Australians back bacterial theory for bowel disease

Richard Chesworth was diagnosed in 1995 with Crohn's disease after he hemorrhaged about two liters of blood in the bathroom at his workplace. Chesworth was 26 then—and his life soon became hell.

The disease sapped his energy, making even getting out of bed an ordeal. Holding down a job was nearly impossible. He had to watch what he ate and make sure that he was never far from a bathroom. Painful abscesses near his anus and the threat of having part of his bowels surgically removed were a constant strain. The cortisone-based treatment sent him on a rollercoaster ride of mood swings and weight fluctuations.

Then he became one of the first patients of Thomas Borody, director of the privately owned Centre for Digestive Diseases in Sydney. At direct odds with most of the medical establishment, Borody supports a trio of antibiotics to treat Crohn's.

Chesworth says the triple-antibiotic therapy “has been a life-changing experience.” He now lives an energetic life, with two children and a busy job, cycling long distance and enjoying the occasional curry and beer.

To people like Chesworth, Borody is a hero. But to many gastroenterologists, Borody is the bête noire. “I've been ostracized,” says Borody.

Conventional wisdom holds that Crohn's is a heterogeneous disease caused by an abnormally aggressive immune response to common enteric bacteria. The disease is thought to be triggered and exacerbated by multiple environmental and genetic factors.

But Borody is convinced that, as in the case of stomach ulcers, Crohn's is caused by infection with bacteria not normally found in the intestine—an idea that is dimly viewed by most experts.

“I'd say about 99.5% of gastroenterologists think it is rubbish,” says John Hermon-Taylor, professor of surgery at St George's Hospital Medical School in London, an outspoken proponent of antibiotic therapy for Crohn's.

Borody has a long history in this field. He developed the antibiotic cocktail against Helicobacter pylori used by his compatriots, Nobel laureates Barry Marshall and Robin Warren, to treat peptic ulcers (Med. J. Aust. 153, 145–149; 1990). Borody doesn’t plan on drinking the bug himself, as Marshall did to convince skeptics, but says a phase 3 trial planned for later this year in the US will help prove his hypothesis.

Several studies have reported the presence of Mycobacterium avium subspecies paratuberculosis (MAP) in Crohn's patients. “It's not a coincidence—it can cause the disease,” says Saleh Naser, a molecular biologist at the University of Central Florida in Orlando, who has cultured MAP from the blood, bowel tissue and even breast milk of Crohn's patients (Lancet 364, 1039–1044; 2004).

But mere presence of the bacteria is not proof of cause, skeptics say. “I would love for it to be correct because then we might have a way to cure the disease,” says Balfour Sartor, a gastroenterologist from the University of North Carolina at Chapel Hill, himself a Crohn's sufferer.

“But to date, I'm not convinced by data.”

Instead, many say, MAP is at most an opportunistic bug that moves in once the intestinal lining is compromised.

Part of the problem is that the bacterium is notoriously difficult to culture in the lab. PCR analyses give conflicting results, says Sartor, who recently organized a workshop in Florida to compare results from different labs. “There are highly variable results from within labs and very little agreement between different labs,” he says.

Another challenge is that antibiotics don't completely clear the infection. Even Borody's patients can only hope to achieve remission, but the infection often returns, requiring further treatment.

MAP belongs to the same family as the causal agent of tuberculosis. Early studies with antituberculosis drugs suggested that they had no effect on Crohn's, but researchers later found that the bacterium is resistant to these drugs. Borody has instead concocted a mixture of three antibiotics: rifabutin, clarithromycin and clofazimine, used to treat mycobacterial infections common in those with AIDS and leprosy.

Small-scale clinical trials, including Borody's own study with 12 individuals, have showed promising results (Dig. Liver Dis. 34, 29–38; 2002). A large, multicenter trial of more than 200 people in Australia, the largest to date, has not yet released results, but some experts say the trial has serious flaws in its design.

For instance, they say, the researchers did not take pre- and post-treatment biopsies to determine whether MAP was cleared from the gut. What’s more, so many patients dropped out or were excluded during the three-year trial that the remaining numbers aren’t enough to draw statistically significant conclusions. Lead investigator Warwick Selby, of the Royal Prince Alfred Hospital in Sydney, declined to comment on the trial design or its results.

Still, data from the early phase of the trial show that people given antibiotics fare significantly better compared with those in the placebo group, says Hermon-Taylor. “It leaves a core of people immeasurably improved,” he says.

Borody, who holds the patent on his triple-antibiotic therapy for Crohn’s, is seeking approval from the US Food and Drug Administration to run a larger phase 3 clinical trial with more than 600 participants. The trial will be funded by Giaconda, a company that Borody founded, and another company he declined to name.

