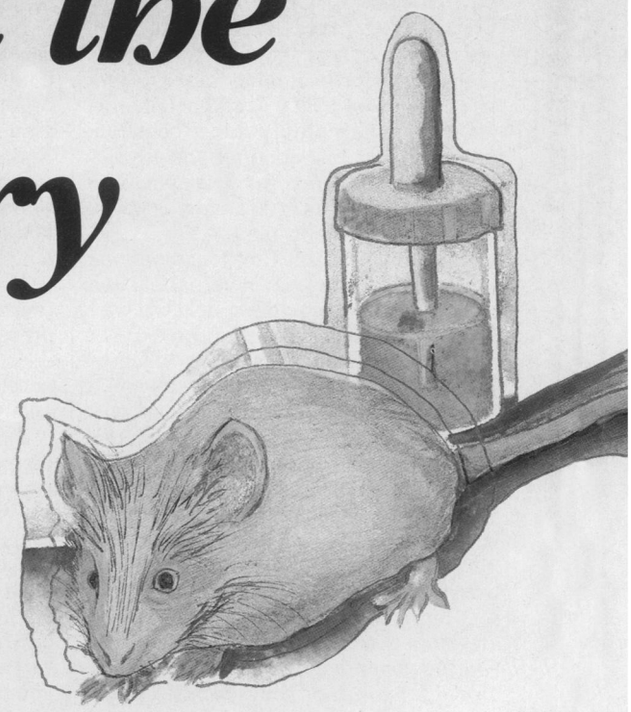
Trouble in the Laboratory

Probing the science of a controversial paper



By KATHY A. FACKELMANN

Scientists reading the April 25, 1986 CELL were surprised by one research team's bold report.

Immunologist Thereza Imanishi-Kari, molecular biologist David Baltimore and their colleagues described experiments with mice that had been engineered to carry a foreign gene. When the researchers examined immune-system cells from the transgenic mice, they found large amounts of a type of antibody displaying the characteristic chemical signature, or idiotype, of the foreign gene.

That would have been a routine finding if the team had also determined that in most cases the inserted gene had "turned on" and directed these cells to produce the antibody it encoded. Instead, they reported that the foreign gene was *not* turned on in most of the cells, but rather it had somehow influenced the mouse's own genes to mimic the foreign gene's idiotype. In other words, many of the mouse's own genes apparently gained the ability to direct immune-system cells to produce "copycat" antibodies carrying the signature of the inserted gene.

This unprecedented finding, later dubbed idiotypic mimicry, provided the central conclusion of the CELL paper. And it was precisely that conclusion that Margot O'Toole—a postdoctoral scientist working with the same mice under Imanishi-Kari's supervision at MIT—challenged in May of 1986.

In discussions with university officials, O'Toole contended the authors of the paper had made serious scientific errors. Their underlying data, she said, did not support their conclusion of idiotypic mimicry. Now O'Toole has alleged outright fraud, claiming that Imanishi-Kari manufactured data after learning of the challenge.

Nearly four years after its publication, the research paper, the authors and O'Toole's allegations remain the focus of a congressional investigation led by Rep. John D. Dingell (D-Mich.) and a renewed inquiry by the National Institutes of Health, which funded the now-famous mouse study.

The following account of the research leading to the 1986 CELL paper and the controversy surrounding it is based on testimony before the House Subcommittee on Oversight and Investigations, the report of a special NIH panel that investigated O'Toole's original complaints, and interviews with scientists familiar with the journal article.

NIH initially assembled a scientific panel in January 1988 to investigate the issue, but had to start over in March 1988 when critics pointed out that two of the three appointed panelists had close professional ties to Baltimore. A second NIH-commissioned panel issued a report in February 1989 clearing the CELL team of "fraud, misconduct, manipulation of data, or serious conceptual error" (SN: 2/11/89, p.85).

Then, during congressional hearings last May, Secret Service agents presented forensic evidence to Dingell's subcommittee showing that someone had altered laboratory pages describing key experiments cited in the CELL paper (SN: 5/13/89, p.294). The new evidence, which NIH learned about before the hearing, prompted the agency to reopen its inquiry.

