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ORI Oversight Report

University of Medicine and Dentistry of New Jersey

ORI 2001-28

Office of Research Integrity



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ORI Overview and Summary of Findings

Overview

The Office of Research Integrity (ORI) reviewed the report of an inquiry carried out by the University of Medicine and Dentistry of New Jersey (UMDNJ) into allegations of possible scientific misconduct on the part of Dr. Anupam Bishayee, Research Associate, Department of Radiology, UMDNJ. The complainant, Professor Helene Z. Hill, alleged that Dr. Bishayee had falsified data in October 1999, but that when she brought this to the attention of the head of the laboratory, Associate Professor Roger Howell, Dr. Bishayee's supervisor, her concerns were ignored. Instead, Dr. Howell included the disputed data in his National Institutes of Health (NIH) grant application, which was reviewed and funded by the National Cancer Institute (NCI). In March 2001, Dr. Hill had concerns brought to her attention by Dr. Marek Lenarczyk, a senior post-doctoral fellow, about an ongoing experiment of Dr. Bishayee. She and Dr. Lenarczyk observed and monitored the experiment for several days. She then brought an allegation of falsification of research and her documentation of it to Dr. Howell, to their departmental chairman, and then to the head of the Committee on Research Integrity. That committee carried out an inquiry between April 2001 and June 2001 and concluded that the matter did not warrant an investigation.

This case came to ORI in August 2001 in the form of a request that ORI review the UMDNJ decision. ORI verified that the questioned 1999 research data had been included in a grant application submitted to and subsequently funded by the U. S. Public Health Service (PHS), and that the questioned 2001 experiment was research funded by the PHS. On September 4, 2001, the Division of Investigative Oversight (DIO) of ORI asked Dr. Karen Putterman, Vice President for Academic Affairs, UMDNJ, to send the institution's Inquiry Report to ORI for review.

Summary of PHS Issues

PHS Issue 1 That Dr. Anupam Bishayee fabricated or falsified data in an experiment in September/October 1999 in which he measured the cell survival and induction of mutations following the irradiation of cultured mammalian cells with cesium-137.

PHS Support: The questioned data was included as Figure 7 in grant application 1 R01 CA83838-01A1.

PHS Issue 2 That Dr. Anupam Bishayee falsified data of an experiment done March 26-30, 2001, on the viability of "bystander cells" incubated for three days in the cold in contact with cells that had incorporated tritiated thymidine into their DNA and the separation of those cells by fluorescence activated cell sorting.

PHS Support: This questioned research was supported by PHS grant R01 CA83838.



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PHS Issue 3: That Dr. Anupam Bishayee falsified data showing an effect of tritiated thymidine on the survival of bystander cells presented in a PHS grant application (R01 CA83838-01A1, Figures 2 & 4) and in two published articles, Bishayee et al. (1999),¹ **Radiation Research 152**, 88-97 (Figures 3 & 6) and Bishayee et al. (2001)² **Radiation Research 155**, 335-344 (Figure 2A).

PHS Support: The questioned data appeared in the PHS grant application CA83838-01A1 and was supported by PHS grants R01 CA83838 and S10 RR14753-01.

For Discussion:

That DIO **not concur** with the institution's determination that there was insufficient evidence to warrant an investigation and that DIO request that UMDNJ proceed to an investigation. The basis for this recommendation is that (1) examination of the data of 1999 by DIO suggested that the numbers showed unexpected properties: very striking reproducible replicates and repetitive appearance of certain numbers and digits in purportedly machine generated numbers; (2) the inquiry was incomplete, since it did not verify the experimental basis of the bystander effect on survival, which was crucial to the funded research grant, even though this finding was alleged to be not reproduced by others in this laboratory and, therefore, was falsified (or erroneous); (3) the committee apparently was not sufficiently knowledgeable to evaluate these experiments; (4) the inquiry committee appeared to be biased against the complainant; (5) the head of the laboratory, when asked to provide further information, failed to provide experimental data to support the claimed bystander effect (of tritium decay) that was the basis of his funded research.

PHS Relevance³

¹Bishayee, A., Rao, D.V., and Howell, R. W. (1999) "Evidence for pronounced bystander effects caused by nonuniform distributions of radioactivity using a novel three-dimensional tissue culture model," *Radiat. Res. 152*: 88-97 (1999) (Attachment 3), cited in grant application 1 R01 CA83838-01A1, pp. 2, 26 and p. 48 (as ref. 66) (Attachment 1).

² Bishayee, A., Hill, H.Z. Stein, D. Rao, D.V. and Howell, R. W. (2001) "Free-radical initiated and gap junction-mediated bystander effect due to nonuniform distribution of incorporated radioactivity in a three-dimensional tissue culture model," *Radiat. Res 155*: 335-344 (Attachment 4), also reported in grant application R01 CA83838-02, p. 6. (Attachment 2)

³**PHS Definition of Misconduct:** Scientific misconduct is defined in the PHS regulations at 42 C.F.R. § 50.102 as "fabrication, falsification, plagiarism, or other practices that seriously deviate from those that are commonly accepted within the scientific community for proposing, conducting, or reporting research. It does not include honest error or honest differences in interpretations or judgments of data."



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The questioned research was reported as preliminary data in an National Institutes of Health (NIH) grant application or was supported by the following NIH grant:

1 R01 CA83838-01A1 and -02, "Effects of non-uniform distributions of radioactivity", Roger Howell, P.I., submitted October 21, 1999, and awarded July 1, 2000, to June 30, 2005. (Attachments 1 and 2)

Background

A caller who sought confidential status from ORI in August 2001 had originally questioned an experiment, carried out by Dr. Bishayee and Dr. Howell in 1999, measuring the effects of radiation on cell survival and the induction of mutations in bystander cells. In the next year, supported by a PHS grant, more experiments were carried out to test the hypothesis that animal cells that have not been irradiated (bystander cells) are killed by close association with irradiated cells (the bystander effect).⁴ Their laboratory published data suggesting that the effect required the formation of gap junctions between irradiated and bystander cells.² However, the validity of the bystander effect on survival was challenged in the laboratory in 2000-2001 by the data of a senior postdoctoral associate, Dr. Marek Lenarczyk,⁵ who was unable to confirm the bystander effect on cell survival. The caller claimed that Dr. Howell himself also had not been able to replicate the key experiments that he had presented in the grant and published. The caller now questioned a more recent experiment, claiming that the evidence she had gathered suggested that Dr. Bishayee continued to falsify data. Thus the allegation that two particular experiments may have been falsified and that the effect of tritium decay on bystander cell survival has not been reproducible led the caller to challenge the basis and the integrity of the research being carried out with PHS support in Dr. Howell's laboratory. (Attachment 5)

The caller also alleged that Professor Howell had retaliated against the respondent, the complainant, and a witness after the inquiry was completed, taking actions that included forcing the respondent to resign, not renewing the research appointment of Dr. Lenarczyk, a witness to the alleged falsification of research, and, with the cooperation of the Department Chairman, Dr. Baker, abolishing the research section of the complainant and attempting to exclude her from the departmental laboratory. The caller considered these actions to be further evidence of an attempt by Dr. Howell to protect and retain his grant funding, even when the bystander effect was not reproducible.⁶

⁴ Howell, R.W. and Bishayee, A.(2002) "Bystander effects caused by non-uniform distributions of DNA-incorporated ¹²⁵I", *Micron* 33, 127-132, cited in CA83838-02, p. 6 (Attachment 2).