A well-conducted clinical trial could confirm—or dismiss—the connection between the bacteria and the disease, but experts caution that it would be better to nail the cause before rushing into clinical trials.

For those with Crohn’s, however, the issue is more urgent. “The sooner full-phase clinical testing gets going, the better,” says Chesworth. Carina Dennis, Sydney
US court rules to allow experimental drugs for dying patients

People dying from a terminal illness have the right to buy experimental drugs from companies before the US Food and Drug Administration (FDA) has approved them, a US federal appeals court ruled in May.

If upheld, the ruling could bring hope to people desperately trying to extend their lives, but it could also shake up the government’s drug approval process, legal experts say.

“If it’s not overturned, it could have a mind-boggling effect,” says Jerry Menikoff, a health law expert at the University of Kansas. “Not allowing access to experimental drugs is the way we get studies done.”

Because experimental drugs have not yet been fully evaluated, taking them carries a risk of nasty side effects or even death. The FDA forbids companies from selling these drugs. Some people might be able to access the drugs by enrolling in clinical trials or, in circumstances such as a life-threatening illness, by appealing to companies’ ‘compassionate use’ programs.

The new ruling is the result of a lawsuit filed against the FDA by the advocacy group Abigail Alliance.

Frank Burroughs created the group after his daughter Abigail died in 2001 while trying to enroll in a clinical study of Erbitux, a cancer treatment that has since been approved by the FDA. Burroughs argues that companies should be permitted to sell to terminally ill people drugs that have passed phase 1 trials. “The patients are willing to take on the unseen risks,” he says.

A Washington, DC district court dismissed the lawsuit in 2004, but in May, an appeals court agreed with the alliance and sent the case back to the district court.

The FDA can request that the US Supreme Court or the appeals court revisit the decision. As of 23 May, the agency had not yet announced its move.

The ruling could give companies complete control over which terminally ill individuals receive the drug before approval. It could also eliminate the incentive for people to enroll in clinical studies, effectively slowing down the approval process, legal experts say.

“In the real world, this could create the ultimate nightmare,” says Peter Hutt, a partner at the law firm Covington and Burling, and a former head counsel for the FDA. “It might almost eliminate placebo trials. And if a phase 2 shows efficacy, no one would show up to phase 3.”

Despite its radical implications, the policy is similar to one that other countries are moving toward. In November 2005, the European Agency for the Evaluation of Medicinal Products set guidelines to help European countries broaden their compassionate use programs and allow easier access to experimental drugs.

“What right do we have to take away a dying patient’s last hope?” asks Hutt. “Give them anything they want.”

Emily Waltz, New York

Odd epidemic injects shot of doubt about mumps vaccine

At some point last winter, a single person, probably traveling from the UK, brought the viral illness mumps to the US state of Iowa. From that one individual, the disease has spread to more than 3,090 Americans in 13 states, including ones as far away as New York.

The outbreak has left most Americans scratching their heads—if they’re lucky enough to have escaped the fevers, headache and swollen glands typical of infection: isn’t the mumps vaccine supposed to prevent outbreaks?

The epidemic first cropped up in December, when the Iowa state public health department picked up on a handful of cases. As of 18 May, Iowa had confirmed 1,327 cases, with hundreds more suspected. Most cropped up in college-aged students, and a startling 63% had been vaccinated at least once for the disease.

Experts have long known that the vaccine for mumps—given along with shots for measles and rubella in the so-called MMR vaccine—is one of the weaker childhood jabs. One dose of the mumps vaccine confers about 80% immunity in children and the booster bolsters that to between 90% and 95%. Compare that with measles, which has a 95% efficacy rate after one shot and up to 99% after the booster.

“There’s no evidence that the mumps vaccine isn’t working as expected,” says Patricia Quinlisk, Iowa’s state epidemiologist. “But it’s not the greatest vaccine. I wish it were more like the measles shot.”

The vaccine strains first used in MMR may have given higher titers in earlier clinical trials because the disease was then still endemic, and conferred a degree of background immunity.

Drug companies have since been trying to improve the vaccine, primarily by switching the mumps strains included in the shot. The latest innovation came last year, when the US Food and Drug Administration approved ProQuad, which combines the MMR vaccine with a shot against chickenpox.

Most people now in college were only required to get one MMR shot before entering elementary school. But after 1991, children in Iowa have been required to get two doses. In a teleconference with reporters on 19 April, Jane Seward of the US Centers for Disease Control and Prevention said that teenagers who got two doses of the vaccine have been better protected. “That would lead us to believe—that we are getting very good protection from the MMR vaccine,” she said.