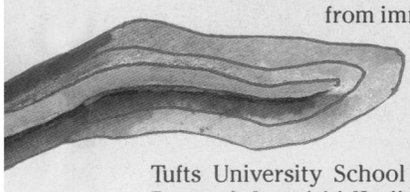
In the end, the dispute's resolution—and the careers of some of the researchers involved—may hinge on further forensic evidence now being compiled by Dingell's subcommittee with the help of the Secret Service. If the subcommittee finds evidence that points to fraud or perjury, it can turn the matter over to the Department of Justice for investigation.

The science of the CELL paper tends to get lost in the sometimes-acrimonious debate in Washington, yet those scientific details are crucial to a full understanding of the affair. A number of researchers in the field say they were skeptical of the paper's central claim of idiotypic mimicry from the start. Nonetheless, most seem to view the Dingell inquiry as an onerous government intrusion that has unfairly targeted Baltimore, a Nobel laureate who directs the MIT-affiliated Whitehead Institute for Biomedical Research in Cambridge, Mass., and who will become president of

Rockefeller University in New York City on July 1.

At the same time, a few scientists say Baltimore and Imanishi-Kari too quickly dismissed O'Toole's legitimate scientific concerns, and they are disturbed by the questions raised at the Dingell hearings. For the general public, the case prompts questions about whether scientists can adequately police their own ranks to rout out cases of misconduct and fraud.

The CELL paper was a collaborative report, combining data from molecular studies directed by Baltimore at the Whitehead Institute and results from immunologic studies directed by Imanishi-Kari at MIT. (She has since moved to Tufts University School of Medicine in Boston.) Imanishi-Kari's team analyzed the antibodies produced by the mouse cells, providing the bulk of the scientific evidence for idiotypic mimicry. In Baltimore's laboratory, postdoctoral scientist David Weaver studied some of the genes directing antibody production, a relatively minor component of the evidence presented in the paper.



The data furnished by Baltimore's lab have not been challenged. However, as a leader in the scientific community, the most prominent member of the research team and a vocal defender of Imanishi-Kari and the paper's findings, Baltimore was questioned extensively in the House subcommittee hearings.

When contacted recently by SCIENCE NEWS, Baltimore (through a spokesman) and Imanishi-Kari declined requests for interviews. Other scientists familiar with the CELL paper, including O'Toole, agreed to discuss it, though some did so only on the condition of anonymity.

Most of the scientists interviewed by SCIENCE NEWS said they were startled by the central claim of idiotypic mimicry when the CELL paper came out in 1986. Since that time, at least one research team has reported finding "no evidence" of idiotypic mimicry in a similar study of engineered mice (see box, p.203). Now some scientists say they simply don't believe the CELL paper's main conclusion. Mark Ptashne, a molecular biologist at Harvard University, calls the notion of idiotypic mimicry "almost certainly wrong."

Because the paper's results were so surprising, most scientists expected to see unusually convincing data. Yet NIH investigators and the Dingell subcommittee have found evidence that seems to undermine those very data.

Here's what the CELL authors did and what they found, as described in their paper:

The team selected a gene that codes for a specific component of an antibody belonging to a class called immunoglobulin M (IgM). They removed this gene from one strain of mice and inserted it into the fertilized eggs of a different strain of mice. They then studied the genetically engineered mice that resulted by removing white cells from the lymph nodes and spleen and fusing each of these immune-system cells with a type of cancer cell, creating "hybridomas" that would proliferate in culture indefinitely — a standard research tool. Each hybridoma produced large quantities of antibody.

When the researchers looked at the antibodies produced by the hybridomas, they found that 28 percent of the hybridomas from spleen cells and 68 percent of those from lymph nodes produced antibodies carrying the distinctive idiotype of the foreign gene. In contrast, fewer than 1 percent of their control hybridomas — derived from the immune-system cells of normal mice — made antibodies with that particular idiotype signature.

There's no surprise in finding an elevated number of hybridomas in which a foreign gene is expressed. However, the CELL authors claimed that in most hybridomas, the transferred gene didn't get turned on at all but somehow forced the mouse's own genes to direct production of antibodies with the same idiotype as the foreign gene.

