Antidepressant reputation falls to new lows

Antidepressants are seeing their popularity quickly wane as the US and UK take steps to warn consumers about their side effects.

On 22 March, the US Food and Drug Administration (FDA) issued a public health advisory on 10 antidepressant drugs, warning doctors and patients’ families to watch closely for signs that patients are feeling suicidal. The agency also said it would ask manufacturers to label the drugs with stronger warnings. An FDA scientific advisory board made those recommendations at a public meeting in February. The Canadian government has also issued warnings for antidepressants, and is considering changing the drugs’ labels.

The UK’s Medicines and Healthcare products Regulatory Agency has told doctors there that the drugs paroxetine, venlafaxine, sertraline, citalopram, escitalopram and fluvoxamine—most of which are selective serotonin reuptake inhibitors (SSRIs)—do not work better than placebos and should not be prescribed to depressed children. In clinical trials, four of the drugs increased the risk of suicide attempts or suicidal thoughts.

SSRIs have been popular because, until recently, they have generally been considered safe. In 2002, US doctors alone wrote 157 million prescriptions for the 10 drugs named in the FDA advisory. But some doctors now say they have been given incomplete information about the drugs.

The heated debate over the drugs’ safety—particularly when patients begin treatment or change their medication dose—began last year. Patient advocates have been increasingly vocal in expressing outrage that the FDA had not dis- closed data on SSRIs and suicide in children, which it has been collecting over the past few years. Critics also charge that the FDA’s new data from a single study, giving the impression that more evidence has been collected on the drugs than is actually available, Garland notes. Negative clinical trial results are not published, and the physicians who conduct the trials are usually banned from discussing them by nondisclosure contracts. “We’re trying to do evidence-based medicine on less than half the data, and that’s a real problem,” Garland says.

Because antidepressants do seem to help many children and adults, Garland and others say they don’t want the drugs banned. But they have joined the growing movement of patients in urging caution about the drugs.

The European Union recently launched a €7.3 million, five-year effort to develop new antidepressants and some clarity may be en route on existing drugs: the FDA has asked Columbia University researchers to reexamine the data from 25 clinical trials of the 10 antidepressants used most often in the US. That study is expected to be complete by September.

Erika Check, Washington, DC

China launches new molecular medicine institute

China is set to launch a new Institute of Molecular Medicine (IMM) in partnership with an existing institute of the same name at the University of California in San Diego. The new institute, to be formally opened in November, will focus initially on translational research in cardiovascular science and metabolic diseases.

“China was building a lot of institutes in basic sciences, but no one was really taking it to human disease,” says Kenneth Chien, director of the IMM’s sister institute in San Diego.

The Chinese IMM will be housed in a new building at Beijing University and led by Rui-Ping Xiao, now a senior investigator in cardiovascular science at the US National Institute of Aging.

Cardiovascular disease is the biggest killer in China. In 2000, 3.3% of the population had coronary heart disease, but that number is expected to balloon to 12.4% by 2030. “The problem is enormous,” says Xiao. “But the research is far behind international levels.”

The IMM will be first national institute in China to focus on cardiovascular diseases and will combine genomics, engineering, computational biology, molecular biology and disease-oriented research. Xiao says the institute has initial funding of about $12 million, but is actively seeking new partnerships.

The institute will host about eight investigators, but Xiao expects to double that number in the next few years. It will also help train physician-scientists familiar with Western standards of science, Xiao says. Selected students would complete their medical training at the IMM in China and spend up to three years at a research institute in San Diego.

Apoorva Mandavilli, San Diego
In Mumbai, a small firm that used to translate legal documents is making a fortune translating informed consent forms into a dozen local languages. Contract research organizations (CROs), which compete with each other to provide clinical trial services for pharmaceutical companies, are mushrooming across India. US companies are acquiring Indian CROs and turning them into hubs of their clinical research activities. These are just a few signs of the next trend in India—outsourcing of clinical trials.

“It is a business opportunity India cannot afford to miss,” says Vasudeo Ginde, who ran the Mumbai-based CRO DiagnoSearch until the US company iGATE acquired it six months ago.

A huge patient population, genetically distinct groups, specialty hospitals with state-of-the-art facilities, nearly 700,000 hospital beds and 221 medical colleges, and skilled, English-speaking investigators are India’s trump cards. “Most importantly,” says Sudhakar Bangera, director of the Hyderabad-based company Asian Clinical Trials, “the trials can get done fast and at a cheaper cost than in the West.” In the US, trials for a single drug can cost about $150 million. Early estimates are that drugs could be tested in India at 60% of that price.