⁵ According to his Biographical Sketch in CA83838-02, Dr. Lenarczyk received his Ph.D. in Poland in 1988 in Biology/Radiobiology, had 10 years of post-doctoral experience, and was a Research Assistant Professor at the National Institute of Hygiene, Warsaw Poland, before joining Dr. Howell at UMDNJ. He listed seven current publications therein (Attachment 2, p. 2).

⁶ According to ORI policy, the allegations of retaliation were forwarded to DEI, ORI..



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Dr. Anupam Bishayee received his Ph.D degree from Jadavpur University, Calcutta, India, in 1996. He was a Research and Teaching Specialist in Dr. Howell's laboratory from 1997 to 2000, when he was promoted to Research Associate. He resigned in July 2001, returned to India, and at the end of 2001, returned to join a different laboratory at UMDNJ. At the time of the inquiry, Dr. Bishayee's research at UMDNJ was on the effects of radiation on cultured mammalian cells.

Dr. Roger Howell is an Associate Professor of Radiology at UMDNJ. He was awarded a Ph.D. in Physics in 1987 by the University of Massachusetts. He was P.I. on NIH grant R29 CA54891 from 1991 to 1997, investigating the biological effects of alpha particle emitters as they relate to radon exposure. Dr. Howell is P.I. on NIH grant, R01 CA083838, that is based on and supports the questioned research on the effect of radiation on bystander cells (funded 2000-2005).

Dr. Helene Hill, the complainant, is Professor in the Departments of Radiology, Microbiology and Molecular Genetics, and Biochemistry and Molecular Biology at UMDNJ. She was awarded a Ph.D. in Biology by Brandeis University in 1964 and joined UMDNJ in 1981. At the time of the allegation, Dr. Hill was a co-investigator on NIH grant R01 CA083838 (Attachment 1, p.2). Her biographical sketch lists many publications on DNA damage and radiation resistance, many using *in vitro* systems and mouse melanoma cell lines (Attachment 1, pp. 8-9).

Institutional Inquiry: Process

On April 10, 2001, Dr. Helene Hill and Dr. Roger Howell met with Dr. Elizabeth Raveché, Chairman of the Newark Campus Committee on Research Integrity (Attachment 6, Inquiry Report, p. 2). Dr. Hill submitted a written allegation against Dr. A. Bishayee of falsification of data with documentation of her observations. Dr. Raveché, after consultation with Dr. Putterman, Vice President for Academic Affairs, instituted an inquiry into the allegations.

A formal inquiry into two allegations was carried out by the Newark Campus Committee on Research Integrity (CRI), consisting of the following participating members:

- Neil Cherniack, M.D., Professor, Departments of Medicine and Pharmacology and Physiology, and Associate Dean for Research and Sponsored Programs
- Daniel Fine, D.D.S., Professor, Department of Oral Pathology, Biology and Diagnostic Sciences, and Dean for Research
- Anthony Forrester, Ph.D., R.N., Professor and Assistant Dean, UMDNJ School of Nursing,
- Teresa Marsico, M.Ed., D.N.M., UMDNJ School of Health Related Professions
- Elizabeth Raveché, Ph.D., Professor, Department of Pathology and Laboratory Medicine (Committee Chair).



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A sixth member of the CRI, Dr. Anthony V. Boccabella, Ph.D., L.L.D., Professor in the Department of Anatomy, Cell Biology and Injury, was absent from the first meeting and did not participate in the inquiry.⁷

Sequestration of Evidence

Research notebooks and materials were sequestered by Dr. Raveché on the day she received the allegations, April 10, 2001. Aided by Dr. Howell, she sequestered “32 binders, 4 notebooks, 46 diskettes, 7 zip disks and 38 petri plates.” Dr. Hill gave to Dr. Raveché a binder containing her written allegations, narrative, diaries, photographs, copies of original data from Dr. Bishayee’s notebook and original data of Dr. Hill. Later, the committee obtained additional materials: the grant application, “all publications on which the grant was based,” all publications appearing subsequent to receipt of the grant that reported data developed under the grant, all abstracts pending presentation, and the biographical sketches of Drs. Bishayee, Hill and Howell. These materials were stored in the Office of the Vice President of Academic Affairs and reviewed by the committee (Attachment 6, p. 3).

The respondent, Dr. Bishayee, was informed in writing on April 12, 2001, that the inquiry committee was considering “questions about whether you falsified or fabricated data for NIH grant R01 CA83838” (Attachment 6, Appendix B)

The inquiry was restricted to two specific experiments performed by Dr. Bishayee and questioned by Dr. Hill:

Allegation 1

That Dr. Bishayee had fabricated and/or falsified and/or plagiarized data . . . [in an] experiment [that] took place in September/October 1999 and involved survivability and mutagenicity following irradiation of mammalian V79 cells with the mutant gene HPRT.(sic)⁸ (Attachment 6, p. 2)

Allegation 2

That Dr. Bishayee had fabricated and/or falsified data in a second experiment done March 26-March 30, 2001, concerning the “bystander” effect on mammalian cells. (Ibid.)

⁷ DIO believes Dr. Boccabella might have contributed needed expertise in the basic science and cell biology of the research at issue- see ORI Conclusion (p. 20).

⁸ DIO has found that cell line V79 was not mutant in the gene for HPRT, it was established in 1958 from normal Chinese hamster lung tissue, and a clone established in 1968 is available as V79-4 from commercial collections (ATCC catalog, 7th edition, p. 56).



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Dr. Hill's written allegation was reviewed by the committee on April 11, 2001, and the members decided to proceed with an initial inquiry.

Institutional Inquiry: Findings

The CRI concluded that "there was insufficient credible and definitive evidence of misconduct in science to warrant further investigation."⁹ (Attachment 6, p. 14)

The committee reviewed the sequestered materials, the questioned grant application, and additional materials listed above. Dr. Hill was interviewed on April 17, 2001, and Drs. Howell, Bishayee, and Lenarczyk were interviewed on April 27. In additional meetings on May 9 and June 7, the committee considered additional comments of Dr. Hill and interviewed Dr. Bishayee a second time. The minutes of the committee meetings included summaries of the interviews.¹⁰

Allegation 1: The experiment measuring induction of mutations.

Dr. Hill alleged that an experiment done by Dr. Bishayee in October 1999 included fabricated data.

Background: Dr. Bishayee and Dr. Hill carried out a joint experiment in September 1999, which was followed immediately by a repeat experiment carried out entirely by Dr. Bishayee (September 20-October 12, 1999). Drs. Bishayee and Hill followed a protocol for measuring mutations called "the Banbury Protocol" (Attachment 6, p. 3). It is described also in the R01 CA83838-01A1 grant application (Attachment 1, p. 34, ref. 81) as the "CHO/HGPRT mutation assay." As Dr. Hill described it (Attachment 6, attachment 1b, p. 5), in the first run-through, Dr. Hill performed the mutation arm of the experiment while Dr. Bishayee assayed the effect of on cell viability of cesium-137 irradiation. In the second experiment, Dr. Bishayee performed both assays.

Allegation: Dr. Hill alleged that Dr. Bishayee had falsified data in the second experiment. Dr. Hill doubted that Dr. Bishayee had assayed the mutation frequency at all because she found many dishes of cell culture medium in the incubator after October 12, the date when his experimental dishes should have been fixed and stained and the colonies counted. She found Dr. Bishayee's explanation to be unconvincing. He claimed that he had completed the experiment and discarded the plates, and that the many large dishes in the incubator were part of

⁹ This language is taken from the Policies and Procedures of the university.

¹⁰ Those minutes were not included in the inquiry report, but were provided to ORI as a part of the file, along with transcripts of the interviews and are included in this report at Attachment 6.