"This was a seminal paper," says O'Toole. "They were making the claim in that paper that more than 68 percent of the immune system of this mouse has been diverted." Nobel laureate Walter Gilbert, a molecular biologist at Harvard University, says he found that claim "very unusual and exciting" upon reading the report. Ptashne adds: "The essential thing that struck everybody when that paper came out was this claim that the transgene can elicit an antibody that has the same idiotype."

The report captured scientists' attention because, as one researcher observes, it appeared to provide the "first convincing" proof of a controversial theory of immune-system regulation proposed in 1974 by immunologist and Nobel laureate Niels K. Jerne, then at the Basel (Switzerland) Institute of Immunology. According to Jerne's theory, a powerful network of activated white cells regulates the production of antibodies with a specific idiotype. The CELL team's findings hinted that scientists might someday harness this network by injecting a foreign gene into human immune-system cells. In principle, once the cells were reinfused into the person's bloodstream, the transgene would activate the network, which in turn would influence the person's own genes to direct wholesale production of a specific antibody. If such a scenario ever became reality, researchers would gain a powerful weapon in the battle against AIDS, cancer and a host of autoimmune disorders.

A preliminary study conducted by O'Toole in 1985 had indicated the presence of these activated white cells in the transgenic mice. The CELL report cited that early finding as support for the claim of idiotypic mimicry.

But in successive attempts, O'Toole was unable to repeat her initial results, and by early 1986 she had formed other doubts about idiotypic mimicry, she says. The unsuccessful repeated attempts, coupled with her other work with the engineered mice, suggested to her that there were no mysterious "me-too" antibodies and that most of the antibodies with the foreign idiotype were nothing more than routine transgene products, O'Toole says.

The science of the CELL paper tends to get lost in the sometimes-acrimonious debate in Washington.

Then, in early May 1986, while looking through the MIT lab for some breeding data on one of the mice, O'Toole came across 17 pages of raw data used for Table 2 and Table 3 of the published report, according to her congressional testimony. Those laboratory pages, she told the subcommittee, confirmed her suspicions that Imanishi-Kari's data did not show copycat antibody at all and that most of the "idiotype-positive" antibody instead came from the inserted gene.

By themselves, O'Toole's objections might have been dismissed as a personality conflict with Imanishi-Kari. O'Toole acknowledged in her congressional testi-

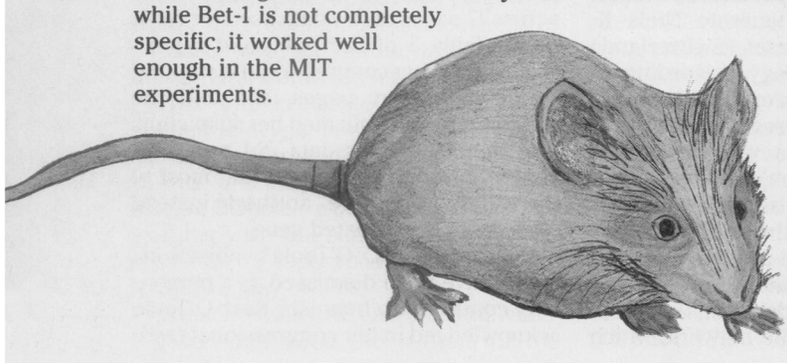
mony that by the spring of 1986 her relationship with her supervisor was strained — as a result, she told SCIENCE NEWS, of her failure to repeat the dramatic preliminary finding of activated white cells. But a growing body of evidence compiled by outside investigators suggests Imanishi-Kari may have made serious mistakes that undermine the paper's conclusion.

Several inquiries have cast doubt on Table 2, where the authors present data showing that 130 of 172 hybridomas (76 percent) were secreting copycat antibodies encoded by the mouse's own genes but carrying the signature idiotype of the transgene.