The authorities have been quick to respond to the trend. The Mumbai government’s Cancer Research Institute has set up a clinical trial center linking major hospitals. The federal government has also shown support by exempting customs duty on research supplies and trying to set up the country’s first Institute of Clinical Research.

With sponsors donating expensive equipment, the benefits for local hospitals extend beyond cash. For instance, Pfizer has donated $100,000 bone density–measuring instruments to six hospitals testing its new osteoporosis drug.

“Hospitals and research labs in the West earn 60 to 70% of their income by conducting clinical trials for the industry,” says Rupam Borghain, a neurologist at Nizam’s Institute of Medical Sciences in Hyderabad. “Why can’t we do that?”

For the time being, at least, there are several reasons why not. Regulatory approvals in India can take three months or more, compared with 30 days in the US. Indian CROs have yet to learn to deliver data of international standards. More worrying is the lack of confidentiality. Unlike China, India does not yet grant protection for data gleaned from clinical trials, which makes it easy for generic drug makers to copy the drug under trial. “[India’s] opportunities are limited unless you have a strong patent law and a mechanism to enforce it,” says Michael Alder, executive director of the Biotechnology Association of Alabama.

Clinical trials in India have a checkered past that could scare multinationals away (Nature 412, 466; 2001). The field is dogged by complaints that Indian trial investigators recruit patients unethically, exaggerate claims and downplay the risks of trial drugs. Institutional ethics committees aren’t much help either. “The committees do not meet often or are staffed by the wrong people,” says one CRO official.

At the federal level, the central ethics committee at the Indian Council of Medical Research issues guidelines but has no policing powers. There are plans under way to convert the current ethical guidelines into law, says Vasantham Muthuswamy, the agency’s deputy director general.

Under India’s existing laws, only those drugs that have already passed phase 1 safety trials in the country of their origin can be tested on Indians. Raghunath Mashelkar, who chaired a panel to draft amendments to the law, says the committee has not recommended phase 1 trials of foreign drugs “as this will make our people, who are mostly illiterate, guinea pigs.”

Even once the myriad hurdles are resolved, India’s potential as a host for clinical trials is limited. The US Food and Drug Administration does not approve data from trials in which more than 20% of subjects are from developing countries. Although the agency has inspected 64 trial sites outside the US, it has yet to inspect any clinical trial facilities in India.

“Clinical research outsourcing provides a big opportunity, no doubt, but India’s business model for [information technology], which is based on cheap labor, may not work here,” warns William Rutter, chairman emeritus of Chiron Corporation. “What US companies look for is quality data, reliability and confidentiality—and not just low price.”

K S Jayaraman, Hyderabad

Puerto Rico takes on clinical cancer research

With an $18 million, five-year grant from the US National Cancer Institute, and initial annual funding of $4 million for 10 years from the local government, the island of Puerto Rico is gearing up to build a comprehensive cancer center.

Cancer is the second highest cause of death in Puerto Rico—and the incidence is expected to grow. Initiatives in cardiovascular treatment and prevention have in recent years cut the island’s mortality rates. Updating the cancer research infrastructure is expected to similarly address the alarming cancer rates, says Emma Fernandez-Rebollet, interim vice president of Research and Technology at the University of Puerto Rico in San Juan.

The new program, a cooperative effort between the university and the M.D. Anderson Cancer Center in Houston, Texas, focuses on basic, clinical, preventative and epidemiological research, community education and outreach. The island is home to six medical schools and 3,800 students, but physicians have not traditionally been trained to conduct clinical research. As a result, students wishing to pursue clinical research generally leave the island and stay overseas, says Edna Mora, associate professor of surgery at the university.

Under the new program, the students can train at M.D. Anderson, with the goal of returning to the island. The university, which plans to offer graduate programs in clinical research, will soon begin recruiting faculty and will start construction on a biomedical sciences building.

M.D. Anderson will also benefit from the program. Its students will be able to train in Puerto Rico and gain exposure to issues of health disparities among minorities.

Vicki Brower, New York
European Commission questions commercial blood bank benefit

Citing ethical concerns, an advisory body of the European Commission (EC) has recommended against private, for-profit banks of umbilical cord blood as a source of hematopoietic stem cells.

In a report released in March, the European Group on Ethics in Science and New Technologies (EGE) questioned the legitimacy of commercial cord blood banks for autologous use “as they sell a service which has presently no real use.” The report, commissioned in 2001 by EC president Romano Prodi, says the banks “promise more than they can deliver.”

There are about 100 cord blood banks worldwide, 40% of them in Europe. About 75% are public, non profit banks, but recent years have seen the emergence of commercial banks, which offer to conserve cord blood for up to 15 years for one’s own use or for use in close relatives.

