A Diversion of the Quest for Truth

A $750,000 research project at Mass General eventually collapsed, leaving a legacy of invented data and useless cell lines

It was around mid-October 1979 that Steven Quay began to suspect that John Long, his senior colleague at the Massachusetts General Hospital, had never performed an experiment they had published together earlier that year. Each time he asked to see the raw data, Long insisted they had been lost and angrily inquired if Quay realized what kind of accusation he was making.

Quay, a resident at the hospital, realized only too well the seriousness of what his request implied. Reporting false data is the worst misdeed a researcher can be accused of. The person who dares impute such behavior to their superior had better be right. Quay had mentioned his doubts to the department chairman, who suggested he prove them. For 2 months Quay was in anguish over whether to persist or to drop his request.

A few days before Christmas, his worst fears came true. Long presented him with a notebook full of the data that had been reported. Quay took one glance at it and was appalled at ever having doubted his colleague's integrity. He sat down with Long, distraught at what he had done, and poured out his regrets. Long accepted the apology graciously.

Two weeks later, Quay had still been unable to bring himself to look at the notebook in detail, but realizing he would soon have to return it to Long, he took it home for study. Late one night, after his wife and daughter were in bed, he had the notebook open in his living room. "The light was hitting the pages at an angle which showed me something I had never seen before," says Quay. "Taped onto the page were photos of Ouchterlony plates. The light was throwing into relief a ridge underneath the tape. I removed it and saw there was part of another piece of tape underneath, as if the photo had been torn out of some other notebook and taped into this one. That fortified me enough to go through the rest of the data."

What Quay then discovered was reason to suppose that the pertinent section of the notebook had been forged. At that point began the unraveling of much of Long's research activities, including work that had hitherto been considered an interesting contribution to the understanding of Hodgkin's disease.

John Long, now contrite and no longer doing research, works as a pathologist in a midwestern hospital. But until his resignation from Mass General in January 1980, he was in mid-flight of a reasonably promising research career. His field of

expertise was Hodgkin's disease, and he was widely known for his almost unique achievement in establishing permanent cultures of the cells that are characteristic of the disease. Long's work is cited and respectfully described by Henry Kaplan of Stanford University, one of the world's leading authorities, in the 1980 edition of his standard textbook on Hodgkin's disease. Long coauthored papers with the group of Nobelist David Baltimore. He was favorably judged by the peer review system which funnels government funds to worthy researchers. Long received a 3-year grant for $209,000 in 1976 and a further grant of $550,000 in 1979.

Mass General is one of the world's leading teaching hospitals and as such is a magnet for physicians who wish to pursue a career in medical research. John Long first joined the staff as a resident in 1970 and from 1972 to 1974 did research in the laboratory of Paul Zamecnik, a member of the National Academy of Sciences. Interested in seeing whether Hodgkin's disease is caused by a virus, Zamecnik was trying to establish cultures of the cells associated with the disease. Most such cultures die out after a time, but Long succeeded in establishing permanent cell lines, which he and Zamecnik described in a series of papers published in the *Proceedings of the National Academy of Sciences* and other journals between 1973 and 1977. The cell lines have been cited as a promising tool for studying the nature of Hodgkin's disease, and also as evidence that the disease originates from the class of cells known as macrophages.

The study of these cell lines became the focus of Long's research. As his career progressed, he acquired two research fellows. He was highly regarded in the hospital, and in July 1979 was promoted to associate professor in the department of pathology.

He would probably still be there, but for a decision he took in May 1978. With Steven Quay's help, he had prepared a paper on the immune complexes formed by the Hodgkin's cell lines. In one of the experiments described in the paper, Quay had measured the density of the immune complexes by ultracentrifugation, and had come up with a figure indicating the complexes were considerably smaller than expected. The paper had been rejected for publication on the advice of a referee who suggested the anomalous measurement should be better substantiated.