Perhaps the most publicized complaint about Table 2 involves the MIT researchers' use of Bet-1 as one of the two key reagents in their experiments. Having observed that some hybridomas were secreting idiotype-positive IgM, Imanishi-Kari's laboratory relied on the Bet-1 reagent to identify IgM resulting from transgene expression as opposed to IgM resulting from expression of the mouse's own genes. They concluded that 11 hybridomas were producing the latter type — the copycat IgM. But O'Toole told the NIH panel that Bet-1 never reliably distinguished between the two types of IgM, and the NIH panel called Bet-1 a "problem" reagent in its 1989 report.

The CELL paper implied that Bet-1 always worked in Imanishi-Kari's experiments. Yet in a letter dated Sept. 6, 1986, Baltimore seemed to suggest Bet-1 was less than reliable and that Imanishi-Kari knew of the problem from the start. "The evidence that the Bet-1 antibody doesn't do as described in the paper is clear," he wrote to MIT immunologist Herman Eisen, who was conducting an early MIT review of O'Toole's challenge at the time. "Thereza's statement to you that she knew it all the time is a remarkable admission of guilt."

More than three years later, Baltimore told the congressional subcommittee his letter was sparked by Eisen's own misunderstanding of what Imanishi-Kari was trying to say about Bet-1. Baltimore noted that Imanishi-Kari, whose native language is Portuguese, has a poor command of English. He went on to say that while Bet-1 is not completely specific, it worked well enough in the MIT experiments.



There are allegations that Table 2 reflects another, deeper flaw. Walter W. Stewart and Ned Feder, two NIH scientists with a long-standing interest in cases of possible scientific fraud, analyzed the 17 lab pages obtained by O'Toole. After several unsuccessful attempts to publish the results of their analysis in scientific journals, Stewart and Feder circulated the manuscript among the scientific community. In their report, dated September 1987 — and later attached to the NIH panel's 1989 report and entered into the House subcommittee's official documents — the two scientists argued that Imanishi-Kari's laboratory used a faulty method of classifying hybridomas as producers of the copycat antibody. The CELL authors had reported exposing the fluid surrounding hybridomas to Bet-1 and to an idiotype-detecting reagent, then categorizing hybridomas as idiotype-positive and/or positive for the transgene product by using the same numerical cutoff point for both reagents. Stewart and Feder maintained, however, that Bet-1 was not as sensitive as the idiotype reagent and thus required a different cutoff point. The end result of that invalid classification system, they contended, was that Imanishi-Kari's laboratory marked many hybridomas as secreting copycat antibody when in fact those hybridomas were making transgene product. That conclusion goes hand in hand with O'Toole's original complaint that the data underlying the CELL paper contained no evidence of idiotypic mimicry. Under an agreement with NIH, Stewart is now assisting in the congressional inquiry.

The report captured scientists' attention because it appeared to provide the "first convincing" proof of a controversial theory of immune-system regulation.

As additional evidence of idiotypic mimicry, the CELL paper cited the authors' discovery that 119 of the 172 hybridomas were secreting other antibodies, primarily immunoglobulin G (IgG), that carried the signature idiotype of the transgene. Scientists who read the 1986 paper say this finding in so many of the hybridomas seemed to provide "dramatic proof" of the idiotypic mimicry claim: Since the transgene didn't code for IgG, only the mouse's own genes could have directed its production.

Yet despite the importance of the finding, the paper did not include data showing the researchers had done the experiments on the 119 hybridomas. After describing the presence of these molecules as one proof of idiotypic mimicry, the report states simply: "Data not shown."

The authors later acknowledged to the NIH panel that they had never tested these particular hybridomas to see whether they were indeed secreting idiotype-positive IgG. The panel's 1989 report calls the CELL paper's claim regarding the 119 hybridomas "inaccurate" and blames the lapse on "poor interlaboratory communication."

The panel concluded, however, that it had found no evidence of scientific "misconduct." Then, in a subcommittee hearing three months later, the panel chairman conceded that this judgment might not be correct. Joseph M. Davie, vice-president for research and development at G.D. Searle & Co. in Skokie, Ill., made that statement under questioning by subcommittee special assistant Bruce F. Chafin:

Chafin: So they described an experiment that was not done?
Davie: That's correct.
Chafin: Is that misconduct?
Davie: I believe it is misconduct.
Chafin: Did you say misconduct in your report?
Davie: We called it a serious error. It is a subtlety. I'm not sure I can defend it at this juncture.