In contrast, public banks store cord blood cells for allogeneic transplants in unrelated recipients. The probability of needing an autologous transplant is about 1 in 20,000 during the first 20 years of life, the EGE notes. Moreover, the possibility of using stem cells from one’s own cord blood is “currently purely hypothetical” and research in the field is at an early stage, the report adds.

In exceptional cases where autologous use may be justified—for families at risk of specific diseases, for instance—the EGE recommends storing cord blood in public banks.

Although they are not used widely, cord blood cells have some advantages compared with bone marrow. Collecting the cells is relatively easy and noninvasive. Because the cells are less likely to induce immunological reactions, the subtype for allogeneic transplants does not need to be a perfect match.

Cord blood is also a source of high-quality stem cells for research, notes Jordi Petriz, a researcher at the Barcelona-based IDIBAPS institute. For instance, stem cells from umbilical cord blood are more naive than any other hematopoietic stem cell, Petriz says. Because commercially available cord cells are expensive, he adds, more commercial firms might increase competition and decrease prices.

Xavier Bosch, Barcelona

Sub-Saharan Africa is home to two-thirds of the world’s 40 million HIV/AIDS cases. But experts are still debating whether unsafe injections or unprotected sex is the culprit behind the region’s skyrocketing statistics.

Some studies estimate that up to 40% of transmissions in the region are attributable to unsafe injections, but the World Health Organization (WHO) recently published a scathing critique of that theory (Lancet 363, 482–488; 2004). Pennsylvania-based consultant David Gisselquist and his colleagues first published estimates that up to half of the injections administered in sub-Saharan Africa are given with reused equipment (Int. J. STD AIDS 13, 152–159; 2002).

Based on multiple studies, Gisselquist’s team concluded that “general population studies through 1988 suggest that medical exposures were responsible for more African HIV than sexual exposures.”

The WHO acknowledges that unsafe injections and other substandard health-care practices have become a significant problem in many parts of the world. But the organization maintains that dirty needles are responsible for only 2.5% of HIV transmissions in Africa.

George Schmid, a WHO medical officer and lead author of the Lancet critique, admits that such a wide discrepancy in estimates leaves the door open for debate.

“It’s obvious [with differences of] a magnitude of 10 to think, ‘could one side be that wrong?’” Schmid says. “To be honest, there’s basically no conclusive evidence on the issue.”

To some researchers, the entire discussion seems superfluous. “[The debate] is rubbish,” says Elly Kataibira, associate dean of research at Kampala’s Makerere University Medical School. “Cleaning needles is standard practice, even without AIDS. We’ve been sterilizing needles for 30 years.” To assume that the developing world fails to grasp a simple concept like needle sterilization, he says, smacks of racism.

Ironically, Gisselquist reaches a similar conclusion about the WHO’s stance. “It’s a racist idea, and a manipulative one, that you’ve got to tell Africans that they’ve got to be careful about their sexual behaviors and not worry about their health care,” he says. “It’s a racist proposal to be saying that they can’t handle information about both risks.”

Gisselquist’s ideas have captured the attention of the US Congress, which in January earmarked up to $75 million as part of its Global AIDS Initiative toward “safe and appropriate” injections.

That is a reasonable sum to reduce patients’ risk, Schmid says. Still, he adds, scientists should investigate other potential pitfalls, such as contamination of breast milk, administration of circumcisions and continued reliance on informal community surgical procedures. “If the part of the health-care system that’s unsafe is not unsafe injections, then you’ve really spent the money in the wrong way,” he says.

But tracing the transmission source of an HIV-infected patient can be tricky—as seen in a recent study of 14 HIV-positive South African children whose infections were attributed to “inexplicable causes” (S. Afr. Med. J. 94, 188–193; 2004).

Each of the children’s mothers was HIV negative, says lead investigator Mark Cotton of the University of Stellenbosch. In at least two cases, the children initially tested negative and were discovered to be positive only after health-care workers reported needle-stick injuries.

Researchers found that 12 of the 14 children were given intravenous lines. It is possible that overburdened health-care workers shortchanged sterilization procedures and flushed the lines with HIV-contaminated saline, Cotton says. But that’s just one hypothesis—other explanations for the infections include unidentified sexual abuse and hospital-contaminated breast milk.

Cotton admits that evidence of hospital-acquired HIV among the children is inconclusive, but fears there could be many more cases.

To identify suspect health-care practices, the Human Sciences Research Council of South Africa is launching an extensive case-control study in Botswana, Zimbabwe and South Africa’s northwestern provinces. The project will also evaluate hospitals’ infection-control practices and test “sterilized” medical and dental instruments for the presence of residual viral contamination, says Olive Shisana, the council’s executive director.

