A Bitter Battle Over Error

A long-running and still unresolved dispute among scientists over possible error in a published paper has erupted into a cause célèbre in Congress

This is the first in a series of occasional articles on conduct in science.

A BITTER AND PROTRACTED argument among researchers from the Massachusetts Institute of Technology and Tufts University over alleged error in a scientific paper has recently reached the front pages of American newspapers, as well as the hearing rooms of the United States Congress, where it has become the focus of a continuing debate about the extent of fraud, misconduct, and just plain error in science. There is even talk in Congress of introducing legislation that would take investigatory responsibility out of the hands of universities and the National Institutes of Health.

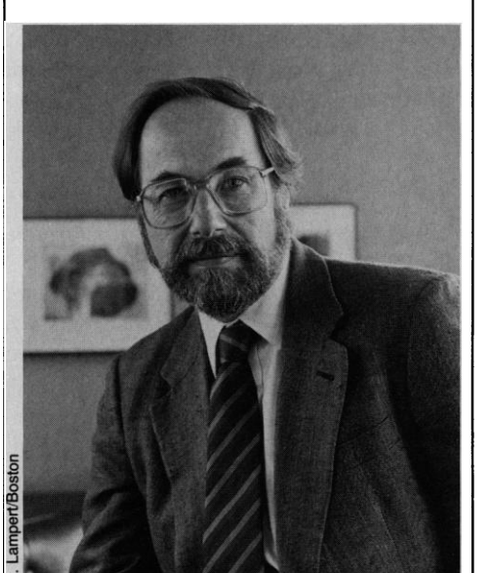
The paper that has been the target of two congressional hearings so far is titled "Altered repertoire of endogenous immunoglobulin gene expression in transgenic mice containing a rearranged Mu heavy chain gene." Published in the 25 April 1986 issue of *Cell*, the paper describes research in a complex area of immunology and serology that even sophisticated scientists find difficult to understand.

What people can readily understand is that a postdoc at MIT named Margot O'Toole believes she has evidence that the data reported in the paper are not consistent with data in some of the laboratory records. For more than a year in 1985 and 1986, O'Toole persisted in telling her superiors that Thereza Imanishi-Kari, the paper's principal author, misrepresented her data in important ways. (Imanishi-Kari, then at MIT, has subsequently moved to Tufts.) Two informal institutional reviews of the dispute have generally concluded that the issue is one of data interpretation, not misrepresentation. The final resolution lies with new experiments and new data, in the traditional pattern of science, the reviewers argue.

But the traditional pattern of science has come up against the investigatory instincts of the United States Congress in a clash of cultures in this case that leaves each side dissatisfied with the other.

How did a scientific dispute between two unknown researchers reach Capitol Hill and the front page? First, it must be noted that Nobel laureate David Baltimore is one of the coauthors of the disputed paper. Director of the Whitehead Institute at MIT, a man who won his Nobel when he was only 34, Baltimore is a prominent and articulate spokesman for the scientific community. Controversy involving Baltimore makes news.

Second, even though O'Toole was prepared to let the matter drop, Charles Maplethorpe, a former graduate student in Imanishi-Kari's lab, decided to press the issue. Maplethorpe, who got a Ph.D. from MIT a year before the *Cell* paper was published, was not involved in the research. But he was suspicious of the data. Maplethorpe brought O'Toole's case to the attention of Walter Stewart and Ned Feder, two researchers at NIH who have taken upon themselves the cause of purity in the scientific literature. It was on the basis of Stewart and Feder's assertions that the MIT and Tufts reviews had not adequately dealt with O'Toole's challenges that the dispute landed in Congress, where it has become a cause célèbre.


M. Lampert/Boston

David Baltimore. *Because of his role as coauthor, a dispute about data in a scientific paper has become news.*

Now, nearly 2 years after the dispute arose, a special three-person committee appointed by NIH has been dispatched to Boston to resolve the matter (see box.)

On 11 April, Representative Ted Weiss (D–NY) held a hearing on "scientific fraud and misconduct." The next day, Representative John Dingell (D–MI) also held a hearing (*Science*, 22 April, p. 386). Stewart and Feder were key witnesses on each occasion. In Boston, Margot O'Toole had only alleged scientific "error." But in Washington, the congressmen talked about "fraud" and "misconduct." News stories on the hearings highlighted a Nobel Prize winner and possible fraud. Distinctions of language fell away; error merged into fraud.