Epidemiologists say the spread of the virus in a college-aged population isn’t surprising. Colleges are full of highly social dorm denizens sharing sodas and swapping spit—the perfect breeding ground for any epidemic. Young Iowans presumably incubated and spread the virus to other states through travel, especially during spring break. The epidemic appears to be winding down, partly due to a targeted vaccination campaign and the end of the college year.

But how the virus got to Iowa remains a puzzle. The strain of mumps circulating in the US, genotype G, is the same one that has caused an epidemic in the UK for two years, which bolsters the popular theory about the origin of the virus. More than 70,000 people in the UK have fallen ill with the disease and unvaccinated UK travelers have started US mumps outbreaks before—most recently, at a summer camp in New York last year.

The epidemic there has been driven by fears that vaccines can lead to autism, despite evidence to the contrary.

Erika Check, San Francisco
Questions linger about unexplained gene-therapy trial death

Gene therapists are waiting nervously for the outcome of investigations into the death of a participant in a pioneering gene therapy trial in Germany, expected in the next few weeks.

One of three individuals enrolled in the trial, set to treat the rare but life-threatening immunodeficiency disease chronic granulomatous disease (CGD), died on 10 April after his colon perforated and consequent septic shock caused organ failure.

Scientists reported the death at the annual meeting of the German Society of Internal Medicine on 26 April, adding that an investigation into the exact cause of death is ongoing.

“Then we will all be left with uncertainty,” says Harry Malech, a gene therapist at the US National Institutes of Health. “We will all be left with uncertainty.”

CGD, whose victims suffer incessant infections, is caused by a defective gp91phox gene, which prevents normal maturation of leukocytes, a type of immune cell. The therapy involved using a retroviral vector to insert a replacement gene into blood stem cells.

The cells of the trial participant who died had successfully incorporated the gene and, at least in the first 16 months after therapy, the gene appeared to be functioning. Cells with the gene were able to kill infections in vitro (Nat. Med. 12, 401–409; 2006).

That individual underwent gene therapy in January 2004 and enjoyed a life without hospitalization until late 2005. The others—one treated in Frankfurt in May 2004 and the other in Zurich in May 2005—are also progressing without severe infections.

The trial investigators have already ruled out any leukemia-like diseases such as those seen in 2003 and 2004 in gene therapy trials for the so-called ‘bubble boy disease.’

“The death was definitely not a direct consequence of the transferred gene,” says Manual Grez, the molecular virologist who led the CGD trial. But an indirect effect cannot be ruled out until the investigation is finished.

The researchers are trying to determine the number of gene-modified immune cells to see if they have fallen below levels required to fight infections. And they are testing to see whether the transferred gene has stopped functioning efficiently.

They are also trying to identify the kind of infections in the trial participants. Some infections, such as with the bacterium Borkhalderia cepacia, are unique to CGD, notes Malech, and its presence would be an indication that the death was a result of underlying disease that the therapy had failed to cure.

Regulatory bodies have not halted gene therapy trials as a result of the death, but recruitment into the Frankfurt trial is temporarily suspended. Malech has also put on hold his plans to apply for permission to conduct similar trials at the US National Institutes of Health.

Alison Abbott, Munich

Scientists assail South Africa’s ‘vanity’ publications

South African scientists are demanding urgent reform of the country’s research publishing system, following a report that most of its journals have no international credibility.

The devastating analysis, released in May by the Academy of Science of South Africa, found that one-third of the 255 government-accredited journals are essentially vanity publishers, with not a single article in the past 14 years mentioned outside—or even inside—the country.

A six-member panel of the academy in 2004 launched the investigation at the request of the government’s Department of Science and Technology.

South Africa is considered the leading research publisher in Africa, but the Pretoria-based academy found that nine of ten journals are virtually invisible internationally. Fewer than 25 are mentioned in the Institute for Scientific Information (ISI) databases that rank journals.

The report singled out institutions such as the University of Pretshofstrom, which until a decade ago was an Afrikaans-language, whites-only campus under South Africa’s apartheid policy of racial segregation, for particular criticism. “Many journals are written, edited and peer-reviewed by colleagues from within the same university and sometimes from within the same department,” says study co-author Johann Mouton, director of the Centre for Research on Science and Technology at the University of Stellenbosch.

Frans du Preez, a spokesperson for the University of Potchefstroom, which has since merged with a predominantly black university to form the North-West University, concedes that the complaint has merit. It was difficult for researchers working “in the isolation years,” du Preez says, when academic sanctions in opposition to apartheid banned them from international conferences and collaborations.

“Alternative ways had to be created because South African academics were not recognized,” he says. “Perhaps that was the reason why we went that way to create our own publications.”