“In the event we do find there are things that have to be corrected, the action has to be very swift,” says Shisana. “Science should be the way that guides policy, on the basis of data.”

Bruce Diamond, New York
Despite hype, not all statins are the same, experts say

Statins do more than prevent heart attacks—that much is clear. But scientists are just beginning to unravel the drugs’ panoply of effects.

In the decade since clinical data confirmed that the drugs could prevent heart attacks in patients with coronary artery disease, they have achieved the status of blockbuster drugs. Now, as a third generation of ‘super-statins’ come on line, it is increasingly clear that all statins are not the same. They differ in their efficacy and produce a range of effects—both good and bad—beyond cholesterol reduction.

With six different drugs vying for shares of a $20 billion market, the pharmaceutical industry has set much of the statin research agenda. Scientists have been busy comparing the drugs using an array of doses, endpoints and study populations. Still, important questions linger, and clinicians trying to choose between statins find themselves faced with what Curt Furberg, editor of the journal Current Controlled Trials in Cardiovascular Medicine, calls the “industry paradox.”

“If one member of a class is effective, they say they are all effective,” says Furberg, professor of public health sciences at Wake Forest University Baptist Medical Center in North Carolina. “If one member of a class has a bad effect, they will say that they are all different.”

Topping the list of ill effects is rhabdomyolysis, a potentially fatal form of muscle toxicity that seems to occur more frequently with the newer, more powerful, drugs. More than 30 fatal cases led Bayer to pull its cerivastatin from the market in 2001, and the US watchdog group Public Citizen wants the Food and Drug Administration to do the same for rosvastatin. In a searing editorial, The Lancet charged AstraZeneca with rushing its rosvastatin to market without adequate safety or efficacy data (Lancet 362, 1341; 2003). Several insurers refuse to cover the drug, and sales, while robust, have not been as high as predicted.

David Waters of the University of California in San Francisco advocates the aggressive use of statins in high-risk patients, noting that the benefits outweigh the slim possibility of an adverse effect. “Millions of patients have taken statins for longer than a decade now, and the older ones have turned out to be remarkably safe,” he says. Still, Waters does not prescribe rosvastatin. Statins have also been linked to a range of unexpected health benefits, many of them bolstering the concept of inflammation as a bad player. Scientists are examining the drugs’ usefulness in treating multiple sclerosis, some cancers, osteoporosis, Alzheimer disease and memory loss. Meanwhile, a study at the University of California in San Diego is investigating possible links between statins and problems with aggression and memory loss.

Based on statins’ ability to lower C-reactive proteins (CRP), Paul Ridker at Brigham and Women’s Hospital in Boston is evaluating the role of CRP in heart disease. Statins reduce cardiac mortality in patients regardless of baseline cholesterol levels, suggesting that the drugs’ benefit may be due to another mechanism.

“Are we misreading the biology of how these drugs work?” Ridker asks. “If the biology is giving us a signal, let’s answer the question.”

The JUPITER trial, designed by Ridker and funded by AstraZeneca, will test whether rosvastatin reduces mortality in healthy patients with normal cholesterol and high CRP levels. It will also supply the safety data many doctors want to see before they consider using the drug.

The demand for superstatins could surge if studies confirm that reducing cholesterol to levels lower than currently recommended can save lives. Three ongoing trials with different doses of the same statin could also help reveal whether the dose—rather than the specific drug—determines how statins work.

A panel of cardiologists, including Ridker and Waters, recently gathered in New Orleans and examined the known differences in the statins. All statins exhibit the same broad pharmacological effects. “Nevertheless, important differences exist,” the group wrote in their March report. “For this reason, it is incorrect to view all statins as being interchangeable.”

Tinker Ready, Boston

Europe urged to step up applied cardiovascular research

Cardiovascular research in Europe urgently needs funds for continent-wide applied research projects, more than 100 researchers argued at a conference in Brussels in March.

According to John Martin, a researcher at University College London and the European Society of Cardiology’s chief liaison to the European Union (EU), the conference’s main purpose was to lobby for funds from Europe’s Seventh Framework Programme, set to distribute up to €30 billion between 2006 and 2010.

Early ideas for the program have suggested focusing on basic, rather than applied, research, as the former is expected to benefit many diseases. But favoring such ‘horizontal’ funding over a ‘vertical’ approach would not sufficiently benefit the fight against cardiovascular disease, Martin said. Despite declining mortality rates in western and northern Europe, cardiovascular disease is Europe’s top killer. What’s more, said Daiva Rastenyte of Lithuania’s Kaunas University, death rates in eastern and central Europe are on the rise.