Neither Baltimore, Imanishi-Kari, nor the MIT and Tufts reviewers were invited to either congressional hearing.

Dingell's House subcommittee on oversight and investigations is revered by some because of its reputation as a court of last resort for whistle-blowers. Others, who regard its way of doing business as arbitrary and heavy-handed, view the subcommittee with a sense of intimidation.

The Dingell subcommittee has the power to subpoena witnesses and documents, and uses it. O'Toole, who has dropped out of science, was reluctant to cooperate with the subcommittee. Dingell sent her a subpoena.

Now, Dingell wants Baltimore and Imanishi-Kari to send him all of their original data. Through their lawyers, they have refused to do so voluntarily. "Congress is not the proper forum for resolution of a scientific dispute," Baltimore says, adding that "error is the stuff of science" and should not be treated as misconduct. Dingell's staff investigators, known in Washington for their previous forays into fraud in Defense Department contracting, say simply that if they can't get the data voluntarily, Dingell will get the data by subpoena.

For researchers, this is tough stuff.

The high visibility of what has come to be called the "Baltimore case" makes it significant way beyond the scientific substance at

issue and encompasses many elements.

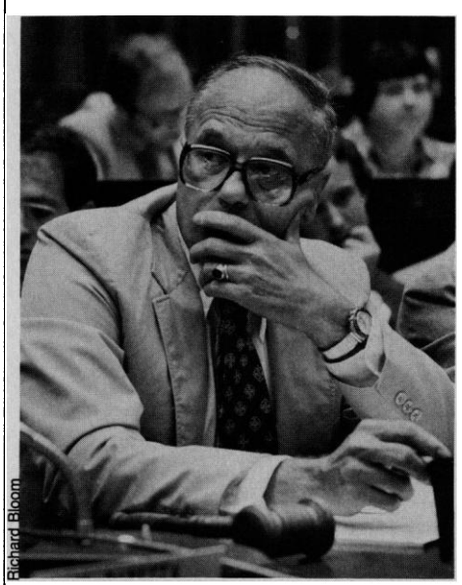
- Baltimore's reputation may have been irreparably damaged, even if he is exonerated. So may Imanishi-Kari's. So, for that matter, may O'Toole's.
- The Baltimore case is but one instance among many that have prompted Congress to question the capacity of universities and the NIH to police themselves. Both MIT and Tufts have been criticized by Congress for the way they reviewed O'Toole's charges of error, leaving the reviewers who thought they had done a fair job feeling unjustly rebuked for their efforts. NIH has been pushed to beef up its own fraud office, which until now has been understaffed and slow to respond.
- The role of outsiders like Stewart and Feder is being widely debated among scientists, while Congress is asking how they are treated by their universities.
- Perhaps most threatening to many scientists is the possibility that Congress will create a watchdog or auditing agency to look into scientific disputes. The scientific community now is galvanizing to make sure that doesn't happen.

Science is preparing a series of articles that will examine the multifaceted, complex issues pertinent to integrity in research. We will begin with reports on the events in Boston surrounding the *Cell* paper; the role Stewart, Feder, and NIH have played in this drama; and the action that has taken place on Capitol Hill.

In a way, this story begins as many as 4 or 5 years ago when David Baltimore collaborated with Frank Costantini of Columbia University on the creation of a "transgenic" mouse, using a gene from a system that Imanishi-Kari had already characterized. Baltimore and Costantini transferred a gene coding for Mu immunoglobulin from one strain of mouse to another, in this case from a BALB/c mouse to a C57Bl, or Black, mouse. According to Baltimore, who has given his side of the facts in a "Dear Colleague" letter sent last month to hundreds of scientists, the main reasons for creating the transgenic mice were to see what happened to the Mu transgene and to see whether this "rearranged gene" would have any effect on the regulation of natural or endogenous genes in the Black mouse.

One thing that can happen when a foreign gene is inserted into a host animal is that the transplanted gene will begin to function, producing the antibodies, idiotypes, or whatever it makes in its usual state. A second, more remarkable, possibility is that the transgene will actually affect the production of the host animal's natural cell repertoire. Thus, the transgenic mice would be a fine model for exploring a number of important questions in immunology and cell regulation. Baltimore, Costantini, and their colleagues published a paper on the transgenic mouse in the October 1984 issue of *Cell*.