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a different experiment.¹¹ Dr. Hill claimed to the inquiry committee that Dr. Howell had told her in 1999 that no other experiment involving so many plates was being done at the time (Report, Attachment 6, p. 4). Dr. Hill noted that the dishes that provoked her questions disappeared from the incubator and the laboratory soon after she spoke to Dr. Bishayee about her concerns. She also related that the Banbury Report volume with the published protocol was unaccountably missing from the laboratory. She concluded that the plates had not been counted and that the data for the mutation evaluation was fabricated or copied from the missing Banbury Report by Dr. Bishayee.

In October 1999, Dr. Hill immediately reported her concerns to Dr. Howell, who “did not believe her.” (*Ibid.*, p. 4) Dr. Hill claimed that, instead, Dr. Howell included the data she questioned in the grant application that he was then revising (CA83838-01A1), despite Dr. Hill’s objection to the experiment and her status as a “co-investigator” on this grant application. At the time, Dr. Hill did not pursue the matter further.

During the inquiry in 2001 Dr. Hill examined a library copy of the Banbury Report and concluded that the 1999 data she questioned had not been copied from those articles (*Ibid.*, p. 4). She did not know where the data came from. However, on May 22, 2001, Dr. Hill met with Dr. Raveché and stated that she had reviewed Dr. Bishayee’s colony count data from the questioned experiment and regraphed his survival and mutagenicity results. She contended that Dr. Bishayee’s recorded counts did not agree with his graphed experimental results. The committee reviewed these comments, as they were relayed by Dr. Raveché. They did consider Dr. Bishayee’s cell counts inconsistent with the expected (lethal) effects of gamma radiation from cesium-137. It is not clear whether they decided whether his recorded data were accurately represented by his graphs. (Attachment 6, p. 6)

The committee met again with Dr. Bishayee and reviewed the Coulter counter measurements that he obtained on the day of irradiation and three days later. Overall cell killing by the radiation was determined from colony counts on plates prepared immediately after irradiation. Mutation was measured in cells that were irradiated, maintained in culture, counted, and then plated and assayed for mutation in the HPRT gene by plating in a selective medium in which wild type cells are killed but HPRT mutant cells grow and form colonies. The committee concluded that Dr. Bishayee’s explanation of the Coulter counts was satisfactory. He suggested that the lethal effects of radiation may not have been expressed immediately and that some cells may have continued to divide for a few days but then did not form colonies. The committee also concluded that the Coulter counter measurements of Dr. Bishayee may have been “unreliable, due to technical flaws in the measurements,” but they considered them “not integral to the experiment in question.”

¹¹ DIO believes that she thought that the stained plates should have been retained as a permanent record of the primary data.



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Allegation 2: The questioned experiment carried out March 26-30, 2001

Dr. Hill alleged that Dr. Bishayee had falsified data on March 30, 2001, by substituting new hamster cell cultures for cells that were radiolabelled (or not) but became contaminated. Next he misrepresented the data he obtained as coming from cells labeled on March 26, 2001, which was not true.

On March 26, 2001, Dr. Lenarczyk observed in the laboratory that Dr. Bishayee's V79 cells were contaminated. Dr. Lenarczyk talked to Dr. Hill and expressed his doubt that Dr. Bishayee, if he proceeded to use cells from a contaminated culture, could obtain valid experimental results. Drs. Hill and Lenarczyk agreed that they would monitor Dr. Bishayee's experiment without his knowledge and see how it turned out. They retrieved flasks that Dr. Bishayee had discarded and documented the visible contamination with photographs, which Dr. Hill gave to the Committee. (Attachment 6, p. 8)

Dr. Hill also told the committee that she had herself observed contaminated flasks in the incubator on March 28, 2001, and that she presumed that these flasks were dilutions made on March 26th, when Dr. Bishayee had harvested cells and initiated an experiment on the bystander effect of tritiated thymidine radiation. Dr. Hill stated that she and Dr. Lenarczyk had sampled the supernatant medium from two of the seven centrifuge tubes (Helena tubes¹²) in the cold incubator on March 28, and that they assayed those samples for microbial contamination and obtained a positive result.

Dr. Hill stated that Dr. Lenarczyk had told her that he had given new, non-contaminated V79 cells to Dr. Bishayee on March 29, and that she believed Dr. Bishayee must have introduced the uncontaminated cells into his experimental protocol, but without restarting the experiment by labeling fresh cells with tritiated thymidine or incubating cell mixtures for three days in the cold. Drs. Hill and Lenarczyk photographed the Helena tubes stored in the cold incubator, but they did not observe two sets of seven tubes, only the one set. After the tubes should have been removed from the cold to do the FACS separation on March 30, she stated that she and Dr. Lenarczyk noted that six tubes remained in the cold incubator until April 5. On March 31, Dr. Hill found one tube (#7) discarded in the regular trash bin.¹³ Dr. Hill concluded that Dr. Bishayee had not collected the pellets from six of the seven tubes to generate seven cell suspensions that he claimed to have analyzed by fluorescence activated cell sorting (FACS) on March 30, 2001. Drs. Hill and Lenarczyk claimed that they assayed samples of the six centrifuge tubes remaining in the cold incubator for microbial contamination and measured radioactivity in tubes 1(check), 3,4,5, & 7. The Helena tubes disappeared from the incubator after Dr. Bishayee was told by Dr. Howell that his experiment was being monitored. When Dr. Hill searched the lab, she could

¹² Helena tubes are supplied by Helena Plastics, Inc., and are 400 µl capped, sterile microcentrifuge tubes.

¹³ This tube should have been discarded into the radioactive waste bin ~~since~~ if it had contained tritiated thymidine.



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not find the contested tubes in the trash. Dr. Hill turned over the photographs, some digitally dated, of flasks, centrifuge tubes and plates in the incubator to the committee chairman, along with her contemporaneous notes and her written allegation.

Dr. Hill told the committee that she concluded that Dr. Bishayee had sorted samples on March 30 using the uncontaminated cells that he had obtained from Dr. Lenarczyk, and that he left the irradiated cells in the cold incubator, instead of sorting them, because he knew that they had been prepared from a contaminated stock, as he could see from his cloudy flasks. Dr. Hill concluded from her observations that Dr. Bishayee had not performed the experiment as planned, but he had generated data by sorting and plating cells that had not been exposed ~~to the bystander effect of~~ radiation for three days as the protocol required. The bystander effect is supposed to take place during the cold storage of the cell pellet, so this is an essential part of the experiment. If Dr. Bishayee had used the cells that he obtained from Dr. Lenarczyk on March 29 for FACS runs and cell viability measurements on March 30, then he had falsified whatever data he obtained. Dr. Hill thought Dr. Bishayee had simply plated cells at an extra 100-fold dilution to generate data showing 1% survival. Additionally, he had to have again contaminated some of the samples after the FACS separation, since he had found half his plates contaminated when he tried to count the survival.

Could have been dry run?

