease AIDS still is, and how much courage it takes for people with HIV to be open about their condition. And yet, as you [Mbeki] stated on 9 October 1998, it is only by breaking the silence about AIDS . . . that we will defeat this terrible epidemic."

Adele Baleta

## US military face punishment for refusing anthrax vaccine

North American armed-forces personnel face various punishments for refusing to submit to anthrax vaccination. Currently, at least two US Marines and one Canadian flight engineer are awaiting court martial.

In Okinawa, Japan, seven US Marines refused the vaccine last month because of their concerns over its safety. Five of them have received non-judicial punishment for failing to follow orders.

According to Mary Cooper, mother of Adam Cooper, one of the punished Marines, the five have, so far, been restricted to base, reduced by one rank, and lost half a month's pay for 2 months for refusing to follow orders. The two others, Awoh Ojong and Altas Aras, have requested court martial in order to have a hearing on the issue. "I feel they should have a

choice [over vaccination]", Mary Cooper told *The Lancet*. "Why, because you join the military, should you lose that right?"

Canadian flight engineer Sergeant Michael Kipling has been awaiting court martial since March 15, 1998. Kipling refused immunisation mainly because military medical personnel were unable to respond satisfactorily to his concerns over the vaccine, including a lack of data on efficacy, especially against inhalation anthrax, and unknown long-term health effects. "I'm here to protect the rights of the Canadian citizens, but I guess I cannot participate in them", he said. Since Kipling intends to pay for a civilian lawyer rather than be defended by a military lawyer, he is facing a large legal bill. If he is found guilty, he can expect up to 2 years in jail.

The current US anthrax vaccine, which has also been used in Canada and Britain, was licensed in 1970 after small-scale trials. Some experts have expressed doubt over its efficacy, particularly against possible engineered biowarfare strains. No long-term safety studies have been done in human beings, and post-immunisation surveillance was not systematically done on the 150 000 US troops thought to have received the vaccine in the Gulf War. When UK armed forces were offered the vaccine on a voluntary basis, 73% are reported to have refused.

Meanwhile, US authorities have been tested over the holiday season by several anthrax hoaxes. In one incident, 800 people were quarantined inside a nightclub for hours. On Dec 24, 200 people in a Palm Desert shopping centre had to remove their clothes and be rinsed with bleach after another scare, according to postings on ProMED-mail.

Kelly Morris

## Abortion issues highlighted in Ireland

**T**he issue of abortion availability in both Northern Ireland (NI) and the Republic of Ireland is likely to remain a major issue this year. In the North, the Moderator of the Presbyterian Church, John Dixon, called on Northern politicians to put divine principles to the fore especially on abortion and euthanasia issues. And a senior Catholic bishop in the North, Patrick Walsh is seeking assurances from the 18 NI members of parliament at Westminster that they will not seek to have the British 1967 Abortion Act extended to the North.

Last month, an all-party parliamentary committee recommended that abortion be available in NI. It is estimated that at least 60 000 women from NI have had terminations in Britain since 1967. Such terminations are not available on the National Health Service to women from NI. Meanwhile, south of the border, the Irish government has still not published its long-awaited report on abortion legislation that was promised last summer by the Minister of Health.

Last week it emerged that the number of women from the Republic having terminations in Britain is likely to be the highest-ever at 6000 for 1998. According to the Irish Family Planning Association, two-thirds of women in crisis pregnancies have told family or friends before counselling whereas 4 years ago more than half those going to Britain had told no one of their pregnancy.

Karen Birchard

## Invasive aspergillosis outbreak in Spain

**T**he Health Department in Galicia, Spain, acknowledged on Jan 1 that 4 patients have died in the past 4 months from invasive aspergillosis acquired during cardiac surgical interventions (mainly heart valve replacements) performed at the Meixoeiro Public Hospital (Vigo, Spain).

Necropsies confirmed the fungal infection in 3 of the patients; in the fourth patient, the clinical outcome was strongly suspicious of invasive aspergillosis. 7 patients are known to be infected with *Aspergillus* so far. All underwent cardiac procedures between May and July last year. Although the first 2 cases were detected in July, their outcome was favourable. 120 other patients who underwent cardiac surgery between May 1 and July 31 in the same operating room were screened and showed no evidence of *Aspergillus* infection. Another 180 patients who have had cardiac surgery more recently (since early August) have also been screened. The cardiac-surgery unit's operating theatre has been closed since Dec 5.

The existence of the organism in the operating room was demonstrated in July at the time of a routine bacteriological inspection. According to hospital authorities, the most likely source of the fungus was building works 30 m from the cardiac-surgery unit. In particular, one of the unit's

emergency exits would have permitted direct communication with the building works zone through a torn canvas. The humid weather at the time might have facilitated fungal colonisation of the operating theatre. The emergency exit was completely blocked on July 27.

The fungus, which may have a long incubation period, is usually harmless for healthy people but may become dangerous for patients who are critically ill or immunocompromised such as those undergoing high-risk cardiac surgery procedures.

The outbreak has triggered a political storm with the background of the recent controversy around the creation of public-health foundations (see *Lancet* 1998; 352: 1918). The operating theatres of Meixoeiro hospital are managed by private management company. The company, for example, has the autonomy to contract personnel and acquire technology. In the opinion of Angeles Maestro, parliamentary spokesperson of the Communist Party's health commission, the ultimate cause of this "accident" may be cost-cutting. She says that "a consequence of these public and private mix is a carelessness of quality control . . . since cost reduction takes precedence over health-care quality".