According to Baltimore, after the initial molecular biology was done on the mouse, "it was evident that the transgene was being expressed." He entered into a collaborative project with Imanishi-Kari to see if they could find out what the implications were for immune regulation. "The types of methodology involved in doing the immune characterization were not then available in my laboratory and she had many years of experience" with the complex serology and related methods, Baltimore says.



John Dingell *challenges institutions' ability to police themselves.*

The Imanishi-Kari experiments, done at MIT with David Weaver, one of Baltimore's postdocs, and others, soon turned up surprising data about the expression of the transgene from BALB/c in the Black mouse.

One question at issue in the experiments reported in the Imanishi-Kari *Cell* paper is this: Did the transgene from the BALB/c mouse affect the expression of immune cell production in the Black mouse?

The authors and reviewers say "Yes." There is good evidence that cells normal to the Black mouse are producing elevated levels of an idiotype that closely resembles molecules from the transgene. But O'Toole says that "the data do not support the claim of elevated expression of endogenous idiotype," thus clearly challenging the central conclusion in the paper. O'Toole suggests that hybrid molecules may account for the finding.

It is crucial that the NIH committee reaches a judgment about this.

The next question, which has yet to be answered to everyone's scientific satisfaction, hinges on the first. If the expression of transgene idiotype is real, the question is one of mechanism. The *Cell* paper postulates three explanations, while recognizing that the data do not conclusively support one or another. Imanishi-Kari favors the idea that she has found preliminary evidence of a real regulatory effect.

Niels Jerne won a Nobel Prize in 1984 for his still controversial hypothesis that the immune system is governed by a self-regulating network that depends on the generation of anti-idiotype antibodies—that is, antibodies to its own antibodies. If Imanishi-Kari has good experimental evidence that such a regulatory network exists it would be an important contribution to immunology.

From the outset, Baltimore was not inclined to the network idea as an explanation for the data. In his "Dear Colleague" letter he says that he and Imanishi-Kari "had somewhat different interpretations of these experiments. She felt that there was strong argument for network interrelationships causing the endogenous genes to selectively express idiotypic cross-reactivity. I felt that the explanation probably lay elsewhere."

NIH to Review Disputed Data

As this issue of *Science* goes to press, an NIH-appointed committee of three immunologists is expected to arrive in Boston to begin an official investigation of disputed data that were published in *Cell* a little more than 2 years ago. Joseph M. Davie of Searle Pharmaceuticals, Hugh McDevitt of Stanford, and Ursula Storb of the University of Chicago have agreed to look into events surrounding a paper whose coauthors include Nobel laureate David Baltimore of the Whitehead Institute and Thereza Imanishi-Kari, then of MIT, now at Tufts.

NIH officials had hoped to find five scientists expert in the field of transgenic animals, antibodies, and idiotypes, to investigate charges that the paper misrepresents the underlying data. But it could not find that many who were available to get on the case quickly. "It was a case of numbers versus speed," an NIH official told *Science*.

Baltimore first asked NIH to step into the dispute more than a year ago. ■ **B.J.C.**

According to Weaver, one of the co-authors, "the results section of the paper makes clear that we don't know exactly what is going on."

At this stage of the story, Margot O'Toole's place in all this should be elaborated. O'Toole got her Ph.D. in immunology in 1979 from Tufts University, under the tutelage of Henry Wortis. She was his first graduate student. Doctorate in hand, O'Toole went to Philadelphia where she had two successive research fellowships. Then, in 1985, she moved back to Boston when her husband accepted a position at Tufts in the same department in which Wortis works.

O'Toole hoped that she, too, would get a position at Tufts—as an assistant research professor. However, her grant application to NIH was turned down, with the indication that a "favorable decision was more likely if I reapplied after I had more preliminary data to prove the feasibility of my proposal." No grant, no job at Tufts.

Wortis came to the rescue. He introduced her to Imanishi-Kari who needed someone with O'Toole's technical experience in cell transfer technology to join her lab at MIT. They struck a deal. O'Toole would work one more year in the capacity of a postdoc, this time doing experiments that might confirm or extend Imanishi-Kari's thesis about evidence of a regulatory network in the immune system. Imanishi-Kari would give O'Toole enough time on the side to continue work on her previous study so that she could reapply for a grant of her own. "I was delighted by this offer," O'Toole testified.

