

Experiment reveals deficits in European regulation

An advisory body to the Spanish Ministry of Health (MoH) is to investigate the part played by a Spanish scientist in experiments published in the May issue of the journal *Human Reproduction*. Carmen Mendoza, professor at the Department of Biochemistry and Molecular Biology of the University of Granada, is thought to have carried out research involving human oocyte nuclear transfer without permission, which is against Spanish law. The case highlights differences in the regulation of human fertility experimentation across Europe.

Immediately following publication of the article—which reports alternative methods for human oocyte nuclear transfer into enucleated oocyte cytoplasts, aimed at alleviating infertility due to deficient ooplasmic factors—the Commission on Assisted Reproduction (CNRA) announced that it had received no request from Mendoza to

authorize the work and that it was opening an investigation into the issue. Javier Rey, the CNRA's general secretary, told *Nature Medicine* that although Spanish law allows research on gametes, it prohibits their use in creating pre-embryos (up to 14 days after fertilization).

Ironically, as no attempts were made to fertilize the oocytes in the experiment, Mendoza's group could probably have obtained permission for the study if they had applied. They did not. "Mendoza has committed a grave law infringement and, accordingly, she or her department may be penalized," he says.

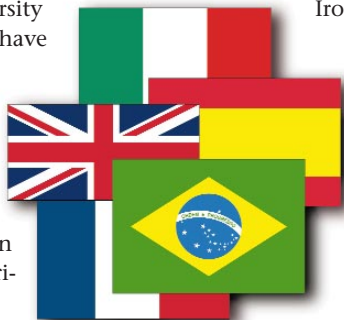
Speaking to the Spanish media, Mendoza explained she had not requested authorization "because the human oocyte assays were not done in Spain but in Italy...so the CNRA had nothing to authorize." She has demanded a public apology from the commission,

saying, "If not, I'm prepared to sue." She told *Nature Medicine* that the MoH has already opened proceedings against her, her department and the Faculty of Sciences of the University of Granada.

In the paper, the group writes that it made no attempt to test the fertilization ability and post-fertilization developmental potential of the reconstituted oocytes because the formation of human embryos for research purposes is banned by law in France and Spain, and is subject to strict regulation in Italy.

However, Mendoza says "that to take the research a step further" they have to search for places where laws are not prohibitive. The lead investigator of the group, Jan Tesarik, who is also Mendoza's husband, is now looking into the possibility of carrying out fertilization experiments of reconstituted oocytes in Brazil, because this country, he says, has no legal constraints on this type of research. Tesarik points out that he could also conduct these experiments in the UK.

Xavier Bosch, Barcelona



No dismissal for hate-mail author

Being an accomplished medical researcher and teacher is sufficient to excuse behavior that includes destroying institutional equipment, harassing colleagues and lying to them and to superiors—at least at the University of Toronto (UoT) and at the Hospital for Sick Children (HSC) in Toronto. This is the conclusion reached by a panel investigating the misconduct of Gideon Koren and recorded in a report signed by UoT president Robert Prichard and HSC president and CEO Michael Strofolino.

Between October 1998 and May 1999, Koren sent anonymous hate mail to colleagues regarding Nancy Olivieri's clinical trials of the drug deferiprone. After denying that he was the author, and impeding an independent investigation into the situation initiated by HSC, Koren was eventually trapped by DNA evidence from the anonymous correspondence (*Nature Med.* 6, 364; 2000). But although a nine-page report says that Koren's actions "...constitute gross misconduct and provide sufficient grounds for dismissal," the penalty of discharge has been mitigated based on Koren's

hitherto-unblemished career record.

Instead, his punishment involves re-payment of CAN\$35,000 (US\$23,500) over five years to the HSC as part of the cost of the investigation; removal from the CIBC-Wood Gundy Children's Miracle Foundation Chair in Child Health Research and from the position of deputy director of the UoT Interdepartmental Division of Clinical Pharmacology; and a six-month suspension—including only two months without pay—that ends today. The report states, "Your lying triggered an expensive investigation. You abused the trust reposed in you and failed to live up to your responsibilities."

In addition, the report states that "specific allegations of alleged research misconduct remain outstanding," and these have been referred to the dean of the Faculty of Medicine. It also returned an open verdict on allegations that Koren submitted false evidence to the 1998 inquiry by Arnold Naimark, a professor at the University of Manitoba,

into Olivieri's claims that the HSC did not support her in trying to make discoveries about deferiprone public.

Koren claims to have sent two letters to Olivieri on 18 December 1996 and 8 February 1997. However, it is thought that these letters were actually prepared at a later date to buttress Koren's submission to the Naimark inquiry and to discredit Olivieri. The report states that the case on this allegation is not closed and adds, "In throwing away the computer in which you typed these letters, you might have destroyed the evidence that could have proved or disproved this allegation."

Bill Graham, president of the UoT Faculty Association, told *Nature Medicine*, "The [Koren] decision fails to ensure an harassment-free environment that is critical to scientific work...and that the hospital and the university have damaged themselves by their failure to protect academic freedom and prevent harassment of scholars."

A second HSC/UoT scientist, Sergio Grinstein, who admits to sending an



anonymous letter on the deferiprone subject to a prominent Canadian physician (*Nature Med.* 6, 485; 2000), is understood to have fared even better than Koren. HSC spokesperson Cyndi DeGuisti says the hospital has investigated Grinstein's conduct and taken the appropriate action and that further details will not be released because this is an internal matter.