In his interview Dr. Lenarczyk told the committee that he believed that Dr. Bishayee could not have carried out the experiment and gotten the claimed data if he had used contaminated cells, and that he was convinced by March 30 that the cells used for the cold incubation of cell pellets from March 26 to 30 were contaminated. He had observed the contaminated flasks and discussed his suspicions with Dr. Hill, who he trusted, and she was a senior co-investigator on the grant, whereas he was relatively junior. When asked, he had given Dr. Bishayee fresh, uncontaminated cells on March 29. He also observed the set of centrifuge tubes in the cold incubator on March 30, the day that they should have been harvested and counted, and he explained that special, recognizable centrifuge tubes ("Helena tubes") were used for aggregated cell incubations in the cold incubator and the seven tube design was characteristic of Dr. Bishayee's experiments studying the bystander effect at different levels of radiation exposure. Dr. Lenarczyk observed Dr. Bishayee working in the hood on Friday, March 30, but he also observed Bishayee's set of tubes in the cold incubator on Friday and that the tubes remained there over the next few days. Dr. Lenarczyk told the committee that he sampled the remaining tubes of Dr. Bishayee on Friday, March 30, after they should have been harvested and counted, according to the usual protocol.

Dr. Lenarczyk explained that not all the digital photographs were dated because the camera was new, and he had learned how to set it to record dates after he took the first photographs. When pressed, Dr. Lenarczyk admitted that he may have sampled the contents of the centrifuge tubes on Thursday, March 29, rather than Friday, and incubated them overnight to test for contamination. Dr. Hill's written notes state that they sampled two tubes on March 28 and sampled six or seven tubes on March 31. (Attachment 5, pp. 2-3). Dr. Lenarczyk stated that he never saw Dr. Bishayee's recorded results. (Attachment 6, pp. 10)



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When the committee interviewed Dr. Bishayee, he stated that his experiment was partly successful and that half the plates showed contamination, as he had noted in his laboratory notebook. The committee verified that the sequestered culture dishes showed such a pattern. Dr. Bishayee stated that he had not thought the cells were contaminated when he did the experiment, and that he had harvested the cold-incubated cells on March 30. He said that the tubes Dr. Hill observed remaining in the incubator had been his, but that he had been doing an experiment on a new cell line, and that the remaining tubes contained these other cells. Dr. Bishayee said he had no notes of his second experiment or any written observations.¹⁴ He stated that he had been observing the cell line's growth characteristics. He did not mention any use of tritiated thymidine with these cells. (Attachment 6, p. 11)

Dr. Bishayee said he thought that the photographed Helena tubes were his experiment, and he could not explain why there were only six tubes in the continuing incubation. He said he did not recall why he had asked Dr. Lenarczyk for new cells on March 29, 2001, but he denied using new cells for the sorting on March 30. He said there was nothing unusual in his getting cells from Dr. Lenarczyk, that scientists often do this. (Attachment 6, p. 11) Finally, Dr. Bishayee claimed that Dr. Hill and Dr. Lenarczyk were conspiring against him because of jealousy and conflict between Dr. Hill and Dr. Howell. (Ibid.)

In his interview, Dr. Howell expressed doubt that all of Dr. Bishayee's cells were contaminated at the start of the experiment. He based this on the observation that the plated cells counted after 7 days incubation at 37 degrees showed that only the samples of separated cells that should have been labeled with tritiated thymidine were contaminated and that the separated bystander (unlabeled) cells were not contaminated. He said he had watched Dr. Bishayee count the plates. He stated that this experiment focused on the tritium-labeled (irradiated) cells, rather than the bystander cells.¹⁵ Dr. Howell said that for this particular experiment, it would have made no sense at all to substitute new cells for contaminated unlabelled bystander cells. He stated that Dr. Bishayee could not have known about the cell contamination on Friday, March 30, just by observation of the Helena tubes. (Dr. Howell evidently did not understand that Dr. Lenarczyk had observed the contamination in Dr. Bishayee's flasks in the warm incubator on March 26, not in the opaque centrifuge (Helena) tubes in the cold incubator.) Dr. Howell thought that Dr. Bishayee could not have known about the contamination unless he had plated out cells at the beginning of the experiment. (Attachment 6, p.11). (Dr. Howell did not mention that the flasks that were innoculated on March 26 were indicators of contamination at the start of the experiment.) The conclusion that the tubes in the cold incubator were contaminated came from assays done by plating out samples of the supernatant medium and from observations of contaminated flasks in the warm incubator. Also, Dr. Bishayee had requested cells from Dr.

by Dr. Hill + Lenartz?

¹⁴ He had offered a similar undocumented experiment explanation in 1999.

¹⁵ He did not explain further what he was trying to observe about the labeled cells, and the protocol did not provide this information. It appeared to be a test of whether the FACS separation worked well and that the separated cells still showed different survival curves diagnostic of the bystander effect.



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Lenarczyk on March 29, presumably because he had lost his flasks of V79 cells to the contamination that Dr. Hill and Dr. Lenarczyk noticed and photographed.

Dr. Howell thought that Dr. Hill should have confronted Dr. Bishayee directly, rather than sampling his tubes. He also said that because Drs. Hill and Lenarczyk had done experiments that focused on the bystander cells, they would not have known that this experiment was focused on colony formation by the separated, radioactively labeled cells. (Attachment 6, p. 12) Dr. Howell commented on how it made no sense to substitute uncontaminated cells for the non-radioactive, non-dyed cells. (Ibid.) (by FACS)

Dr. Howell had no explanation for the presence of tubes in the cold incubator after Friday, March 30th. He stated the six tubes in the cold incubator could have been a second experiment on the new cell line, but they should not have been radioactively labeled, as marked on the rack and as measured by Dr. Lenarczyk. (Ibid., p. 13)

Dr. Howell said that Dr. Bishayee had been a productive scientist, whereas Dr. Hill and Dr. Lenarczyk had not been productive in his laboratory.¹⁶ Dr. Howell stated that the protocol was difficult and acknowledged that Dr. Bishayee had experienced contamination in earlier experiments. Dr. Howell thought that the cells may have been contaminated by the phosphate buffer that the fluorescent dye was diluted in, and that therefore only the radioactively labeled cells became contaminated.¹⁷ Dr. Howell had no explanation for the photographs or the observations of Dr. Bishayee's experiment made by Drs. Hill and Lenarczyk. (Attachment 6, p. 13)

The committee found no apparent explanation for the photographs if they were taken as represented by Dr. Hill and if Dr. Bishayee's testimony about the conduct of the experiment was truthful. They could neither confirm nor disprove Dr. Bishayee's statements nor confirm nor disprove the validity of the photographs. (Attachment 6, p. 14)¹⁸ The committee thought that Dr. Hill's scenario of falsification of the experiment was not credible, and remarked that "any such effort on Dr. Bishayee's part to fabricate the experimental results in this experiment would

¹⁶ It may be that Dr. Howell therefore disregarded their observations, or that he was suggesting that they falsified their purported observations to discredit Dr. Bishayee and question his productivity, perhaps his evaluation was irrelevant. *or*

¹⁷ However, the protocol calls for bystander cells and fluorescent-labeled, tritium-labeled cells to be co-incubated as cell pellets in the cold- this would have led to contamination of all the cells in the pellet, even if the fluorescent dye solution was the only source of contamination.

¹⁸ In fact, Dr. Bishayee had not denied that his flasks were contaminated or that he had a set of Helena tubes in the cold incubator after March 30. The question seems to remain whether there were ever two sets of tubes that Dr. Hill did not see or photograph.

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have been greater than simply repeating the experiment with fresh uncontaminated cells.¹⁹ (Attachment 6, p. 9, first paragraph.) Dr. Hill thought that he had indeed continued the experiment with fresh, uncontaminated cells, and used such cells for the FACS separation. Previous FACS separation experiments had not given good data, due to contamination. (See previous experiments in Dr. Bishayee's notebook, Attachment 6).