EU money is needed for large-scale clinical studies not carried out by pharmaceutical companies, said Silvia Priori of the Salvatore Maugeri Foundation. Priori noted that several questions remain over the safety and efficacy of drugs in distinct European populations, women and elderly patients. She also pleaded for surveys of clinical practice across Europe, as notions on optimal therapies vary wildly among countries.

It is not yet clear how the European Commission (EC) plans to respond. Because EU money accounts for just 6% of all European public research funds, the commission’s health director, Octavi Quintana Trias, said he would hesitate to divide it into smaller chunks earmarked for many diseases. In principle, he said, the commission tends toward a horizontal approach. But, “we will still need some special attention for diseases that represent a major burden.”

The first EC proposal on the Seventh Framework Programme is expected to be published in May.

Peter Vermij, Brussels
India set to build new animal facility

Indian officials have announced plans to build the country’s largest animal facility on a 100-acre plot near the southern city of Hyderabad. The $50 million National Animal Resource Facility (NARF) will be ready in 2005, says Nirmal Kumar Ganguly, director general of the Indian Council of Medical Research (ICMR).

After January 2005, Indian pharmaceutical and biotech companies will no longer be allowed to copy patented drugs and must discover molecules on their own. Equipped with state-of-the-art laboratories and containment facilities, NARF will serve as a “one-stop solution” for companies and help them meet the challenge by avoiding the cost of expensive toxicology tests in accredited laboratories abroad, Ganguly says.

NARF will breed and supply genetically defined, large and small animals, mutants and transgenics. The US National Institutes of Health has trained 10 ICMR scientists and will provide assistance. The facility will be established with bank loans, government equities and company contributions, but will be run with minimal government oversight, Ganguly says.—KJ

Scientific groups support open access to papers

Forty-eight medical and scientific organizations have announced that they would support open access of published research under specific circumstances, such as access for scientists in low-income nations.

Many open-access publications are subsidized by fees charged to authors to publish their work. In their statement, organizations including the American Cancer Society, the European Molecular Biology Organization and the American Society for Microbiology say they would support access to “important articles” immediately or within months of publication. But publication fees “should not be borne solely by researchers and their funding institutions,” they said.

Meanwhile, publishers from Macmillan, Blackwell, Wiley and Reed Elsevier told a UK House of Commons science and technology committee in March that open-access publishing would force them to publish papers of poorer quality and to accept papers from wealthier authors. They also noted that many developing countries already receive free or reduced-cost access to journals.—AS

US set to study environment–child health link

The US government is planning the largest study of its kind to determine the connection between environmental factors and children’s health. But budget constraints are forcing various groups to lobby for the money needed to begin the study.

The Children’s Health Act of 2000 authorized federal agencies, including the US National Institute of Child Health and Human Development, to conduct the National Children’s Study, which will monitor 100,000 children from the womb to age 21.

Scientists will examine the effects of the environment on children’s health, including chemical factors, cultural influences, geographic location and genetics. The study could begin as early as next year.

Congress granted about $12 million annually for planning the study the past three years, and expects to give the same in 2005. But scientists say they will need up to $50 million next year for costs such as hiring a laboratory to store more than 2 billion samples, including participants’ blood and DNA. Environmentalists, the American Chemistry Council and other groups are lobbying for more funds.

The last major children’s study was completed in the 1960s, when researchers studied children of 55,000 pregnant women from conception to age seven to understand the causes of cerebral palsy.—AS

International system to track clinical trials launched

The World Health Organization (WHO) and Current Controlled Trials (CCT), an independent publishing house that provides free access to peer-reviewed biomedical research, in April announced a system that would allow scientists worldwide to easily track clinical trials.

The initiative will assign randomized, controlled trials an International Standard Randomized Controlled Trial number (ISRCTN), and will include them in a database (http://www.controlled-trials.com). Because a particular trial may be reported under different titles in several places, and many trials might share the same title, assigning each trial a unique number will be helpful, the WHO says.

The system will also allow researchers, particularly those in developing countries, to easily obtain information on “neglected diseases that disproportionately affect poor and marginalized populations,” the agency says.

The ISRCTN register holds information on human reproduction trials approved by the WHO’s ethics board. Trials on infectious diseases, pediatric diseases and vaccines will be added in the future.

“The ISRCTN scheme was conceived to address the confusion experienced by the research community,” says the CCT’s managing director Anne Greenwood. “For controlled trials to be useful on a global scale, it is critical that research be coordinated. ISRCTNs offer a way to do exactly that.”—AS

US Treasury reverses publishing embargo

The US Treasury Department’s Office of Foreign Assets Control (OFAC) on 2 April agreed to let the Institute of Electrical and Electronics Engineers (IEEE) peer-review, edit and publish manuscripts from Cuba, Iran, Libya and Sudan, countries that are under US trade embargoes.