In May 1978, Quay left for a 2-week vacation in Michigan. On his return, he learned that Long had repeated the experiment in his absence and obtained a result nearer to the expected figure. Quay, a meticulous experimentalist who trained with Nobelist H. G. Khorana before coming to Mass General, was somewhat surprised that Long had been able to perform the complicated measurement in so short a time.

Long submitted the paper with the new data to the *Journal of the National Cancer Institute*, where it was published almost a year later, in April 1979. Quay was always bothered by Long's result but it wasn't until the fall of 1979 that he decided to reinvestigate the size of Hodgkin's immune complexes by use of a different technique. It was then that he asked Long for the original data.

In January 1980, Quay wrote up a summary of his findings, concluding with

0036-8075/81/0306-1022$01.00/0

a strong suspicion that Long's experiment of measuring the immune complexes had never been done, and took the results to the chairman of the pathology department, Robert McCluskey.

McCluskey confronted Long, who flatly denied the charge. He maintained he had performed the experiments as shown, and he produced the logbooks of the ultracentrifuge to prove it. It seemed to Quay that the entries in the logbook had been written over, but McCluskey said that that was not sufficient evidence to prove Long was lying. Quay then noticed that the logbook also recorded the rotor count of the machine. From the length of run and revolutions per minute recorded in the logbook, Quay computed the expected rotor count. In each case, the count in the logbook was a fraction of what it should have been. An innocent explanation might have been that the machine, as is the wont of ultracentrifuges, had shut down through overheating before the run was completed. So Quay first asked Long if the machine was still running when he came back to it. Long said, yes it was. Quay then explained to him and McCluskey why the inconsistency of the data in the logbook meant that the experiment could not have been undertaken as described.

"He admitted that this was a mistake made under great pressure, and said it was made under pressure for a grant application," notes McCluskey. Long also stated—and still maintains—that this one experiment, amounting to only a few paragraphs in a nine-page article, is the only scientific data he has ever contrived. Long resigned from Mass General as of 31 January 1980.

Then began in earnest the process of trying to unravel what Long had done. The faked experiment, of no great import in itself, raised the more serious question of whether there was anything amiss with the Hodgkin's disease cell lines around which he had built his scientific career. It fell to Long's other research associate, Nancy Harris, to tackle this perplexing issue.

Harris, a pathologist, had almost no experience of research when she joined Mass General in summer 1978, but quickly noticed that there was something peculiar about the cell lines. As Long had stated in his grant applications to the National Cancer Institute, three of the cell lines had a characteristic (the type A form of the enzyme glucose-6-phosphate dehydrogenase) which is typical of HeLa cells. These are the malignant human cells which are notorious for contaminating and overgrowing other human cell cultures in the laboratory. The type A G-6-PD is one of HeLa's trademarks because the cells were derived from a black woman, and the trait is common among blacks but very rare among whites. It so happened that patients from whom the three Hodgkin's cell lines had been derived were white.

But Long discounted the obvious possibility of HeLa contamination, noting that there was no sign of the other known HeLa markers; also, he told his colleagues that one of the patients had been tested and found to be heterozygous for the type A G-6-PD—in other words, that she had genes for both the "black" and "white" variants of the enzyme. The other two patients must have been heterozygous as well, he implied. Harris did not openly dispute this rather implausible assumption because she was beginning to suspect that the three lines were somehow related to each other.

Long's four cultures of Hodgkin's disease cells were designated FQ, RB, SpR, and RY. It was the first three lines which possessed the HeLa-type marker. The fourth, RY was different. It had been established by Zamecnik, Harris learned later, when Long was absent from the laboratory.