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Inquiry Committee's Conclusions

The committee, based on its review of the evidence, recommended that there was insufficient credible and definitive evidence of misconduct to warrant further investigations. The bases of this conclusion were stated as:

1) There was insufficient evidence of the falsification or fabrication of data by Dr. Bishayee in September/October 1999, based on the content of the Banbury Protocol and an examination of Dr. Bishayee's notebooks. The committee found Dr. Bishayee's explanation of his recorded Coulter counter counts of cells to be satisfactory since the committee considered those measurements to be prone to technical error compared to the count of colonies of cells.

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2) The major evidence concerning the March 2001 experiment was the set of photographs taken by Hill and Lenarczyk.²⁰ The committee considered the dating of the photographs to not be definitive and the photographs to be possibly unrelated to the experiment that Dr. Bishayee claimed to have performed March 26-30. The report stated: The date of the photographs claimed by Dr. Hill could not be reconciled with what Dr. Hill believed they demonstrated about Dr. Bishayee's experiment and Dr. Bishayee's recorded notes and account of what he carried out.

3) The evidence that Dr. Bishayee's cells were contaminated from the beginning of his experiment was "insufficiently credible" to support Dr. Hill's allegation that Dr. Bishayee could not have obtained the data he recorded from the experiment that he actually carried out.^{21 22}

¹⁹ DIO considers this a particularly flagrant demonstration of the lack of understanding of this research by the committee members.

²⁰ DIO would disagree. The major evidence was the recorded observations of two witnesses, their lack of motive to fabricate evidence such as the photographs, and to a minor extent, the photographs themselves, which were not disputed by Dr. Bishayee.

²¹ The evidence of contamination was the testimony of what Hill and Lenarczyk observed in the flasks. They took photographs, presumably to demonstrate cloudiness due to cell detachment, bacteria or fungi. Either the photographs are unclear, or the committee simply did not believe the complainants' testimonies were truthful.

²² The committee may not have understood that Dr. Hill believed that Dr. Bishayee carried out his experimental protocol with fresh cells that he had obtained from Dr. Lenarczyk on March 29 and harvested on March 30, labeled with dye, and took to the FACS facility.



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4) The committee found that Dr. Hill and Dr. Lenarczyk gave conflicting testimony regarding the dates of their observations of Dr. Bishayee’s tubes in the cold incubator and what they did, when they did it, when they sampled or collected evidence regarding Dr. Bishayee’s experiment.²³

one had notes, other did not

5) Dr. Hill and Lenarczyk admitted sampling tubes (“tampering” with) Dr. Bishayee’s experiment, possibly before it was completed. (The committee disapproved of this, and called their observations “secret investigations.”) The complainants stated that they sampled the supernatant of two tubes on March 28 for an assay of microbial contamination and that they sampled the (supernatants) of the remaining six tubes in the incubator on March 30.²⁴

6) The committee could discern no reason for Dr. Bishayee’s [alleged] falsification, fabrication or plagiarism of the data for his experiments of 1999 or 2001.²⁵

The committee recommended that Dr. Putterman ask Dr. Howell to take corrective actions to improve the conduct of research and the environment in his laboratory.²⁶ (Attachment 6, p. 15).

DIO Analysis

DIO reviewed the Inquiry Report and its attachments.

Expertise: Four of the inquiry committee members were deans and do not have Medline citation records indicating bench science backgrounds. Dr. Raveché, a pathologist, may or may not have appropriate experience to evaluate the questions about the performance of these experiments. However, the complainant alleged that Dr. Raveché suggested that Dr. Howell simply terminate Dr. Bishayee when she was first informed of the allegation. If Dr. Raveché did so, that was

²³Since Dr. Hill provided her written notes, which she claimed to have made at the time of the experiment, it is not clear why the committee could not determine more clearly what the witnesses did. The report does not make clear how Dr. Hill’s oral testimony differed from these notes. Dr. Lenarczyk submitted no notes and gave only oral testimony.

²⁴ Unless they did not use sterile methods, it is unclear to DIO how this might have affected the experiment, especially if done after Dr. Bishayee had harvested his cells for FACS analysis.

²⁵The committee evidently discounted testimony that the bystander experiment could not be repeated by Drs. Lenarczyk or Howell. If true, the doubt about the bystander effect would be a substantial motive for Dr. Bishayee to falsify data showing such an effect

²⁶ Dr. Hill alleged that immediately after the inquiry decision, Dr. Howell’s actions were to stop his collaboration with Dr. Hill, exclude Dr. Hill from the departmental laboratories, to not renew Dr. Lenarczyk’s appointment, and to force Dr. Bishayee to leave the laboratory.



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clearly inappropriate. The complainant later alleged to ORI that Dr. Howell forced Dr. Bishayee to resign, however, Dr. Putterman was not able to confirm this, although she did find that Dr. Howell had not written a letter of recommendation for Dr. Bishayee. Dr. Putterman said such a letter was unnecessary, because Dr. Bishayee's next appointment was with ~~UMDNJ~~. (Attachment 7).

The University provided no information about the professional experience of the committee members relevant to the questioned experiments, which involved radiation damage to in vitro cultured mammalian cells. Several statements in the inquiry report indicated a lack of such knowledge. For example, Dr. Hill had questioned the counts of induced HPRT mutations in assays where colonies of surviving mutant (thioguanine-resistant) cells were evaluated. It was very unsettling to DIO to find that the Inquiry Report referred to this 1999 experiment as "irradiation of mammalian V79 cells with the mutant gene HPRT" (Attachment 6, p. 2).²⁷ They also considered it harder to substitute new cells than to restart the experiment in 2001, a pretty naive statement.

(The committee report)

Dr. Raveché wrote to Dr. Hill that she would be given an opportunity to comment on the report. (Letter of April/May 2001.) However, Dr. Hill has stated to DIO that she was not provided with a copy of the report nor with that portion of the report that described her views. Perhaps as a consequence, Dr. Hill strongly objected to the decision of the inquiry, and the committee had no opportunity to correct factual mistakes in the report. When UMDNJ sent the report to ORI, no comments on the inquiry were included from any of the principals.

The inquiry was performed in a timely manner and the institution has been cooperative in providing additional materials.

PHS Issue 1 That Dr. Anupam Bishayee fabricated or falsified data in an experiment in September/October 1999 in which he measured cell survival and induction of mutations following the irradiation of cultured mammalian cells with cesium-137.

DIO examined the allegation materials provided by Dr. Hill to the Inquiry committee and materials sent to ORI (Attachment 5, Attachment 6). These included a set of data and a protocol for the two experiments carried out by Dr. Bishayee and herself in 1999. The protocols for the evaluation of radiation effects on viability and mutation of cells was described in the grant application (Attachment 1, p. 34) as the "Banbury Protocol." The notebook materials include

²⁷ The cells that were irradiated were not mutant in that gene to start with, the mutants were created by the irradiation, and mutated cells were selected and counted. The number of mutant colonies was evaluated at different doses of cesium-137 irradiation and compared to unirradiated control cultures. Dr. Bishayee should have been able to answer Dr. Hill's questions about his results by simply showing her the plates that were fixed and stained on October 11 or October 12 (according to Dr. Hill's notes, see Attachment 6, exhibit 1b, p. 12-13). For Dr. Bishayee to discard the stained plates (the primary data) was definitely not standard practice, especially when the technique was new to him.