But neither perceptions of an outsider status nor difficulties with the English language are an excuse for inferior quality, says Dan Ncayiyana, the Durban-based editor of the South African Medical Journal, one of the few listed in the ISI.

Not everything in the report is negative. Co-author Anastassios Pouris of the University of Pretoria cites immunology and microbiology, including HIV/AIDS research, as areas in which South African scientists are increasingly producing world-class research.

The academy has asked the department of education to cede some of its control over funding research publications, revamp the system and promote international collaborations.

The report also encourages journal editors to push for open-access online publication in addition to print versions so that scientists worldwide can assess whether their African colleagues’ research is—to use a common South African word for excellent—‘lekker.’

Christina Scott, Cape Town
Pandemic prevention schemes threaten diversity, experts warn

Fear of a bird flu pandemic is threatening the survival of many rare avian species—and could ultimately put people in developing countries at greater risk of disease, experts say.

The deadly H5N1 bird flu virus has struck at least 84% of known avian species. In a bid to forestall human infections, governments have ordered culls of millions of both healthy and infected birds.

Depleting the numbers of species cuts down on the genetic diversity of bird populations, putting future generations—and people—at risk, experts say.

If all birds had a similar genetic makeup, a particular viral strain might be able to wipe out an entire species, notes S. Reuben Shanthikumar, a veterinarian and former epidemiologist with the Food and Agriculture Organization. “This is certainly going to cause lack of animal protein and malnutrition and death of people, especially children, because it is the cheapest animal protein in many developing countries,” he says.

When virulent strains of bird flu are detected in a region, officials generally slaughter every bird within a designated radius, turning lakes into shooting ranges.

In April 2004, for instance, several poultry flocks in Fraser Valley, British Columbia, tested positive for the H7N3 bird flu virus. Only about 7% of the 19 million birds in the region tested positive, but the Canadian Food Inspection Agency ordered all the birds killed. The valley provided at least 75% of British Columbia’s poultry.

The practice may be destructive both economically and ecologically, but it is still the best way to contain the virus, some experts argue. Vaccines for birds can stop the spread of the disease if a region is equipped with proper surveillance and security techniques, but is often not practical, particularly in developing countries.

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In contrast to the MRC, “the NHS was strikingly ineffective, with a nominally large budget which funded minnow, and often ill-conceived, projects,” says Steve Bloom, chief of the Genesis Research Trust. “Most of the money was, in reality, going to prop up the health service,” he says.

MRC chief executive Colin Blakemore says that the scheme offers the UK a chance to improve the quality of its clinical research. But “we should not underestimate the problems to be solved if NHS and MRC funds are to be combined,” Blakemore says.

For instance, it is not clear whether the new body would be accountable to both the Office of Science and Innovation and the Department of Health. “If so,” he asks, “would it be truly at arm’s length from ministerial interference?”

Others note that the combined total of the two funding streams exceeds the proposed $1.9 billion budget. “Perhaps the biggest risk will be a temptation to reduce overall research expenditure,” says Richard Hobbs, head of primary care at the University of Birmingham.

The new proposal for allocating funds to university research is also making some scientists nervous. The quality of research in universities and subsequent distribution of their funds is now assessed by peer review. But the exercise requires huge administrative costs and a lot of time and does not reward interdisciplinary research.

The new procedure will be implemented after a 2008 ‘transitional’ exercise and will be based on readily available figures such as research income, publications and numbers of research students.

“The proposed move to a purely metric system based on electronic databases will simply concentrate even more money in those few medical schools who already have the lion’s share of the national resources,” warns Woody Caan, professor of public health at Anglia Ruskin University in Chelmsford.

Consultation on the government’s proposals will run until October this year.

Emily Waltz, Louisville

UK eyes single source of funds for biomedical research

The UK government is seeking feedback on its proposed scheme to establish a single funding agency for both basic and clinical research. The plan also suggests scrapping the traditional peer-review system for allotting research funds to universities.

Both initiatives, announced in late March by Gordon Brown, Chancellor of the Exchequer, build on discussions about improving medical research in the country.

Public funding for medical research in the UK is split between the Medical Research Council (MRC), which funds basic research, and the more clinical National Health Service (NHS). For the fiscal year 2006, the MRC had an annual budget of $874 million and the NHS had set aside $1.4 billion for research.

Under the new scheme, a single $1.9 billion annual fund would be jointly held by the MRC and the NHS.

MRC funding is distributed on a highly competitive basis, but a bulk of funds from the Department of Health, which oversees the NHS, is in the form of institutional grants.