Xavier Bosch

## FDA approves first new narcolepsy drug in USA in decades

**J**ust before the new year, the US FDA approved the first new therapy for narcolepsy in 40 years—Cephalon's (West Chester, Pennsylvania, USA) modafinil (Provigil). About 125 000 Americans have narcolepsy, which is marked by persistent drowsiness and sudden attacks of sleepiness.

Modafinil is not an amphetamine, but promotes wakefulness. "It really is, to our knowledge, the first selective wake promoting agent," says Cephalon senior director of pharmacology Matt Miller. The drug's mechanism of action is not well understood, but in cat studies, it

worked discretely in the hypothalamus, says Miller.

Modafinil was discovered by the French pharmaceutical company Laboratoire L Lafon and is already approved in France, the UK, and Ireland. Unlike conventional stimulants used to treat narcolepsy, modafinil does not cause withdrawal. It does not work through dopamine or bind to other relevant receptors for sleep-wake regulation, so there is no hyperactivity and minimal cardiovascular effects, says Miller.

Even so, because it works in the brain, the US Drug Enforcement Administration will put modafinil on

its list of controlled substances. In trials, patients taking once-daily doses of modafinil had a statistically significantly greater ability to stay awake, and an improvement in symptom severity. Patients rated themselves as having less propensity to fall asleep during the day. The drug did not affect night-time sleep, said Cephalon. But the company added that insomnia was a common adverse event. Other side-effects included headache, infection, nausea, nervousness, and anxiety. A 200 mg daily dose was approved.

Alicia Ault

## Canada lifts ban on blood donors with Creutzfeldt-Jacob disease

Saying that there is no scientific evidence that "classic" Creutzfeldt-Jacob disease is blood-borne, the Canadian government has lifted a 4-year policy obligating the quarantine of blood products made from plasma donated by people with CJD.

After ordering a mid-December quarantine of thousands of vials of fractionated blood products made from plasma donated by a Utah man who was thought to have had variant CJD, Health Canada's Bureau of Biologics late last month freed Canada's blood agencies to use albumin, immunoglobulins, and factor VIII made from the man's plasma, after it was determined the 29-year-old had had classic CJD. He had donated blood over 100 times in the

past 2 years, including some after he had begun to show signs of CJD.

"In this case, we are absolutely sure that this is a case of classical CJD, and the expert advice that we have received in the past several months is that there is no evidence whatsoever that there has been any

transmission or is any transmission of classical CJD through blood or blood products", Bureau of Biologics director Keith Bailey told reporters. "Our assurance would be that to the best of our knowledge, there isn't a problem with these products", Bailey said.

While acknowledging that there is still a theoretical possibility that classic CJD could be bloodborne, Health Canada officials said the preponderance of the evidence suggests it is not, so there is little rationale for maintaining the bureau's quarantine policy, which was introduced in 1995.

The new policy mirrors that of the USA and only obligates the withdrawal of plasma from donors with variant CJD.

Wayne Kondro

## Italy appeals against European gene-patent Directive

At the end of last year, the Italian government decided to join the Dutch government and appeal before the European Court of Justice against the European Union's gene-patent directive. This directive was approved on May 12, 1998, by the European Parliament in Strasbourg (see *Lancet* 1998; 351: 1500), with Italy's abstention. Member states of the European Union were given 2 years to enact the directive. It specifies which "biotechnological

interventions" can be granted protection under national patent laws. In March, the Italian parliament had voted against motions which are contained in the European directive. The Ministry of Health criticised the directive and announced it will submit amendments to national legislation enacting it.

Opposers to the directive fear that it will legalise "meddling with genes". A spokesman for the Italian ecological movement, *i*

*Verdi*, explained that opposition to the directive is based on the "principle of caution" which entails "abstaining from undertaking experiments whose consequences can neither be foreseen nor controlled". However, supporters of the directive claim that protection and support for European research and development in pharmaceutical biotechnology is long overdue.

Bruno Simini

## Report reveals link between poverty and ill health among Israel's children

One in every 5 Israeli children suffers from adverse health effects that result from poverty. This is the message of *Children in Israel—1998*, which was reported by co-editor Asher Ben-Arieh during the annual presentation of the National Council for the Child before the Israeli Knesset on Dec 28.

And with growing socioeconomic disparities and inadequate education, nutrition, healthcare, and cultural support, these children are losing any chance of catching up says Yitzhak Kadman executive director of the Council. The 1997 data present a gloomy view of the present and for the next generation says the report's co-editor Yaffa Zionit.

At the end of 1997, children formed 34.4% of Israel's total population; 436 000 of them (21.8%) live in poverty. Bleak economic hard-

ship, combined with increasing numbers of children exposed to violence, as victims, participants, or witnesses, paints a "very disturbing portrait of Israel's children" says Kadman.

"If health funds were not collapsing, closing down needed services and cutting hours and parents unable to pay for private physicians, then at least the health of these children might be secured under National Health Insurance" says Ben-Arieh. Instead, almost a quarter of the country's children spent some time in a hospital emergency room; 67% of these 495 000 presentations were for illnesses that should have been treated in their community clinics. Plus, 1692 children hurt in domestic violence were admitted to hospital, an increase of 88% over 1995.

The Israel Medical Association has asked physicians and other health workers to be on the alert for signs of physical and sexual violence in women and children, and to report these to the authorities.

Nearly 171 000 children lived in families subsisting on welfare assistance in 1997, a 109% increase since 1990. Arab children were twice as likely to live in poverty as Jewish children (36.7% vs 17.9%). Arab families have about twice as many children per wage-earner with worse economic status, and usually only one worker per dwelling which frequently houses three generations. Families that define themselves as ultra-orthodox—Jewish, Muslim, or Christian—are three times more likely to be poor than other families.

Rachelle H B Fishman