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two graphs that show the induction of mutations (in the HPRT gene) in two sets of cell samples represented by circles and squares. (Attachment 6, Attachment 1a, p. 1,2, page dated 9/28/99). For the experiment done jointly the circles are data for mutants ~~cells~~ obtained after irradiation of resuspended cells (aerobic), the squares are cells irradiated when the cells are clustered (actually loose cell pellets created by low speed centrifugation) (hypoxic) (Ibid., page dated 9/28/99). Both samples were exposed to variable doses of strong gamma radiation from cesium-137. In the second experiment carried out by Dr. Bishayee alone, the results were again graphed, and, as before, circles are resuspended cells, and squares are clusters. (The open circles may be survival curves for experiment #1.) In the grant application CA83838-01A1, this same data was included in the Preliminary Results section as Figure 7A (survival) and 7B (induction of mutants) (Attachment 1, p. 29) . The Figure 7 legend noted that all the cells had been incubated (as cell pellets) at 10 degrees centigrade for three days and then exposed with or without resuspension to varied doses of gamma irradiation from cesium-137. This information agrees with the protocol contained in the material provided by Dr. Hill (Attachment 6, attachment 1a). This experiment is described in the text as testing for an oxygen enhancement effect. //

In the text of the grant, the result of this experiment was described as showing that slightly more mutations and more killing of cells were obtained by irradiation of resuspended cells than by irradiation of clustered cells (Attachment 1, p.29). This seems to match the conclusion of the graphed data from Bishayee's experiment #2 (and exp. #1). The data shown in Figure 7 resemble the graphed data obtained by Dr. Bishayee for the experiment (#2) done in October 1999 (Attachment 6, attachment 1a).²⁸ However, on closer examination, DIO noted that the curves in Figure 7 of the grant application did not accurately represent the result obtained: the sets of samples (curves) had been mixed up. The curves showing more killing and more mutations are drawn with filled squares in Figure 7, and according to the figure legend, these are samples of cells irradiated "intact" i.e., as pellets. The second curves are filled circles, they show slightly less killing, and fewer mutations. By exclusion, they should be the resuspended, irradiated cell samples. In the figure legend, resuspended cells are supposed to be open squares, but there are no open squares on the graph. DIO concludes that between the notebook and the Figure 7 legend, the curves have been mixed up. Thus, the results recorded by Bishayee in experiment #2 were summarized in the text in agreement with the data in the notebook (attachment 1a), by the statement that "the cells that remained in clusters were somewhat more resistant to killing by acute gamma irradiation relative to those [cells] that had been resuspended," but the graph suggests the opposite result.

It appears that whoever prepared the graphs for the grant application managed to mix up the symbols and even described a symbol (□) in the figure legend that did not appear in the figure itself. The Inquiry committee evidently did not notice, or if they did notice it, they did not mention it in the report. However, it is clear that the data Dr. Hill had criticized as fabricated

²⁸ On page 2 of the attachment 1a, Dr. Hill had written: "Dr. Bishayee did this experiment completely on his own. It was after this experiment was said to be complete that I found 100 mm dishes in the 37degree incubator with no colonies on them."



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was used in the grant. The contradiction between actual or stated results and its graphic presentation in the grant is most likely due to honest error or just carelessness, since it clearly did not support the text very well.

The data for the experiment that Dr. Hill had done in September 1999 with Dr. Bishayee (Exp #1 09/06/99 to 9/28/99) was also submitted to the committee by Dr. Hill (Attachment 6, attachment 1a, pp. 10-16). The results Dr. Hill obtained (graph on page 10 of attachment 1a) showed no reliable increase with dose in mutants/cell in the cells irradiated under hypoxic conditions, that is as clusters (cell pellets, filled squares) and did show an increase in mutants/cell when the cells were irradiated in suspension (aerobic condition) (filled circles). This experiment supports the statement that cells in suspension were more sensitive to the mutagenic and toxic effects of irradiation than cells left in pellets, as stated in the text of the grant application. Thus, the result obtained by Dr. Hill in the mutation arm of Expt. #1, even with rather erratic values for the (hypoxic) clustered cells, did not contradict the statements in the grant. Dr. Hill was not objecting to the results Dr. Bishayee claimed to have obtained as a wrong or contradictory result, but her objection was that he had obtained his results by fabrication of this data. This conclusion of Dr. Hill was based (1) on the tissue culture plates full of medium that she observed in the incubator. She considered these plates, which had not been fixed and stained, as evidence that Dr. Bishayee had not actually counted surviving and mutant colonies of cells as he claimed. This interpretation was reinforced for Dr. Hill by (2) Dr. Bishayee's inability to produce the stained tissue culture plates that he claimed to have counted, and, (3) Dr. Bishayee's claim that he had a second experiment going on involving the plates in the incubator, but he had no protocol or data from that experiment, and (4) Dr. Howell knew of no second experiment.

Dr. Hill noted that Dr. Howell went ahead and added this disputed data to his grant application. DIO found no data on mutant induction in the two published papers mentioned in the allegation (Attachments 2 & 3).

According to Dr. Hill, Dr. Lenarczyk was carrying out experiments involving the induction of mutants by radiation but he could not confirm the bystander effect on cell viability. From the summary of the interview of Dr. Lenarczyk (Attachment 6, summary follows attachment 8 to the report), this was not discussed with the committee, and the committee may not have known about this issue. No details were given of his experimental system and results, and he was not asked to evaluate the 1999 data obtained with cesium-137 radiation. Dr. Lenarczyk had not been present in the laboratory in 1999. (Attachment 6, Appendix C).

In a memorandum and an interview with Dr. Raveché, dated 5/22/01 (Attachment 6, attachment 22), Dr. Hill questioned the reliability of the Coulter counter data recorded by Dr. Bishayee for the mutation arm of the experiment #2. Dr. Hill argued that the recorded cell counts in the mutation arm exceed the expected cell survival by 6 to 10 fold. She provided comparable data for the samples in the immediately preceding experiment #1, where she herself had carried out the mutation arm. The protocol required that the number of cells be followed at intervals for 10 days before plating equal numbers of cells on the selective medium to measure mutation rates.



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(Attachment 6, Dr. Hill's memorandum dated 5/22/01, attached to minutes of meeting of the committee on June 7).

The committee asked Dr. Bishayee for an explanation of the cell counts that he did with a Coulter counter. He agreed that he had not observed an effect on cell survival when he counted cells, but stated during his interview that the effects on the survival and growth of irradiated cells might be delayed and not evident when the cells are counted on day 3 after irradiation. [The protocol called for counts on days 0, 3, 7 & 10 days after radiation, and his dated excel sheet showed counts on days 0 (9/24/99), 5, 7 and 10.] The committee reported that they members were satisfied with Dr. Bishayee's explanation (Attachment 6, p. 14).

DIO reviewed the counts recorded by Dr. Bishayee for this experiment. Although the committee considered Coulter counting to be subject to variations, Dr. Bishayee's counts in this experiment were remarkably close for the replicate samples. The counts for 3 samples from each culture barely show the variation expected from recounting the same sample (square root of N) according to a simple analysis done by DIO. (Attachment 8) When Dr. Howell was asked about this variation (Attachment 9) Dr. Howell claimed to Dr. Putterman that he also obtained Coulter counts that were in close agreement.

In contrast, Dr. Hill obtained quite highly variable Coulter counts in Experiment #1. In fact, she switched to counting cells with a hemocytometer. Dr. Hill's cell counts on 9/20/99 appeared to show a two fold decrease in total cells due to radiation (comparing sample 4 vs. sample 2), however Dr. Hill stated that she expected a 10-fold reduction in cell count in Dr. Bishayee's expt (#2). More explanation by Dr. Hill would be needed to conclude anything on this issue. DIO was most impressed by the small variation in Dr. Bishayee's recorded Coulter counts. (Attachment 8).