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Xavier Bosch, Barcelona
US to consider routine HIV tests

In an effort to boost the number of people tested for HIV, the US Centers for Disease Control and Prevention (CDC) plans to recommend that voluntary HIV testing become a part of routine medical care for individuals between the ages of 13 and 64. Repeat tests would be recommended for those at high risk.

The CDC estimates that about 250,000 people do not know they are HIV positive, and account for most new HIV infections each year.

The proposed guidelines, which are expected to be published late this summer, would eliminate pretest counseling and the need for a separate consent form. Current guidelines call for routine testing only of pregnant women and people involved in high-risk sexual activities or needle-sharing.

AIDS advocacy groups have raised concerns that the proposal could lead to coercion, invasion of privacy and testing without informed consent. The CDC’s recommendations also contradict findings published in July 2005 by the US Preventive Services Task Force—an independent panel of experts in primary care and prevention—that there is inadequate evidence to recommend for or against routine HIV testing. —AO

South Korea’s Hwang indicted for fraud

South Korean prosecutors in May indicted disgraced cloning researcher Woo-Suk Hwang on charges of fraud, embezzlement and breach of bioethics law.

The Seoul Central District prosecutor’s office charged Hwang with committing fraud by obtaining research funds based on deliberately falsified data, embezzling KRW2.8 billion (US$3 million) in state funds and private donations for his research, and violating bioethics law by purchasing human eggs for research. The charges are the culmination of a five-month investigation. The office also charged five junior scientists on Hwang’s team with various offenses.

Though discredited, Hwang still has supporters. Four days before the indictment, South Korean Buddhists offered Hwang $65 million to resume his research. Hwang, who has been in seclusion for most of the last five months—in a monastery, according to some accounts—did not comment on the charges or funds. —AO

California stem cell scheme declared legal

California’s $3 billion stem cell initiative drew a step closer to viability on 21 April, when a state judge dismissed two challenges to its constitutionality, filed by right-to-life and taxpayer citizens’ groups.

But the San Francisco–based California Institute for Regenerative Medicine still won’t be able to raise money through the sale of bonds while Judge Bonnie Lewman Sabraw’s ruling goes through appeals, a process expected to last at least into 2007 while the case works its way to the state Supreme Court.

The stem cell institute, created when 59% of the state’s voters approved a ballot measure in 2004, could continue to borrow from investors willing to risk nonpayment of the loans if the courts ultimately quash the program. The institute in April awarded its first grants after raising $14 million in contributions and loans.

Judge Sabraw ruled that the institute’s structure was in keeping with its mandate to aid the development of therapies and diagnostics while helping to stimulate the state’s economy. Sabraw rejected plaintiffs’ claims that the institute could skirt state governmental oversight, and that its managers have conflicts of interest because they also represent research centers that might apply for funding. —BD

Australia set to boost biomedical research

Medical research is a winner in this year’s Australian budget, announced on 9 May, with a boost of AUS$500 million over four years for the nation’s primary funding agency for biomedical research.

Last year, the government announced that the agency, the National Health and Medical Research Council, would be restructured to be fully independent of the health department (Nat. Med. 11, 1131; 2005). Together, the developments are seen as long-overdue improvements for the funding agency, researchers say.

The budget increase is expected to be funded by the government’s imminent sale of its private health insurance company. The plan injects AUS$213 million into new infrastructure for medical research organizations, including the Walter and Eliza Hall Institute, a premier biomedical research facility. The budget also includes a new research fellowship scheme of AUS$170 million over nine years to support up to 60 senior researchers.

Separately, the health minister, Tony Abbott, also announced the creation of a new AUS$22 million adult stem cell center to be established at Griffith University in Brisbane. Abbott, a devout Catholic, opposes embryonic research, preferring to see resources focused on adult stem cell therapy. —CD

Former FDA chief faces criminal charges

A lawsuit against the US Food and Drug Administration (FDA) plans to recommend that the former head of the agency, Lester Crawford, is under criminal investigation for financial improprieties and false statements to Congress.

The investigations were disclosed at a hearing over the emergency contraceptive Plan B, a contentious subject during Crawford’s tenure. The Center for Reproductive Rights, an advocacy group that brought the lawsuit, had claimed that top FDA officials stalled a decision to allow Plan B to be sold over the counter. The center was scheduled to question Crawford on 27 April.

But the day before the deposition, Crawford’s lawyer, Barbara Van Gelder, said she would advise Crawford to invoke his Fifth Amendment right against self-incrimination if ordered to answer questions. She did not discuss the accusations further and the deposition was delayed until late May.