In the fall of 1978 there was another disturbing event. Long had been trying to establish new cultures of Hodgkin's cells and asked Harris to take over the project. She saw that in one of the flasks were growing nests of malignant-looking cells, which eventually took over the culture. Consulting the lab notebooks, she found that on the same day that Long had passaged the cells, he had also been working with the RY cell line. "I debated and debated with myself whether to bring up the possibility of contamination with him," Harris recalls. She first prepared a karyotype of the new line and it seemed identical to that of RY. Long's reaction was again to discount the possibility of contamination, but she persuaded him to send the two lines to Stephen O'Brien, a cell culture expert at the National Cancer Institute. O'Brien confirmed that the supposedly new line was simply a case of contamination with RY cells.

By January 1979 Harris had finished preparing karyotypes of all four of Long's lines and had noticed some puzzling features. Malignant cells kept in culture for a long time are not always very stable, but none of the chromosomes in FQ, for instance, was identifiable with any human chromosome. She asked various experts in human cytogenetics how this could be, but the general answer was a shrug of the shoulders.

The similarity between the FQ, RB, and SpR lines now appeared so strong as to suggest a single origin. She persuaded Long to send these lines too to O'Brien, together with a blood sample from the FQ patient.

When the results came back from O'Brien in the spring of 1979, Long didn't show them to his colleagues. According to Harris, "He gave us a series of confused reports, to the extent that I didn't want to work on those three lines any more." Why didn't she call O'Brien herself to get the results directly? "I had no reason to doubt Long's honesty at that time. He had been represented to me as a reputable investigator who was very highly regarded around here. I had suspicions, but I was eager to quell them," Harris reflects.

The problem about the cell lines stood unresolved for a further 9 months. It was Long's admission of inventing data in January 1980 that broke the impasse. Harris then did call O'Brien and learned that her worst suspicions had not been bad enough. The three lines of cells, FQ, RB, and SpR, were all from the same individual, and moreover the FQ line could not have been derived from the patient whose blood sample O'Brien had tested. Further, the patient was not heterozygous for G-6-PD, as Long had claimed. But where then did the FQ-type lines come from?

O'Brien had studied the lines with a panel of six enzyme tests, and assured Harris that they were of human origin. Thinking again of HeLa contamination, Harris sent karyotypes of the cells to a leading expert in the field, Walter Nelson-Rees of the Naval Biosciences *Lab-*

Nonproliferation Shuffle

The Reagan Administration is moving to make major changes in both policy and organization in the handling of nuclear nonproliferation affairs.

Policy shifts by the new Administration are expected to bring the United States into closer accord with its European allies and Japan on nonproliferation questions.

Organizationally, a move is afoot to centralize most responsibility for nonproliferation matters in the State Department by transferring to it nonproliferation functions from the Department of Energy (DOE) and, particularly, from the Arms Control and Disarmament Agency (ACDA).

Reagan advisers have been sharply critical of ACDA, and talk of a shift of nonproliferation authority is being interpreted as evidence of intentions to reduce the staff and scope of the agency.

James L. Buckley

At the State Department, major operating responsibility for nonproliferation matters will apparently be placed in the Bureau of Oceans and International Environmental and Scientific Affairs (OES). Nominated to head OES as assistant secretary is James Malone, a Washington lawyer who gained familiarity with international nuclear issues as general counsel for ACDA during the Ford Administration and later as an attorney in a Washington law firm specializing in nuclear affairs.

Malone has been serving as acting director of ACDA after working on the Reagan transition organization's State Department–ACDA team.

Other major players in nonproliferation matters at State will be former New York senator James L. Buckley, who is now Under Secretary for Security Assistance, Science and Technology, and Richard Burt, a former correspondent for the *New York Times*, nominee for assistant secretary for political and military affairs. Buckley ranks as Malone's immediate superior in the State Department hierarchy.

Malone, if confirmed, will replace Thomas R. Pickering in the assistant secretary post. Pickering, a State Department career officer and former ambassador to Jordan, is generally credited with improving the effectiveness of OES and establishing it in a stronger position in the department.