Though the OFAC letter referred only to the IEEE, the ruling could be extrapolated to include other scientific publishers whose publishing methods are similar to the IEEE’s, a senior treasury official said at a press conference.

The OFAC, which enforces trade embargoes, has considered reviewing and editing as ‘services’ that are banned if an author, editor or reviewer is affiliated with an embargoed country. After receiving a letter from the OFAC in September 2003, the IEEE, which says it publishes about 30% of the world’s literature in electrical and electronics engineering and computer science fields, began accepting only camera-ready manuscripts from those countries (Nat. Med. 10, 109; 2004).

“Effective immediately, IEEE is returning to its normal publishing process for all authors,” IEEE president Arthur Wilson said in a statement. “This ruling eliminates potentially disturbing US government intrusions on our scholarly publishing process.”—AS

Written by Aparna Surendran and K.S. Jayaraman
Christine Seidman

Many scientists master either basic research or clinical practice, but a career combining the two is not for the faint-hearted. With her unique approach to research, Christine Seidman blazed a trail in cardiovascular science.

Outside a snowstorm was raging, but that was not going to stop Christine ‘Kricket’ Seidman. She had made the trip to Buffalo, New York, on that day in November 2000 in search of 20 members of a family afflicted with dilated cardiomyopathy, a condition that weakens the heart muscle and disrupts efficient blood flow.

Christmas gifts of poinsettias for the family members covered the back seat of the rental car, which Kricket drove through blinding snow. She went from house to house—six in all—in a 30-mile radius of the Buffalo suburbs. At each house, she and her assistant, nurse Barbara McDonough, drew blood, gathered records and explained the study. Ten hours later, they were finally finished. “Kricket was committed in finding the family members,” says McDonough. “Nothing keeps her from getting results.”

It’s that combination of determination, dedication and pure heart that friends and colleagues say has helped Kricket become a preeminent cardiovascular geneticist.

“Kricket is an unusual person,” says Dan Roden, professor of medicine and pharmacology at the Vanderbilt University School of Medicine. “You have to be a very good clinician with a good understanding of patients and the phenotypes you see, and [then] bring it to the bench and answer questions using basic science,” Roden says. Many scientists can do one or the other well, he adds, but few can master both.

Kricket and her husband, molecular biologist Jon Seidman, are credited with discovering many of the genetic causes of cardiac disorders. In 1986, they first identified several families with inherited hypertrophic cardiomyopathy, a disorder in which the heart muscle thickens and significantly increases heart mass. Using linkage analysis, they found that mutated genes encoding sarcomere proteins in heart muscle cause the disorder. The findings were published in the early 1990s.

“At the time it was a real first, a big first,” says Peter Libby, chief of cardiovascular medicine at Brigham and Women’s Hospital. “It was one of the first molecular defects that was uncovered in cardiovascular disease.”

In the 1980s, scientists thought that metabolic defects caused hypertrophic cardiomyopathy. But the beauty of molecular genetics is that scientists do not need to fashion a hypothesis, Kricket says. “You use genetic tools to define what are the possible disease genes,” she says. When their mapping studies led the Seidmans to a region that contained specific cardiac proteins, she says, they knew they had hit the bull’s-eye.

As a young girl in Long Island, New York, Kricket says she always dreamed of being a doctor. She met Jon in an introductory biology class at Harvard and married him two years later. The couple moved to Madison, Wisconsin, where Jon was doing doctoral work in molecular biology at the university there. Kricket, meanwhile, received a medical degree from George Washington University and completed a residency at the Johns Hopkins Hospital, where she cultivated a lifelong love of research.

After a year at the US National Institutes of Health, she went to Massachusetts General Hospital to complete a fellowship in cardiology. By that time, she says, she was frustrated that treating patients for heart failure only led them back to her with worsening symptoms. In her

“I thought if we just knew the real problem with the heart muscle and fixed it, maybe life would be better for everybody.”

Watching the Seidmans work together is almost like theater, says Libby. “You are able to be a spectator to how their brilliant minds work and you are also entertained by their affectionate but no-holds-barred sparring,” Libby says. “It is a great deal of fun.”

The Seidmans’ partnership inevitably extends beyond work, but Kricket says that’s an added perk. “It is fun to be able to have a good idea over the weekend and talk to your closest scientific collaborator right then and there before you forget it,” she says. The only downside, she adds with a laugh, is that their three children did not always enjoy the scientific talks at the dinner table.