Reports of Crawford’s financial ties emerged shortly after his resignation from the FDA in September 2005. Documents released by the government showed that in 2004—while he was an acting commissioner—either Crawford or his wife had sold shares of companies regulated by the agency. —EW

News briefs written by Carina Dennis, Bruce Diamond, Alisa Opar and Emily Waltz.
When Dorota Wozniak was a child, her foot was smashed in a car crash. It had to be partly amputated and was rebuilt using her own skin. More than 30 years after the accident, her foot is riddled with infected ulcers that won’t heal.

On a chilly day in early April, Wozniak sits in a small outpatient clinic in Wrocław, a city in western Poland, waiting for relief. Next to her is Jan Kieslowski, who for more than a year had a urinary tract infection that caused him excruciating pain. “Last Christmas, I wept like a child because it hurt so much,” Kieslowski says. He has taken eight different antibiotics—to no avail.

In this cramped waiting room, there are five individuals, all a living indictment of modern medicine. They suffer from bacterial infections resistant to available antibiotics. But the doctors at this small clinic promise reprieve from the stubborn infections.

Scientists here gave Kieslowski bacteriophages, hardy viruses that attack bacteria. After 26 days of treatment, the bacterial count in his seminal fluid came down from 1,000,000 to 10,000 per milliliter and his urine became sterile. “Also, the pain is much better,” says Kieslowski.

**Anecdotal evidence**

In 1919, Félix d’Herelle, one of the two discoverers of phages, began using phage therapy to treat Parisian children with bacillary dysentery. At the time, there were no real means to fight most infections, and pneumonia was the leading cause of death in the US and many other countries.

From 1920 to 1940, phage therapy had its heyday.

But once doctors ushered in penicillin, the method fell by the wayside in most places. In parts of the Eastern bloc, it survived for decades alongside antibiotics. After the fall of the Soviet Union, Western scientists were intrigued to note the parallel medicine behind the wall, their interest boosted by the growing problem of antibiotic resistance.

Despite decades of anecdotal evidence to back phage therapy’s promise, however, many infectious disease specialists remain skeptical about its benefits. “The data [from earlier studies] are weak at best,” says Steven J. Projan, vice president and head of Biological Technologies at Wyeth Research. “The better done the study, the less efficacious phage therapy appears to be,” Projan says.

To date, phage-based drugs have not been approved by any drug regulatory agency—except those of some republics in the former Soviet Union—or even come close to that goal. The clinic in Wroclaw, which is part of the Institute of Immunology and Experimental Therapy, is the only place in the European Union where patients can officially get phage treatment. “This is a crucial step for phage therapy,” says institute director Andrzej Górski.

Although neither the US Food and Drug Administration (FDA) nor the European Agency for the Evaluation of Medicinal Products, its European equivalent, has approved phage therapy, Wroclaw’s bioethics committee has granted the clinic a license to use phages in cases where all else fails. But the license is an important first step toward approving the contentious therapy. The clinic’s doctors are only allowed to use phages in cases where all else fails. But the license is an important first step toward approving the contentious therapy, says Wim Fleischmann, a German physician and phage-watcher. “This permission is fundamental.”

To some extent, rigorous evidence from animal experiments backs the claims about the power of phage therapy. Studies in mice have shown that phages can eliminate a variety of bacterial infections, ranging from blood poisoning to diarrhea. From 1920 to 1940, phage therapy had its heyday. But once doctors ushered in penicillin, the method fell by the wayside in most places. In parts of the Eastern bloc, it survived for decades alongside antibiotics. After the fall of the Soviet Union, Western scientists were intrigued to note the parallel medicine behind the wall, their interest boosted by the growing problem of antibiotic resistance.

Bug killers

Viruses that can kill bacteria were once wildly popular. Will the rising problem of antibiotic resistance bring them back? Thomas Häusler reports.
human data from about 2,000 individuals beginning in the 1970s. The studies are not randomized or placebo-controlled, but well-documented case studies report positive outcomes in about 80% of individuals3.

Still, skeptics maintain that there is not enough evidence to warrant the therapy’s use in the clinic.

“I think it is premature to do any of this at this time,” says Ryland Young, professor of biochemistry and biophysics at Texas A&M University in College Station, Texas. “I am not convinced that the background phage knowledge is really up to the level we need before embarking.”

Urgent demand

If they do work, phages would be a welcome answer to the growing problem of antibiotic resistance. In the UK, an estimated 39% of infections by *Staphylococcus aureus* in hospitals are resistant to multiple antibiotics4. In the US, this number is closer to 50%5. An estimated 90,000 US patients die each year from infections contracted in hospitals, many of them caused by multidrug-resistant bacteria6. And, in the past few years, some of these bacteria have ventured outside hospital walls and into communities in several states7.