Dr. Howell ignored the objections of his senior colleague and used data of Dr. Bishayee's experiment in the grant application in the absence of verifying, counted tissue culture plates. Dr. Hill was listed as an experienced co-investigator, and she was the only person on the grant application who had experience in mutagenesis. Dr. Howell, on the other hand, was trained as a physicist, and his experience with cell culture was minimal, if judged by his publications (Attachment 1, p. 5-6). It seemed extraordinary to DIO that the committee dismissed the testimony and judgement of Dr. Hill in this matter, since she had 20 years of experience and many publications in this field of research. The committee also accepted Coulter count data that may have been too precise to be likely to be accurately reported.

According to Dr. Hill's written allegation, she reacted to the first incident where she suspected that Dr. Bishayee had fabricated data (in October 1999) by informing Dr. Howell. Apparently, he took no actions except to inform Dr. Bishayee (who then disposed of the plates in the incubator) and to retain the preliminary data (inaccurately graphed) in his grant application. The committee did not appear to take Dr. Hill's allegation about the 1999 experiment seriously. Dr. Bishayee's explanation that the plates were in the incubator for a second experiment was not supported by



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any evidence, and the committee did not pursue this question with Dr. Bishayee or Dr. Howell. Dr. Howell was not asked if the disputed experiment on mutations induced by cesium-137 irradiation of aerobic vs. hypoxic cells was ever repeated. If so, the primary data of the later experiment could have been compared to what was in the grant, and could establish to what extent Dr. Bishayee's Coulter counts usually varied. In the grant application, further experiments were proposed that involved mutagenesis.

According to Dr. Hill, Dr. Lenarczyk was measuring mutagenesis in this laboratory, but he was not asked what results he obtained, and whether he was able to replicate Dr. Bishayee's experimental data. Dr. Lenarczyk's data and notebooks have presumably been left with Dr. Howell and are available to the institution. Dr. Lenarczyk is now employed in Colorado.

More concretely, DIO looked at the numbers recorded by Dr. Bishayee as his coulter count data for four dates in 1999- October 1, 4, September 24 and 29. Those numbers were entered into a spread sheet (JD). (Attachment 8). DIO observed a reuse of two numbers, 72 and 56, and the high frequency of 1,2 and 9's in the terminal place of these three digit numbers. The numbers do not appear to be statistically compatible with an origin in an unbiased counting device, such as the Coulter counter. (Attachment 8).

DIO noticed that the inquiry had ignored or dismissed much of the evidence brought forward by Dr. Hill. The source of their attitude was not clear in the material sent to DIO.

(1) The committee did not comment on Dr. Hill's allegation that the recorded data of colony formation did not match the graphic representation of the data. (Attachment 6, p. 6) The institution did not provide materials that would have allowed DIO to review this claim.

(2) The report did not comment on the significance of Dr. Bishayee's lack of any notes to support his claim that he was performing a second experiment in October 1999, even though he had claimed, according to Dr. Hill, that the dishes that she observed and questioned were part of a second experiment he was doing. Dr. Hill reported that the plates disappeared promptly from the incubator and from the laboratory as soon as she questioned Dr. Bishayee. The committee report did not comment on this, nor did they appear to have asked Dr. Bishayee whether he had discarded the plates that raised Dr. Hill's concerns.

(3) Dr. Howell had been involved in writing and revising his grant application around the time that the 1999 questioned experiment was done. He signed the grant face page on October 21, 1999, and the application was due at NIH on November 1. Dr. Hill had complained specifically that Dr. Howell had gone ahead and used data whose veracity she questioned. However, it is not clear from the report that the committee examined the data that was incorporated into the grant application 1 R01 CA83838-01A1 as Figure 7. DIO has found that the reporting of Dr. Bishayee's data from this experiment was not accurate in the grant, where the data for clusters and resuspended cells have been mislabeled in the figure. The committee did not examine the data closely, did not notice this, or noticed it and failed to comment on it.



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(4) The committee failed to determine whether Dr. Howell, given the questions about the mutation data, had instructed Dr. Bishayee to repeat the experiment, and whether the claim in the grant application was supported by later data.

At CEC, there should be a discussion of whether this issue should proceed to a review by an investigation committee, especially concerning the Coulter count numbers recorded by Dr. Bishayee as noted above.

PHS Issue 2 That Dr. Anupam Bishayee falsified data of an experiment done March 26-30, 2001, on the viability of "bystander cells" incubated for three days in the cold in contact with cells that had incorporated tritiated thymidine into their DNA and the separation of those cells by fluorescent activated cell sorting.

The experiment that provoked Dr. Hill's allegation in 2001 involved radiation from tritiated thymidine incorporated into cellular DNA. The radiation of tritiated thymidine (H-3) is much less penetrating (beta decay) than the gamma irradiation of cesium-137, and is not expected to penetrate far enough from its location in DNA in one cell's nucleus to cause mutations in adjacent cells' nuclei.

According to Dr. Hill, Dr. Lenarczyk had attempted to observe the bystander effect on survival and had not replicated the published effect (provide citation). He knew that Dr. Hill had accused Dr. Bishayee of fabricating data in 1999, before he joined the laboratory (cite Dr. Hill's written allegation or Lenarczyk's interview). Dr. Lenarczyk mentioned his concerns about Dr. Bishayee's ongoing experiment to Dr. Hill, and he provided a fresh cell culture to Dr. Bishayee on March 29, 2001, as confirmed by Dr. Bishayee. Dr. Lenarczyk had observed that Dr. Bishayee's cultures in the warm incubator were contaminated with yeast or bacteria (appeared cloudy), but he also noted that Dr. Bishayee appeared to be continuing with an experiment that he had started earlier in the week. He and Dr. Hill decided to monitor carefully what Dr. Bishayee did with the experiment that was under way. They observed the flasks in the tissue culture room and samples in the incubators. Dr. Hill took notes on what they saw, and Dr. Lenarczyk took photographs of the flasks and tubes to document their observations. Dr. Hill compared what they observed with the results that Dr. Bishayee recorded in his notebook. She then wrote out her concerns and went to talk with Dr. Howell, the head of the research project, and the P.I. on the grant supporting both Dr. Bishayee and Dr. Lenarczyk.

Dr. Howell and Dr. Hill went together to talk to their chairman, Dr. Baker, who sent them to discuss the matter with Dr. Raveche, chairman of the Committee on Misconduct in Research (COMIR). All of this seems to be straightforward, although it is unusual to have first hand observations of this sort.

The committee was skeptical about the photographs offered by Dr. Hill. They cited the lack of definitive dating of the photographs as a reason to doubt that the plates or tubes that were photographed were relevant to the experiment that Dr. Bishayee performed. However, Dr. Bishayee had not claimed to have any other plates in the incubator or any other experiment using



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plates underway, so it is really the set of small centrifuge tubes that are at issue. Dr. Bishayee did not claim that he was using any alternative incubator, nor did he have any notes to indicate that he had prepared more than one set of tubes, or anything to show that he was actually doing a second experiment that Drs. Hill and Dr. Lenarczyk could have mistaken for his bystander effect experiment. The committee actually appeared to be suggesting that the photographs were falsified, rather than just interpreted incorrectly by Dr. Hill. However, the veracity of the photographs did not seem to be disputed by Dr. Bishayee, he was exceedingly vague about what the other experiment would have looked like (since it was not recorded) or how he was noting growth or survival of cells simply put into the cold incubator. Frankly, the observations by Dr. Lenarczyk supported the idea that Dr. Bishayee was trying to grow the new, human cell line, and that they were not growing well- certainly not well enough to generate a set of cell pellets, that were then simply discarded.