Family, Kricket says, is as dear to her heart as is science. Nights and weekends are spent at home with her children, now 22, 17 and 11. She likes to cheer on her children at hockey and swim-team events and take moonlight strolls with her 11-year-old son. “No matter how much that experiment didn’t work and the grant didn’t get funded and the paper got rejected,” she says, “you go home and nothing matters when you get that welcome.”

Kricket’s dedication to family extends beyond her own to those she studies in her research. “Unlike for a lot of bench researchers, there is often a human face associated with the work I do,” she says.

Kricket is committed to the families she is working with, says McDonough, who has often witnessed Kricket’s dedication firsthand. “She always feels it is worth going the extra mile for them.”

Aparna Surendran, New York
The heart of the matter

Can hematopoietic stem cells transform into muscle and heal damaged hearts? Clinical trials are already under way, but the hypothesis remains a matter of hearty debate. Helen Pearson reports.

For the 23 million people worldwide affected by heart failure, the news was enough to make the chest pound. In April 2001, Piero Anversa of New York Medical College in Valhalla reported that the damaged hearts of mice could be revived by an injection of stem cells sucked from their own bone marrow, raising hopes that patients’ broken hearts might one day be similarly healed (Nature 410, 701–705; 2001).

Anversa’s team mimicked heart attacks in mice by tying off a blood vessel to starve it of oxygen, then injecting the stem cells into the animals’ hearts. To monitor the cells, they labeled them with a jellyfish gene that produces a green fluorescent protein. Nine days later, the hearts of the mice were peppered with fluorescent cells making heart muscle proteins, suggesting that the stem cells had transformed into new muscle. More important, the new cells restored some of the heart’s function, improving its ability to pump blood.

Three years on, preliminary clinical results suggest that heart disease patients also benefit from an injection of their own stem cells, and many clinicians are pushing ahead with larger trials. But other researchers dispute the idea that an adult’s hematopoietic stem cells, which normally give rise to blood, could ‘transdifferentiate’ or switch to making a completely different cell type, such as muscle. Without knowing how the process works, they argue, clinical trials are premature and potentially dangerous.

Both camps acknowledge that something other than transdifferentiation—such as the growth of new blood vessels into scarred heart tissue—might be responsible for the positive results. Intensive research is under way to determine what that might be. Meanwhile, some scientists are focusing on other cells that might produce heart muscle—such as innate, but dormant, stem cells nestled within the heart itself.

Researchers have long believed that, unlike other tissues in the body, the heart cannot generate new cells to repair oxygen-starved tissue after a heart attack. Crippled by scar tissue, the remaining muscle struggles to pump harder, which ultimately results in heart failure. The limited array of available treatments and medications, such as angiotensin-converting enzyme inhibitors and beta-blockers, simply slow this decline.

Anversa’s study made a splash because it challenged the assumption that the heart is irreparable. Several groups were experimenting with transplanting different stem cell types into the heart, but generating muscle from blood stem cells seemed radical.

“Everybody was excited—everybody was too excited,” says Stefanie Dimmeler, a cardiovascular biologist at the University of Frankfurt in Germany. Knowing that bone marrow transplants help cancer patients, several groups either launched or accelerated small-scale clinical trials of the technique. The first to publish, in October 2002, was Bodo Strauer of the Heinrich-Heine-Universität in Düsseldorf, Germany. Strauer’s team plugged a catheter into the coronary arteries of 10 patients after a heart attack, and infused them with a mixture of their own bone marrow cells, including hematopoietic stem cells. Three months later, the patients’ hearts contracted about twice as fast and pumped around 20% more blood than those of a comparison group (Circulation 106, 1913–1918; 2002). “We were surprised they helped all the patients,” Strauer says.

A wave of trial results followed hot on Strauer’s heels and, by 2004, an estimated 400 patients worldwide had been given bone marrow stem cells. Each research group used slight variations in the way it collected stem cells and tracked patients’ progress, but almost all reported that patients who received the stem cell transplants fared better than those who did not.

Though buoyed by their results, the scientists acknowledge that it is premature to label the technique a lifesaver. The trials involved only a few patients, and were designed to test feasibility and safety rather than efficacy. Patients were not always randomly assigned to treatment groups and were not compared with a proper placebo—infusion with cells of another type. To resolve some of these issues, several researchers including Dimmeler are planning more extensive, randomized, placebo-controlled trials.

As some scientists forged ahead in the clinic, a small group of basic researchers were muttering concerns in the lab. In particular, scientists who had long worked with and characterized hematopoietic stem cells were skeptical that they could transform into new heart muscle. “People in the field for 20 years were taken aback that it could be as simple as that,” says Silviu Itescu, who studies heart stem cells at Columbia University in New York.