The control hybridomas described in Table 2 posed another problem. The researchers reported in CELL that fewer than 1 percent of the hybridomas made from the cells of control mice secreted idiotype-positive antibody.

But in their report, Stewart and Feder maintained that Imanishi-Kari's laboratory notebooks told a different story. Their analysis of the 17 pages obtained by

O'Toole led them to conclude that fully 39 percent of the hybridomas taken from one control mouse secreted idiotype-positive antibody, contradicting the CELL paper's assertion that the phenomenon appeared only rarely in controls. Imanishi-Kari later told the NIH panel that the control mouse in question had been mislabeled and was actually a transgenic mouse.

Some scientists say the suggestion that the controls did not work prompts serious questions about the rest of the data in Table 2.

"Those [17] pages seem to describe an experimental configuration in which the controls don't work at all – a claim that alarms anybody that maybe the underlying data isn't there," says Harvard's Gilbert.

Although the NIH panel cleared the CELL authors of "fraud, misconduct, manipulation of data, or serious conceptual error" in its 1989 report, Davie said at the May congressional hearing that it was not entirely possible for the panel to determine whether the researchers intended to deceive the scientific community. Among the data considered by the panelists was the CELL paper's Table 3.

By all accounts, the added data appeared to provide conclusive proof of the authors' claim of idiotypic mimicry.

In that table, the authors offer data showing that 18 of 34 transgenic hybridomas (53 percent) were secreting the copycat antibodies under the direction of the mouse's own genes. They describe those 18 hybridomas as transgene-negative, yet the 17 pages of lab notes show that most of them were transgene-positive, Stewart told SCIENCE NEWS.

After hearing all the evidence, the NIH panel apparently found Table 2 too flawed and Table 3 too weak to support the paper's major conclusion. "We decided that the whole thing [study] should be thrown out the window," remarked NIH panel member Hugh O. McDevitt of Stanford University during a panel meeting. But, he added, "it was Thereza coming back the next day and saying, 'Well, we've got subcloning that supports [idiotypic mimicry]' that convinced us that maybe there was something to the thesis."

The results of the subcloning experiments, in which the researchers diluted the hybridoma-containing liquid to isolate single hybridomas, appeared in the May 19, 1989 CELL as an expansion and correction of the original Table 2. By all accounts, the added data appeared to provide conclusive proof of the authors' claim of idiotypic mimicry. In the expanded report, Imanishi-Kari and Baltimore attribute the improved results to a more sensitive method of detecting copycat antibodies and determining their genetic source.

O'Toole insisted to both the NIH panel and the House subcommittee that Imanishi-Kari told her shortly after publication of the original CELL paper that such experiments had not been performed. When the NIH panel asked Imanishi-Kari about the Table 2 subcloning data, she responded: "At no time did I say to Dr. O'Toole that the subcloning analysis of [the hybridoma-containing] wells in Table 2 was not performed."

In a Nov. 6, 1989, letter to the NIH's Office of Scientific Integrity, O'Toole filed a formal allegation of fraud.

The Dingell investigation is awaiting a forensic analysis of the Table 2 subcloning data and has subjected Imanishi-Kari's laboratory notebooks to a detailed analysis by Secret Service agents and congressional staffers.

The renewed NIH investigation, meanwhile, continues. The panel consists of the three previous members plus two new members, Stewart Sell of the University of Texas Health Science Center in Houston and William R. McClure of Carnegie Mellon University in Pittsburgh.

The ongoing dispute raises important questions about the scientific community's ability to handle allegations ranging from scientific error to outright fraud. While most re-

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The question of confirmation

For scientists, the real test of any new finding is whether other researchers can confirm the published results. In the case of the CELL team's claim of idiotypic mimicry, such confirmation remains a murky issue.