One US physician, who wishes to remain anonymous, was so overwhelmed that he began last year to use phages in hopeless cases. “We had a number of patients whose wounds would not heal,” he says. In several patients, “wound-healing behavior changes with phages and it changes very positively.”

Spurred by the potential market, biotech companies and university researchers in the late 1990s took renewed interest in phage therapy drugs. But many commercial projects fell victim to venture capitalists’ wariness. Among the abortive attempts was the only phage drug—called C33 and made by US-based Exponential Biotherapies—to have made it into FDA-approved phase 1 trials.

Between 1970 and 1999, hospitals all over Poland sent the bacterial samples from their patients to scientists at the Wrocław institute. Beata Weber-Dąbrowska, the head of the institute’s phage lab, would check her vast collection for viruses able to infect the bacteria.

This is a key step in phage therapy because each phage usually only infects some strains of a single bacterial species. Bacteria can also develop resistance to specific phages, which in turn evolve to counter this resistance. Weber-Dąbrowska had to search continuously for new phages to take on the evolving bacteria. “The 40 phages against *E. coli* we had in the 1970s have practically no activity against today’s strains,” she says.

Weber-Dąbrowska still prepares the phages for the new outpatient clinic. Her source for most phages is Wrocław’s sewage system, a natural repository for the viruses.

This aspect of phage therapy is another hurdle to its introduction to market—it effectively kills its potential to become a blockbuster. Along with having to find a way to patent naturally occurring phages, companies have a tough sell in a marketplace accustomed to antibiotics. About three years ago, most companies refocused their interest to phage therapies for livestock, where drug development is much cheaper.

“It’s taking more time than anticipated to wean the world off the standardized wide-spectrum chemical solutions in favor of the relatively service-intensive phage technology,” says Asher Wilf, head of the Israeli company PhageBiotech. “The fact remains that there are still very few [phage companies] and we are all struggling.”

Proof of principle

As phage therapy strives to gain credibility in the West, one US company has teamed up with specialists in Tbilisi, capital of Georgia in the Caucasus, to help treat infections. California-based Phage International sends people from the US, Australia and other countries to Tbilisi, which was one of the centers of phage therapy. At the same time, institutes from the former Soviet Union have tried to establish their products in the Western market.

But none of these approaches has succeeded in establishing a formal proof of efficacy. The clinical studies done until World War II do not stand up to today’s requirements. A whiff of quackery accompanied companies touting their phages as a panacea that could cure eczema and herpes as well as bacillary dysentery and typhoid fever. Add to that questionable studies from the Soviet era, and the skepticism about phages makes sense.

The clinical trial at the Bietigheim hospital might help change all that. “This study is supposed to show the scientific community if phages work—or not,” says Fleischmann, head of the hospital’s department of trauma and reconstructive surgery.

In the 1990s, Fleischmann played a central role in bringing back another vintage therapy: maggots. The larvae of flies are placed on wounds infected with antibiotic-resistant bacteria where they eat the bacteria and dissolve the deceased and dead flesh, but not the healthy tissue nearby.

Like phages, maggots also met a lot of reservation in medical circles. But for some years, the health authorities of some countries such as Germany and the US approved maggots without applying the same stringent standards as for synthetic pharmaceuticals.

“I think it would be appropriate to apply similar kinds of standards to the external usage of phages,” says phage pioneer Elizabeth Kutter, professor of biophysics at Evergreen College in Olympia, Washington. After all, she notes, people are exposed to phages every day—phages are everywhere, in food and drinking water, and on our own skin.

Fleischmann anticipates the same chain of events he witnessed with maggots if his trial proves the efficacy of phages. “First, people still tell you that it does not work,” he says. “After that, they acknowledge that it works but stress that they’ve got better methods. And finally, everybody agrees that your method is an old hat and that you should not pride yourself on it.”

*Names of individuals have been changed.*

Thomas Häusler is the author of *Viruses vs. Superbugs*, published by Macmillan in 2006

**Unnatural selection:** At a small clinic in Poland, scientists choose phages that can destroy evolving bacterial species.
Neal Barnard

Descended from a long line of cattle ranchers, Neal Barnard seems an unlikely advocate for animal rights. But this doctor is not afraid to take on the entire medical establishment.

Fifty years from now, Neal Barnard will be seen as either a consummate medical crank or a prophet. A psychiatrist turned activist, Barnard is a passionate advocate of diets with no meat or dairy, and an ardent agitator for animal rights.

Barnard’s uncanny political instincts and his medical degree have propelled him into the limelight, from Newsweek to The Oprah Winfrey Show and a cameo appearance in the documentary Super Size Me. “I want to advocate for things that have been neglected,” he says. “We don’t think about diet, we don’t think about prevention, and we certainly don’t think about the ethics of much of what we do in the laboratory.”