In respect to ACDA, there has been speculation that changes would follow lines laid down in the report of the transition team working at DOE. The report recommends that ACDA's nuclear export division should in part be transferred to State. There is said to be sentiment among Reagan advisers for reducing ACDA to a size adequate only to carry out statutory activities.

A major consolidation of authority over nonproliferation matters would require changes in legislation. This applies not only to ACDA, but to DOE as well. The DOE transition team report calls for the centralization of international nuclear affairs in a single office in DOE with the possible transfer of responsibility over exports to the State Department. Such a transfer would require changes in the Atomic Energy Act.

Nuclear policy generally and nonproliferation policy specifically have not yet been staked out by the Reagan Administration. At his recent confirmation hearings, Buckley said that nonproliferation issues are under active study; he indicated that changes from Carter Administration practices could be expected.

Secretary of State Alexander M. Haig, Jr., struck a consonant theme in a brief comment during his confirmation hearings. Haig expressed the view that nonproliferation issues should be judged in the context of the overall security interests of the nation.—JOHN WALSH

oratory in Oakland. Nelson-Rees called back almost immediately to say that the karyotype was of a species he had never seen before and could not identify, but that in any event it was not human. O'Brien, using a larger battery of enzymes, confirmed that this was the case. Meanwhile Nelson-Rees, spotting a feature in one of the chromosomes that is a marker for horse, sent the cultures to an expert in identifying a cell's species, Ward Petersen of the Child Research Center of Michigan in Detroit.

By strange coincidence, Petersen had an associate, Bharati Hukku, who happened to notice certain similarities between the chromosomes of FQ and those of a species she had once worked with, the brown-footed owl monkey. From there it was only a few more steps until N. S. F. Ma, of the New England Regional Primate Research Center, identified FQ and the two other lines as derived from a northern Colombian brown-footed owl monkey (see photo*). Harris,

"The problem was that I had tremendous faith in the cell lines."

Nelson-Rees, and others announced this resolution of the problem in a paper published in *Nature* last month. Apart from brief press accounts which appeared several months after Long's resignation, the *Nature* article afforded the first public glimpse of the Long affair.

Searching back through the notebooks of Zamecnik and Long's laboratory, Harris found that Long had been working with an owl monkey cell line, known as OMK-210, at the same time as the FQ cell line was being established. The explanation for the presence of the HeLa marker is that the owl monkey is one of the nonhuman primates that have the type A G-6-PD. As for the fourth line, RY, it is human, but cannot be said to be of Hodgkin's disease, since no tumors were found in the patient from whom the line was derived.

Was the contamination of the three lines with OMK-210 deliberate or accidental? Contamination is a frequent dan-

*Photo of Colombian brown-footed owl monkey, courtesy of New England Regional Primate Research Center.

0036-8075/81/0306-1024$00.50/0

ger in cell culture work and affords an adequate explanation of what is known. "There is no reason to suspect that it was anything other than an accident," says Harris. Zamecnik, a coauthor of the *Nature* paper, takes a similar view: "In general, my feeling would be that some cell lines were mixed up and were responsibile for putting a blight on his career."

The immune complex measurement and the notebook of forged data are the only material which has been proved to be false and which Long has admitted inventing. He has also admitted suppressing the report from O'Brien, and he agrees that he made an incorrect assumption in telling his colleagues that the FQ patient was heterozygous. Three other questions have so far emerged about his work. One concerns a report on the nature of the tumors formed when the FQ-type cells were injected into mice. In a paper published in 1977, Long stated that the tumors were of a cell type possibly related to Hodgkin's disease. But a review of the original slides by other pathologists shows that the tumors are not of this type. "Long should not have made that misinterpretation—he was a good enough pathologist to be able to tell the difference," notes McCluskey.