Henry H. Wortis of the Tufts University School of Medicine in Boston testified to Dingell's subcommittee last May that no research group had confirmed the CELL paper's central conclusion. Later in the same hearing, however, Wortis said: "The central conclusions have been confirmed; those [confirming data] have not yet been submitted for publication." When contacted by SCIENCE NEWS, Wortis declined to name the research team, saying: "It's unpublished data and I can't comment on it."

Margot O'Toole contends the notion of idiotypic mimicry has never been confirmed in any publication. Other scientists interviewed by SCIENCE NEWS say they agree with that assessment.

In his public statements, David Baltimore has never addressed the question directly. "No result of the paper has been proved wrong, a number have been replicated and there has been significant progress building on the foundation of its results," he told the Dingell subcommittee.

During those hearings, Baltimore cited a study of transgenic mice by Erik Selsing and his colleagues at Brandeis University in Waltham, Mass. But Selsing says that study, described in the April 1989 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES (Vol.86, No.7), cannot bolster the CELL paper's central claim. "We do not believe that our work provides evidence for idiotypic mimicry," Selsing wrote to Baltimore on May 1, 1989.

In the Sept. 15, 1989 JOURNAL OF IMMUNOLOGY, Selsing's group went on to report a study designed to approximate the model used by the CELL team. The Brandeis researchers made hybridomas from immune-system cells taken from transgenic mice and analyzed the resulting antibodies. The finding, as reported in the paper: "No such idiotypic mimicry." Selsing told SCIENCE NEWS his work shows that all antibodies with the transgenic idiotype resulted from transgene expression.

O'Toole told SCIENCE NEWS Selsing's more recent study supports her claim that the copycat antibodies described by the CELL authors were nothing more than transgene products. Selsing, on the other hand, says his work doesn't directly disprove the CELL paper's finding of idiotypic mimicry because the foreign gene in his transgenic mice differs slightly from the one studied in the CELL experiments.

– K.A. Fackelmann

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searchers still believe that self-regulation, rather than outside investigation, is the best way to keep the halls of science clean, some say Baltimore and Imanishi-Kari themselves helped bring on the federal fraud-squad by their failure to resolve the issue and/or publish a correction when O'Toole first voiced her objections.

James B. Wyngaarden, then director of NIH, expressed that view in a letter sent to the CELL authors just before public release of the NIH panel report in February 1989. "Even though the allegations have been known to you and the other coauthors of the CELL paper at least since the spring of 1986," he wrote, "the coauthors never met to reexamine the data to determine whether there might be some basis for the allegation; such an analysis on the part of the paper's coauthors, followed by appropriate action to correct such errors of oversights, may well have made a full investigation unnecessary."

But Baltimore responded with a different version of the events. In a letter published in the winter 1989-90 ISSUES IN SCIENCE AND TECHNOLOGY, he wrote: "Wyngaarden was wrong; Thereza Imanishi-Kari, David Weaver and I met with O'Toole under the aegis of MIT professor Herman Eisen within two weeks of learning of her challenge."

O'Toole told the House subcommittee that Imanishi-Kari and Baltimore acknowledged to her in May 1986 that the necessary experiments had not been done, and stated they did not intend to publish a correction.

Indeed, in his Sept. 9, 1986 letter to Eisen, Baltimore wrote: "The literature is full of bits and pieces now known to be wrong but it is not the tradition to point out each one publicly. A retraction generally goes to the heart of a paper and implies that the data is generally unreliable. If the work came solely from Thereza's laboratory I would wonder about what else might be wrong but I am quite certain that what David [Weaver at the Whitehead laboratory] did is solid."

Initially at least, Baltimore opposed the NIH panel's recommendation that he and his coauthors publish a correction to the flawed Table 2. In their November 1988 response to the NIH panel's draft report, the CELL authors wrote: "It was our belief that [the originally published] Table 2 was the best way to summarize a large amount of data in easily accessible form."

The multifaceted controversy reveals deep flaws in the scientific community's current system for handling internal disputes, Gilbert says. That system, in the form of two university-level reviews, dismissed O'Toole's scientific concerns early on. That's partially because the scientific establishment is something of an insider's club, Gilbert told SCIENCE NEWS, adding: "It's also partially that scientists are not suspicious of human behavior."