Barnard pushes for his beliefs as president of the Physicians Committee for Responsible Medicine. The group has relentlessly lobbied for alternatives to animal research and has been an endless source of vexation for federal nutrition-policymakers.

The committee is also expert at hijacking hot topics for its own interests. In May, after a mild strain of bird flu was detected in a live bird market in New Jersey, it sent out a press release offering a free 16-page vegetarian starter kit “to worried consumers.”

The group began in 1985 as a one-man mission in Barnard’s tiny New York City apartment. But more than 20 years of direct mail, volunteer sweat and savvy public relations has added up to a large office in Washington, DC with a $7.2 million budget and a staff of 70, including 5 lawyers and 10 scientists. Barnard has written ten books of diet and nutrition advice that have collectively sold two million copies.

Barnard’s message is not exactly medical gospel. In 2003, he told a US Food and Drug Administration working group that cheese is “dairy crack,” adding that he was only “halfway kidding.” His latest book, Breaking the Food Seduction, labels chocolate, sugar, meat and cheese addictive substances.

Still, he has fans high in the medical ranks. “He’s a superb man,” says William Roberts, an adviser to Barnard’s group, executive director of the Baylor Cardiovascular Institute in Dallas and editor of the American Journal of Cardiology. “Anybody who devotes their life like he has done to getting us all on the right dietary track, I admire.”

Barnard is an unlikely candidate for the animal-rights barricades. He comes from a long line of North Dakota cattle ranchers and grew up eating roast beef and hunting pheasants with his father. As an undergraduate psychology student, he considered a fellow student “soft” when the student complained about having to dispose of live rats by pouring chloroform over them in a trash can.

But months later, Barnard adopted a white lab rat he called ‘Ratsky’ and nursed it as it suffered from cancer. It was after Ratsky died that he decided his attitude toward animal suffering had been misguidedly cavalier.

In 1977, as a medical student at George Washington University, he refused to participate in a required class in which students tested heart drugs on anesthetized dogs. Barnard’s newfound awareness also led him to rethink his dietary habits.

Barnard says his vegan diet is rooted in his conviction that meat and dairy foods are unhealthy. But it also reflects an intense compassion for animals. As scientists’ understanding of animal biology—and particularly animal consciousness—has exploded over the last two decades, Barnard has doggedly used it to pose fundamental questions about the ethics of experimenting on animals.

“We understand their communication patterns, their social interactions, their hierarchies. We understand their exquisite sensitivity to environmental cues. Yet all of that is suddenly completely ignored when it comes to designing an experiment that would violate all those things,” he says. “It’s as if ethics and science have no relationship anymore.”

For his controversial stance, Barnard has drawn the special ire reserved for those who goad the medical establishment.

“To think that we can rely totally upon [human] clinical trials or totally upon nonanimal theoretical models is irresponsible,” says Joseph Haywood, chair of pharmacology at Michigan State University in East Lansing. “We simply aren’t at the place now that we can advance science without the use of animals in our research.”

Barnard has also irked such powerhouses as the American Medical Association, with which he had a running feud in the 1990s over his promotion of a meatless, milkless diet. Although the group declined to comment for this article, its policy spells out “strong objections” against Barnard’s committee “for implying that physicians who support the use of animals in biomedical research are irresponsible.”

Barnard’s group urges its backers not to give to medical charities that support animal research. The committee has long campaigned for medical schools to stop using animals to train students and takes some credit for the fact that 106 of 125 US medical schools have abandoned the practice.

“We don’t think about diet, we don’t think about prevention, and we certainly don’t think about the ethics of much of what we do in the laboratory.”

The group may seem respectable because it appears to represent physicians’ views, but its connection to the People for the Ethical Treatment of Animals (PETA) is evidence of its radical animal rights agenda, says Frankie Trull, president of the Foundation for Biomedical Research in Washington, which supports animal research.


Barnard dismisses those criticisms. “PETA does a lot of important work,” he says. “But we have a very different mission.”

Indeed, he publishes in reputable peer-reviewed journals such as Lancet Oncology and the American Journal of Cardiology. He’s completing a $350,000 US National Institutes of Health–funded randomized trial to test the impact of diet on blood sugar control in people with diabetes, comparing a vegan diet with the nonvegetarian diet recommended by the American Diabetes Association. According to results he plans to present at the association’s meeting in June, the vegan diet comes out significantly ahead.

Marion Nestle, a professor of nutrition at New York University, disagrees with Barnard’s vegan philosophy. Still, she says, “I think he raises provocative questions that deserve serious attention.”

Meredith Wadman, Washington, DC