But the delight soon paled. O'Toole's first experiment following-up Imanishi-Kari's paper worked. Others failed. "Within a few months, I had done a number of experiments whose results conflicted with hers," O'Toole testified. "I naturally believed that the differences were the result of error and continued to repeat some of my experiments. . . . This took up a lot of my time and expensive laboratory supplies and Dr. Imanishi-Kari became very impatient. She insisted that the discrepancies were the result of my incompetence. . . . Communication between Dr. Imanishi-Kari and me deteriorated steadily."

By all accounts, the two scientists ceased to get along.

While O'Toole was struggling to get her career in shape so she would one day be eligible for a tenure-track job, Imanishi-Kari also was facing decisions about her professional future. Denied tenure at MIT, she secured a position at Tufts, in the same department as Henry Wortis and O'Toole's husband. Imanishi-Kari moved to Tufts a year later.

But along the way, the issue of the *Cell* paper became the focus of real contention. "In the fall of 1985, I received a manuscript describing the study that had suggested the project for which I was hired," O'Toole told Congress. "I had already done experiments that disagreed with some of the findings but Dr. Imanishi-Kari dismissed my results."

"Dr. Imanishi-Kari came to feel that the experiments were not carried out carefully," Wortis says. "Dr. O'Toole believed that she was working on a false premise."

Shortly after the paper appeared in *Cell* in April 1986, O'Toole came across 17 pages of handwritten laboratory records "that caused me to doubt that the underlying data supported the main conclusions of the now published study," she testified. "In fact, it appeared that a number of conclusions were actually contradicted by the records." O'Toole reports that she asked Imanishi-Kari if there were other data that "superseded" the 17 pages she had. "She was unable to find any of these records," O'Toole told the Dingell committee.

In an interview with *Science*, Imanishi-Kari denied that data recorded in the 17 notebook pages are proof of O'Toole's assertion. There are other data that are relevant, she says. O'Toole "would know that only if she had all of the notebooks."

But O'Toole is not satisfied. "I did not Xerox a random 17 pages and go on a rampage," she told *Science*.

(The extent and adequacy of available records is another item the NIH committee is expected to resolve.)

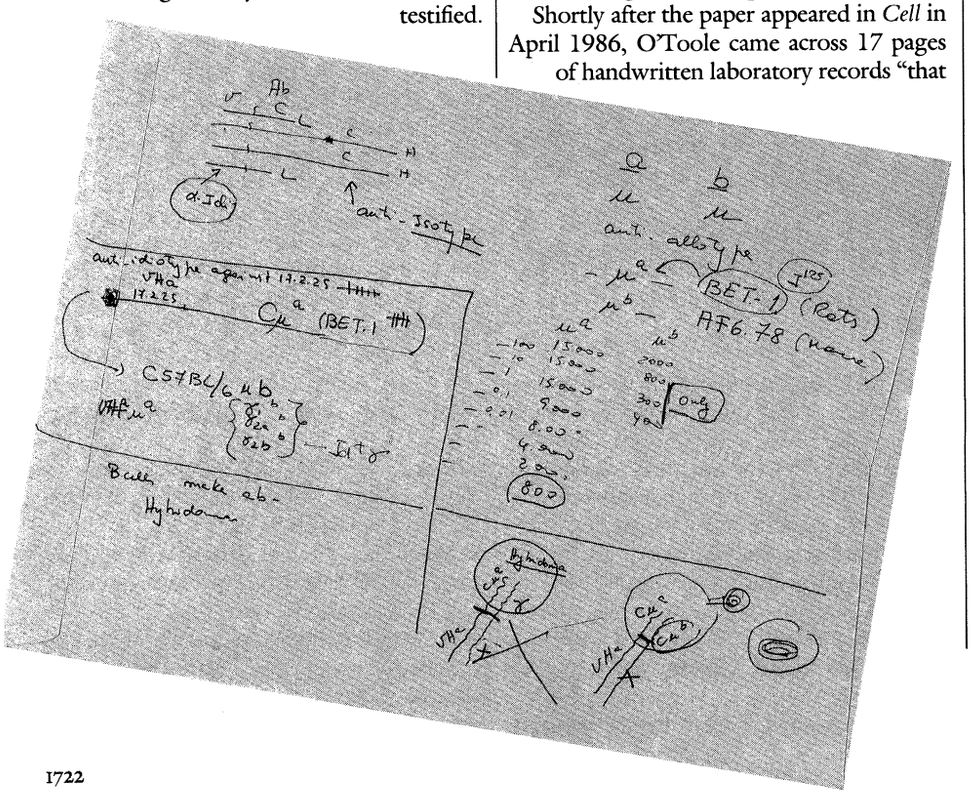
MIT and Tufts officials entered the picture after O'Toole, who took her concerns first to colleagues, and then to higher authorities at each institution. She went to Tufts immunologist Brigitte Huber, who encouraged her to talk to Wortis. She contacted Herman Eisen at MIT, an immunologist who was also the director of the NIH training program through which she had a fellowship. She informed MIT ombudsman Mary Rowe, an assistant to the president, that she thought a paper had been published with significant errors.