Meanwhile, the controversy has exacted a heavy toll from the major players involved. Imanishi-Kari continues to work at her Tufts laboratory with NIH funding. However, says her attorney, Bruce A. Singal, "there has been great cost [to Imanishi-Kari] in terms of adverse publicity, harm to her reputation and distraction from her important scientific pursuits."

For his part, Baltimore's selection as president of Rockefeller University prompted strong opposition last fall when a number of faculty members objected to the appointment because of the ongoing congressional inquiry.

O'Toole has been job-hunting since the summer of 1986 and so far remains unemployed in her field of immunology. "The immunology research community is quite small and it functions basically by word of mouth in terms of recommending who is good and who is not," she told Dingell's subcommittee last May. "I was left without a recommendation. I was left without a job. I was left without any support from anybody in the community." □

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Master vs. machine

Michael Lee Jacobs' comments about Gary Kasparov (Letters, SN: 1/6/90, p.3) are presumptuous, to say the least. Kasparov may have used overly romantic language in claiming that chess transcends logic and calculation ("Computer Chess: A Masterful Lesson," SN: 10/28/89, p.276), but he is far from naive about the mathematical basis of computer chess.

In comparing chess to tic-tac-toe and implying that computers can arrive at an optimal chess strategy simply by using their speed of calculation to enumerate and compare different board configurations, Jacobs misses a fundamental point: No chess computer, in choosing a move, can take into account all possible future sequences of moves by itself and its opponent. If it did, it would take longer than the age of the universe to make a single move. (There are more possible games of chess than there are atoms in the universe.) This is a practical consideration that cannot be ignored.

Wayne Schmittberger
East Windsor, N.J.

Jacobs accuses Kasparov of "innumeracy" and states that chess is a "solvable" game that a computer of sufficient capacity should always win against a human opponent. What Jacobs fails to perceive is that good chess is not just a game; it is also an art, an expression of soul, creativity and elegance. Kasparov's two games against Deep Thought are a case in point. In the first game, he played carefully and soundly and won. In the second game, having taken the measure of the machine, he played more daringly and thrashed the thing in a beautiful game.

A computer lacking a sense of artistry may win, but given a choice between a safe, prosaic win and a somewhat riskier but far more elegant win, can there be any doubt which it would choose? When Gary Kasparov said good chess is more than logic and calculation, he was right, and Jacobs missed the point.

Milton B. Garber
Fulton, Mo.

When humans and computers play chess, they both look at the possible configurations some moves ahead and then compare those *without* considering further configurations. No one has been able to find absolute logical rules to do this comparison. Hence, chess as played by man and machine has proved "wider than calculation and logic," as Kasparov says.

In the absence of absolute logical rules to compare different configurations, a human chess player resorts to intuition and a few guiding principles, which are far from absolute. Intuition has enabled good chess players to beat the best computers, even though the computers look at a far greater number of possible configurations.

Haukur Arason
Gainesville, Fla.

As a former chess expert as well as designer and programmer of Seymour Chess (for the Altair 8800), I beg to differ from Jacobs' criticism of Kasparov as "ignorant of elementary mathematics." Kasparov is right in characterizing chess as wider than calculation and logic, requiring imagination.

The trouble with Jacobs' claim that a computer "theoretically can outwit any human player" is revealed by his qualifying "if armed with enough capacity." Give me a computer whose bits lie as close to each other as atoms in molecules and whose calculations occur at the speed of atomic interactions, but with a memory the size of the galaxy and a time limit equal to the age of the galaxy, and I'll write the program to beat Kasparov or any other human chess expert.

Because no computer has world enough and time, the best chess programs must use a truncated form of the algorithm, plus certain shortcuts, plus some approximation of human chess skills (very hard to define in the precise terms a computer needs). Progress in computer chess comes in several ways: by refining assessments at stopping points, by refining the procedures for ensuring that these stopping points are "restful" and by extending the "look-ahead" to twigs farther down each branch. Eventually a computer will beat a human world champion because its deeper "look-ahead" will more than compensate for its deficiencies in simulating human skills.

Danny Kleinman
Los Angeles, Calif.