One of the most vocal critics is Chuck Murry of the University of Washington, Seattle. Even before Anversa’s study, Murry says he had carried out preliminary experiments suggesting that bone marrow stem cells could not transdifferentiate into cardiac muscle cells. When he presented his results at a February 2002 meeting on cardiovascular biology at Keystone, Colorado, it provoked heated discussion. “I was told I was trying to sing like Pavarotti when I wasn’t Pavarotti,” Murry recalls.

Murry, Robbins and Jacobsen say human trials set out to repeat Anversa’s original experiments but, they claim, with more rigorous characterization of the types of new cells produced.

Out of 145 mouse hearts pumped full of hematopoietic stem cells, Murry’s team did not find a single new heart muscle cell. Robbins and Jacobsen both found abundant bone marrow cells engrafted in the heart a few days after the injection, but only a scattering survived after a month and nearly all showed characteristics of blood cells rather than of new heart muscle. Robbins did, however, find a significant improvement in the animals’ heart function after six weeks.

One reason for the discrepancy in the studies, the authors suggest, is that the cells fluorescently labeled as new heart muscle in Anversa’s study could instead be experimental artifacts. But Anversa strongly disputes this, saying that technical differences can explain the disparate results, and maintains that the bone marrow cells transdifferentiate into new heart muscle. “We don’t back off easily,” Anversa says.

Until the scientific dispute is resolved, Murry, Robbins and Jacobsen say human trials are premature or should at least proceed with extreme caution. They and others are anxious to avert a situation that mirrors the gene therapy field, in which the death of Jesse Gelsinger during a 1999 clinical trial set back the science and its reputation by years. Researchers on both sides agree that it is vital to sort out how the stem cells actually work, and many are pursuing experiments to resolve this. Even if the bone marrow stem cells do not transdifferentiate, experts say, there are several other ways they could work: by fusing with existing cardiac cells, encouraging the growth of new blood vessels that help suffocated heart cells survive, oozing cell survival factors, or provoking innate heart stem cells to start dividing.

Even supporters of the trials acknowledge that bone marrow stem cells may not work as was originally proposed, but say this does not eclipse the cells’ overall benefit. “The real danger is stopping clinical trials that could benefit hundreds of thousands of people,” says John Martin, a cardiovascular researcher at University College London.

Researchers in Houston showed that mice injected with similar cells sprout new blood vessels that help their hearts pump more efficiently (Nat. Med. 7, 430–436; 2001). Researchers say that a population of bone marrow stem cells could both contribute to the growth of endothelial cells that line blood vessels and, perhaps, secrete factors that encourage blood vessels to grow.

The first idea—that a fraction of bone marrow stem cells can boost the growth of new blood vessels—seems to be well supported. Indeed, the same day that Anversa’s 2001 study was published, another from Itescu showed that mice injected with similar cells sprout new blood vessels that help their hearts pump more efficiently (Nat. Med. 7, 430–436; 2001). Researchers say that a population of bone marrow stem cells could both contribute to the growth of endothelial cells that line blood vessels and, perhaps, secrete factors that encourage blood vessels to grow.

One hurdle in sorting out how bone marrow cells work is that trials tend to use an ill-defined assortment of cells harvested from the bone marrow, of which hematopoietic stem cells are only one part. For example, there is fairly strong evidence that a small group of bone marrow cells, called mesenchymal stem cells, can generate new cardiac muscle cells by either transdifferentiating into muscle or fusing with existing cells—and some researchers are exploring clinical trials of mesenchymal stem cells in their own right. But because the mesenchymal cells make up only a tiny fraction of the bone marrow, it is unclear what role they play when injected as part of a broader mix. “Even modest differences in the composition might affect the outcome,” says Michael Schneider of Baylor College of Medicine in Houston.

The idea that latent heart stem cells might repair the heart has also been controversial, because until recently it was unclear whether such cells existed. But the idea gained some traction last year, thanks partly to two studies from Schneider and Anversa (Proc. Natl. Acad. Sci. 100, 12313–12318; 2003 and Cell 114, 763–776; 2003). Both teams isolated a group of mouse heart cells that were able to generate fresh heart muscle in a dish, when injected into the mouse’s heart, or when infused into its blood. Here again, it remains unclear whether clinical injections of bone marrow stem cells kickstarted these innate stem cells into making repairs.

Whatever the outcome of the struggle over bone marrow stem cells may be, some researchers are looking ahead to the clinical opportunities with cardiac stem cells. There seems to be less ambiguity about whether these cells can generate fresh heart tissue, and several groups are already working on techniques to better isolate and understand mouse and human cardiac stem cells from heart biopsies. Says Kenneth Chien, who is one of those involved at the University of California in San Diego, “I think you’ll see some big breakthroughs in that area.”

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