But, in a move that would prove important to the handling of the case, O'Toole refused to make any formal allegation of fraud. Despite suggestions from Eisen and others that her charges amounted to allegations of fraud, O'Toole insists that she was alleging error—only seeking resolution through usual channels of "collegial" debate.

Eisen asked her to prepare a memo listing her scientific objections to the *Cell* paper. That memo, dated 6 June 1986, is scientifically direct, moderate in language, and makes not even an implication that she could be talking about fraud.

But she told Congress that she thought Imanishi-Kari was "manipulating the data." Furthermore, O'Toole testified that Imanishi-Kari "admitted to me that one of the graphs in the paper was misrepresented and that the true results agreed with mine." Nevertheless, she repeatedly resisted suggestions that she accuse Imanishi-Kari of misconduct.

Because there was no formal allegation, neither MIT nor Tufts thought it appropriate to conduct a full-scale investigation.



Imanishi-Kari's *back of the envelope sketch of the complex science.*

First, a full-bore investigation, which would mean impounding records, forming an investigating committee, and notifying NIH, would be damaging no matter what the outcome. Right or wrong, the argument was regarded somewhat as a personal fight between Imanishi-Kari and O'Toole. Like the police who usually do not make an arrest in a domestic quarrel if no one will press charges, the institutions did not want to take an official role in an unofficial dispute.

Nevertheless, at MIT Eisen, as a "committee" of one reviewed the issue at the request of the dean. He went over the points in O'Toole's memo and presided at a meeting of the principals—by this time including David Baltimore. (Eisen never actually reviewed all the data, reasoning that it was not necessary in an informal review.) At Tufts, Wortis informally convened a committee at O'Toole's request. Wortis, with colleagues Huber and Robert Woodland—all expert in the science—agreed that O'Toole's alternative explanations of the data were possible, but not likely (*Science*, 20 May, p. 968).

The upshot of the two reviews is not definitive. In essence, they found that O'Toole had raised interesting scientific points, but that they were necessarily more persuasive than points in the paper itself.

In a memo to the dean of MIT, Eisen wrote "I do not think that I or anyone else present at the meeting felt that Margot O'Toole's disagreements were frivolous. "These kinds of disagreements are, of course, not uncommon in science and they are certainly plentiful in immunology." More experimentation is the way to resolve this, he concluded.

Reviewers at both institutions agree that O'Toole spotted one technical error in the paper. A statement that a monoclonal reagent called Bet-1 "bound only" to Mu-a idiotype is not correct. Bet-1 binds preferentially to Mu-a, but may also bind to Mu-b. Imanishi-Kari says, "There is an error in the paper. With that I absolutely agree." But, she said, it is not important because it does not alter the main conclusions in any way. The Wortis committee, in its report, concurs.

It is obvious, by now, that what started out as an internal laboratory dispute has become a very public mess. Although aware of the basic facts as early as 1986, NIH's office of scientific misconduct decided to stay out of it until the institutions had completed their own investigations. Like MIT and Tufts, NIH resisted a full investigation in the absence of allegations of misconduct. But finally, NIH recognized that it would have to become officially involved if the matter was to be resolved. In fact, Baltimore formally asked NIH to convene an investigating committee more than a year ago.

NIH officials have now gone over the existing reports, as well as a widely circulated draft manuscript by Stewart and Feder that critiques the *Cell* paper on the presumption that the 17 notebook pages are key. "We all agree that the issues raised in the Stewart-Feder manuscript were not answered by either the Tufts or the MIT investigations," Mary Miers of NIH testified at the Dingell hearing. (Wortis agrees this is the case, but makes plain that his report was complete before he ever saw Stewart and Feder's still unpublished paper. Furthermore, he notes that his committee was responding to O'Toole, not to Stewart and Feder after the fact.) Nevertheless, their arguments now will have to be dealt with if the case is come to a close.