Meanwhile, the HSC is referring Olivieri to the College of Physicians and Surgeons of Ontario—a quasi-legal body with the power to subpoena evidence and testimony and to have physicians struck from the medical register—and to the

chair of the Department of Medicine at UoT, for refusing to answer five specific questions regarding her role in the deferiprone clinical trial in 1997. DeGuisti points out that although Olivieri submitted three volumes of written material to administrators, she refused to appear at five meetings on the subject and to answer the questions. At issue is the time delay between Olivieri's discovery that deferiprone was causing signs of liver toxicity, her calling a halt to patient treatment and her reporting the findings to the hospital's Research Ethics Board.

Karen Birmingham, London

NIH researchers receive cut-price BRCA test

Myriad Genetic Laboratories, the Utah-based company that owns the patents on the breast and ovarian cancer susceptibility genes *BRCA1* and *BRCA2*, has struck a deal with the US National Institutes of Health (NIH) for cut-rate prices on its gene tests in exchange for research data. Myriad might be hoping that its action goes some way toward defusing criticism of the company regarding its management of the BRCA-testing business.

Myriad charges \$2,580 for patient-requested BRCA DNA sequencing and mutation analysis (BRCA gene mutations are estimated to cause 7–10% of all breast and ovarian cancers). However, it is licensing the sequencing service to NIH scientists country-wide for \$1,200 per person on the condition that the tests are done for research purposes. The price cut is expected to spur studies of BRCA–environment interactions, the pathological effects of specific BRCA mutations and how BRCA mutations may correlate with cancer treatment outcomes.

It should also improve understanding of the penetrance of BRCA mutations: women with a family history of breast cancer who also have BRCA mutations are at increased risk of the disease. But Jan Platner, director of Programs for the National Breast Cancer Coalition (NBCC), says it is not as clear what the risks are for women with the same mutations but who do not have familial predisposition to breast cancer. NBCC feels Myriad's marketing of BRCA testing has been too aggressive in light of the incomplete understanding of the prognostic meaning of BRCA mutations.

Medical geneticists have seethed for years over the high costs of tests for some patented genes and the restrictions on

who may perform them. Myriad's enforcement of its patent rights—in 1999, it forced University of Pennsylvania researcher Arupa Ganguly to stop offering BRCA tests—coupled with the company's high prices, has made Myriad a particular target of medical geneticists' ire.

But Gregory Critchfield, Myriad's president, argues that critics overlook the expense of sequencing both strands of two exceptionally large genes (combined totaling 17,500 base pairs) in which more than a thousand mutations have been found. He says that Myriad reserves sequencing for itself in part for quality-control reasons; only 13 laboratories are licensed for follow-up, and cheaper, analysis of mutations that Myriad identifies. Ganguly declined the offer of a follow-up license.

Moreover, Critchfield insists that geneticists' fear that high prices prevent people from getting needed tests is groundless in the case of BRCA: Insurers recognize their life-saving value and do not balk at paying for them, he says. But Debra Leonard, president of the Association for Molecular Pathology, feels the time has come to put an end to restrictions on their ability to do genetic testing. The group will ask Congress for a law freeing them from liability for patent infringement if they offer diagnostic tests for patented genes.

Within recent weeks, the company has been awarded two further BRCA-related patents: one for the *CtIP* gene, which suppresses breast and ovarian tumor growth through its interaction with the *BRCA1* gene; and another patent extending Myriad's diagnosis and prognosis position on cancers caused by mutation of the *BRCA2* gene.

Tom Hollon, Bethesda

Can Veronesi transform Italian research?

Umberto Veronesi, the 74-year-old oncologist who pioneered conservative surgical treatment of breast cancer and founded the European Institute of Oncology (EIO), embodies the best hope yet of a catalyst for Italy's biomedical research effort. Veronesi was appointed minister of health in a cabinet reshuffle at the end of April. He is the first ever physician–scientist to take up a top political post in an Italian government.

In an interview with *Nature Medicine*, Veronesi said that his work will be directed towards a vigorous boost of translational research through the creation of a National Agency of Biomedical Research modeled on the German Max Planck Institutes. Achieving this requires the cooperation of universities and private and public research institutions. Moreover, he says “The new agency should have a physical institute of its own, from which to coordinate the country's research on the applications of nanotechnology, genetics and molecular biology,” which will be sponsored by the Ministry of Health and the Ministry of Research. However, the proposal evokes memories of another plan by Veronesi's predecessor Rosy Bindi three years ago to create a biomedical research institute (*Nature* 388, 609; 1997). Arguments between the two ministries over responsibilities destroyed the effort.

But Veronesi does have a successful track record—in Europe at least—in establishing new research initiatives and attracting parties from both the public and the private sector. Since the foundation of the EIO in Milan in 1991, he has been a leading advocate of the special European programs for cancer research, such as the Europe Against Cancer Programme. He says he will increase Italy's investment in European collaborative efforts, and says he favors initiatives such as the creation of a pan-European health database to shed light on the complex interplay between genetic and environmental factors. “More than ever I will be active at the level of the European Commission to marry advances in basic research with programs of epidemiology and biostatistics,” he told *Nature Medicine*.

If he is to achieve any of his goals, Veronesi must act quickly: He could be replaced in the next round of government elections in April 2001.

Martina Ballmaier, Milan