Another problem, though one not related to the Hodgkin's cell lines, concerns immunofluorescence data which Long supplied to David Baltimore of the MIT Cancer Center. The data in Long's notebook do not exactly match those in a published article, but seem to "vary randomly," says Baltimore. The conclusions inferred from Long's data were corroborated by those derived from an independent technique. A third problem is that although all the cell lines were reported in papers by Long, Zamecnik, and others as having been derived from the spleen tumors of Hodgkin's disease patients, the hospital records show that no tumors were seen or reported in the spleen of patients FQ and RY.

Long, who was allowed to resign from Mass General on the understanding that he would not go back into research, expresses contrition at what he did. Asked if the pressure of competitive research was a factor in his contriving data he replies, "My reaction to this is to offer no excuses. I don't think there is any justification for this on the part of a scientist. It was a matter of acting in haste. It was unfair to my colleagues and the writers of the paper. It was a mistake for which I have paid."

Why did he attribute the HeLa-type marker to the heterozygosity of the patients? "It was an assumption that was not correct," says Long. Why did he then not follow up this clue that something was wrong with the cell lines? "I didn't understand how to proceed and I just lost my objectivity," Long remarks; "The thing to have done would have been to pursue it the way it was pursued."

As to the origin of the FQ and RY cells, Long confirms that the patients did not have spleen tumors, even though the cells were reported as coming from such tumors. "After other cell lines, such as RB and SpR, had been successfully grown, the assumption was that there must have been a tumor in FQ which was not observed," Long says. Zamecnik agrees with this explanation, noting that earlier papers made clear that tumors had not been observed.

Long states that the only research he invented was that to do with the size of the immune complexes. But the problems with his research career, whether of this or a purely accidental nature, seem to go right back to the beginning, to the very establishment of the cells in 1973. To the question of whether he may not have contrived a lot more than just the experiment caught by Quay, Long replies, "I realize this hypothesis has to be raised, but it just is not correct." The cells were unintentionally contaminated, he says, and he discussed with others the

problem of the HeLa marker as soon as it came to his attention. "I think part of the problem was that I had tremendous faith in the cell lines. I had worked so hard on them that I believed they were the real thing."

How did the problems with the cell lines escape detection for so many years? Long was not an obscure researcher pursuing some backwater project in a minor institution. He was working in a highly visible research area. Contamination of cell cultures is a frequent and serious problem that has been widely advertised. Long's grant application mentioned that the cells had the HeLa marker, yet the peer review system twice approved the merit of his work and awarded him some $750,000, $305,000 of which had been spent at the time of his resignation. "The nature of the data he was presenting had a sufficient degree of plausibility that the peer review system had little opportunity to make the kind of judgment which might have detected this earlier," says William Raub, the NIH's associate director for extramural research. "With the credentials of background and training that Long presented, the study section would expect that he would be aware of this problem," observes Stephen Schiaffino of the NIH Division of Research Grants.

The Long affair is only one among several instances of scientific fraud that have recently come to light. Several research directors asked about the problem suggest that the increase is only apparent: instances of fraud are just more likely to be brought to public attention now than in the past. "It is unlikely that people are being any more dishonest than they ever were," says Ronald Lamont-Havers, a former NIH official who is now research director at Mass General. Scientists' denunciations of one another, triggered by cutbacks on research funding, are one mechanism that brings fraud cases out into the open, Lamont-Havers believes. According to Baltimore, "There is no question that the pressure on research workers grows because of the limitation of funds and the increasing formalism of the academic world, with its demands to produce and appear successful, and I am sure that everyone has a cracking point. But whether any of this has to do with John Long or not, I have no idea."

Long was able to take his research career so far in part because he was highly regarded by his superiors, and his junior colleagues were reluctant to challenge him. When problems surfaced with the cell lines on which his research career was largely based, he protected his career by concealing the problems. Sympathy may be due to a person caught in such a predicament, but a scientist cannot dally with the temptation to which Long gave in. At whatever point and for whatever reasons he started on the path of deception, he found it difficult to abandon. As Long remarks, he has paid the price for his mistake.

—NICHOLAS WADE