NIH is under great pressure to reach some clear resolution to this case. Whether it can do so is a challenge to its ability to conduct a thorough and convincing investigation of highly complex science and emotion. ■ **BARBARA J. CULLITON**

Next week: Stewart and Feder take on David Baltimore; Baltimore fights back.

IOM Elects New Members

The Institute of Medicine has elected 40 new active members and 10 new senior members. This brings the total active membership to 474 and the total senior membership to 301. A new membership category was established with the election of eight foreign associates. The new active members are:

Francois M. Abboud, University of Iowa College of Medicine; **David Baltimore,** Whitehead Institute for Biomedical Research; **Paul B. Batalden,** Hospital Corporation of America; **Edwin L. Bierman,** University of Washington School of Medicine; **Barry R. Bloom,** Albert Einstein College of Medicine; **L. Thompson Bowles,** George Washington University; **M. Paul Capp,** University of Arizona Health Sciences Center; **Charles C. J. Carpenter,** Brown University; **Donald J. Cohen,** Yale University; **Stanley N. Cohen,** Stanford University School of Medicine; **Linda C. Cork,** Johns Hopkins Hospital; **Barbara J. Culliton,** *Science*; **John R. David,** Harvard School of Public Health; **Paul A. Ebert,** American College of Surgeons; **John M. Eisenberg,** Hospital of the University of Pennsylvania; **Bernard N. Fields,** Harvard Medical School; **Delbert A. Fisher,** Harbor-UCLA Medical Center; **Paul S. Frame,** Tri-County Family Medicine Program, Dansville, NY; **Robert J. Genco,** State University of New York at Buffalo; **Enoch Gordis,** National Institute on Alcohol Abuse and Alcoholism.

Emil C. Gotschlich, Rockefeller University; **David G. Hoel,** National Institute of Environmental Health Sciences; **Barbara S. Hulka,** University of North Carolina School of Public Health; **Lewis L. Judd,** National Institute of Mental Health; **Eric R. Kandel,** Columbia University College of Physicians and Surgeons; **Charles A. Kiesler,** Vanderbilt University; **Sheldon S. King,** Stanford University Hospital; **Luella Klein,** Emory University School of Medicine; **Casimir A. Kulikowski,** Rutgers University; **Norma M. Lang,** University of Wisconsin School of Nursing; **Philip W. Majerus,** Washington University School of Medicine; **Joseph B. Martin,** Harvard Medical School; **Frank A. Oski,** Johns Hopkins Children's Center; **Michael I. Posner,** University of Oregon; **Robert W. Schrier,** University of Colorado Health Sciences Center; **Kenneth I. Shine,** University of California School of Medicine at Los Angeles; **Stephen M. Shortell,** Northwestern University J. L. Kellogg Graduate School of Management; **David B. Skinner,** Cornell University Medical College; **Solomon H. Snyder,** Johns Hopkins University; **Noel S. Weiss,** University of Washington School of Public Health and Community Medicine.

The new senior members are:

Leo K. Bustad, Washington State University College of Veterinary Medicine; **Philip S. Holzman,** Harvard University, McLean Hospital; **Joseph Larner,** University of Virginia School of Medicine; **Aaron B. Lerner,** Yale University School of Medicine; **Bernard Lown,** Lown Cardiovascular Group, Boston; **Jonathan E. Rhoads,** Hospital of the University of Pennsylvania; **Rudi Schmid,** University of California, San Francisco; **Benno C. Schmidt,** J. H. Whitney & Co., New York City; **Albert J. Stunkard,** University of Pennsylvania School of Medicine; **Homer R. Warner,** University of Utah School of Medicine.

The first foreign associates are:

Brian Abel-Smith, University of London, England; **Mario M. Chaves,** National School of Public Health, Brazil; **Richard Doll,** University of Oxford, England; **Adetokunbo O. Lucas,** Carnegie Corporation of New York; **A. Mangay Maglacas,** World Health Organization, Switzerland; **Ian R. McWhinney,** University of Western Ontario, Canada; **Sten Orrenius,** Karolinska Institutet, Sweden; **Michael L. Rutter,** University of London, England.