Dr. Bishayee's explanation of a second set of tubes could not be confirmed because he had no record of carrying out any experiment on a human cell line using Helena tubes nor did he explain what he might have been observing about the growth of cells in a second set of pelleted cells in the cold. (Mammalian cells do not grow at 10 degrees C., and their growth, unlike bacteria, could not have been observed without some kind of quantitative measurement with a microscope or spectrophotometer.) Dr. Bishayee stated that he was evaluating the growth of the cells, but did not explain how he evaluated growth without any recorded measurements. Dr. Bishayee had no protocol, no coherent explanation of what he might have been measuring in pellets of the other cell line, and gave no information that would account for the second set of tubes. Nor did he describe what he intended to measure and why he had not done so. To DIO scientists, based on considerable experience with mammalian cell culture, Dr. Bishayee's claim of a second experiment appears to be unsupported and to not be credible. By comparison, the photographs of Dr. Hill were tangible evidence that supported what they claimed to have observed, and they were accompanied by authentic-appearing notes taken by Dr. Hill at the time of their observations.

The inquiry committee did not explain why they chose to believe Dr. Bishayee's account of his experiment rather than the observations and photographs of other members of the same laboratory. They were contradictory, and Dr. Bishayee's account seemed weak. Stripped of the extraneous details, Dr. Bishayee claimed to have harvested seven tubes of cold-incubated cells and subjected them to FACS sorting on Friday March 30, while Hill and Lenarczyk stated that six of the tubes were still in and remained in the cold incubator until they talked to Drs. Howell and Bishayee the next week. Neither Dr. Hill nor Dr. Lenarczyk observed two sets of Helena tubes in the cold incubator, and in fact, DIO cannot find Dr. Bishayee resolutely claiming that he ever had two sets of tubes in the incubator at the same time. Dr. Bishayee did not show the committee what he had done with the cells he got from Dr. Lenarczyk.

The committee accused Drs. Hill and Lenarczyk of "tampering" with Dr. Bishayee's experiment, clearly disapproved of their secret investigation and appeared to be accusing them of producing falsified photographs. If Drs. Hill and Lenarczyk sampled the tubes as they claimed, after the cell sorting had started, DIO sees no evidence that the sampling that they did would have affected Dr. Bishayee's bystander experiment nor was the sampling intended to affect his experiment. In



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fact, their claim that they observed radioactivity in the Helena tubes seems to DIO to strongly favor their correct identification of those tubes as belonging to the “bystander”/tritiated thymidine experiment, since Dr. Bishayee implied that the second experiment did not involve radiolabeled cells.

2) The major evidence concerning the March 2001 experiment was the set of photographs taken by Hill and Lenarczyk.²⁹ The committee considered the dating of the photographs to not be definitive and the photographs to be possibly unrelated to the experiment that Dr. Bishayee claimed to have performed March 26-30. The report stated: “The date of the photographs claimed by Dr. Hill could not be reconciled with what Dr. Hill believed they demonstrated about Dr. Bishayee’s experiment and Dr. Bishayee’s recorded notes and account of what he carried out.”

DIO understands this to mean that they concluded that the photographs and observations of Dr. Hill were incompatible with Dr. Bishayee’s claim to have done the experiment as planned. It is even less clear whether they thought that the dated (or undated) photographs might have been falsified, or that the evidence simply was not conclusive. The committee was evidently not totally convinced that the photographs and witness testimony proved that the experiment Dr. Bishayee actually carried out was different from that recorded in his lab book. That decision probably should have been made after a thorough investigation, not during the inquiry.

Pattern of behavior:

DIO is struck by the similar alleged behavior of Dr. Bishayee in Issues 1 & 2. In both instances he claimed to be doing another, unrecorded experiment, he is alleged to have substituted samples or data in failed experiments, and to have discarded samples when they were challenged. Had he retained the fixed, counted plates (primary data) in Issue 1, he could readily have supported his experimental data (since they could be recounted). In Issue 2, if he had not discarded the disputed set of six Helena tubes left in the cold incubator, he could have demonstrated the absence of tritium label or even the human rather than hamster origin of the cells and thus had evidence to disprove the allegation. Dr. Bishayee’s actions in discarding crucial evidence after being accused of fabricating or falsifying data is not reassuring.

It is also striking that neither Dr. Howell nor Dr. Bishayee, nor the laboratory protocol and notes of the experiment, revealed in what way the experiment was primarily concerned with the radioactively labeled cells, rather than the bystander cells. The FACS separations clearly were carried out on cell suspensions containing mixtures of fluorescent and non-fluorescent cells. How those cell separations might have been affected by the three day coincubation was not discussed. However, Dr. Howell’s proffered explanation for the contamination of only the fluorescent cells by a dye solution clearly was off the wall. Incubation of a mixture of contaminated, fluorescently labeled cells with uncontaminated, non-radioactive cells for 3 days as mixed cell pellets, could not have yielded uncontaminated separated, non-tritiated cells,

²⁹ DIO would disagree, the major evidence was the recorded observations of two witnesses, their lack of motive to fabricate evidence such as the photographs, and to a minor extent, the photographs themselves, which were not disputed by Dr. Bishayee.



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because there was plenty of opportunity for the contaminating bacteria or yeast to be equally associated with both labeled and unlabeled cells. DIO agrees with Dr. Lenarczyk's comment that the substitution of uncontaminated, unirradiated cells for the cells in the Helena tubes would account for the contamination of only half of the plated samples, if Dr. Bishayee had not excluded his source of contamination (medium, serum, pipettes etc.) by March 30, when the cells were plated out.

Finally, the committee stated that the members did not see any motive for Dr. Bishayee to go forward with this experiment, substituting fresh cells for the contaminated samples. The committee thought it would have been easier for him to restart the experiment. The committee appeared to assume, without sufficient foundation, that it would have been possible for Dr. Bishayee to sort cells at the FACS facility at short notice, had he restarted the experiment on March 30. They did not discuss whether the arrangement with the FACS facility was flexible or whether Dr. Howell would have approved if his grant were charged twice if the experiment was postponed. Either situation could have contributed to pressure on Dr. Bishayee to continue the experiment despite the contamination and have influenced Dr. Bishayee when he considered the option of "simply" restarting it. On the contrary, carrying on with fresh cells clearly was easier than starting over, but it would not give any information about the bystander effect or the effects of exposure of any of the cells to decay of tritiated thymidine.

PHS Issue 3: That Dr. Anupam Bishayee falsified data showing an effect of tritiated thymidine on the survival of bystander cells presented in a PHS grant application (R01 CA83838-01A1, Figures 2 & 4) and in two published articles, Bishayee et al. (1999),³⁰ **Radiation Research 152**, 88-97 (Figures 3 & 6) and Bishayee et al. (2001)³¹ **Radiation Research 155**, 335-344 (Figure 2A).

Dr. Hill claimed to DIO that data showing a bystander effect on survival could not be repeated by Dr. Lenarczyk and was likely to have been falsified by Dr. Bishayee. She also claimed that Dr. Howell was instructed to repeat the experiment by Dr. Reveche during the inquiry, and that Dr. Howell was unable to repeat the experiment.

DIO asked the UMDNJ RIO to ask Dr. Howell about the repetition of the experiment. He denied it, or at least claimed that many others had observed a bystander effect. However, he did not

³⁰Bishayee, A., Rao, D.V., and Howell, R. W. (1999) "Evidence for pronounced bystander effects caused by nonuniform distributions of radioactivity using a novel three-dimensional tissue culture model," *Radiat. Res.* 152: 88-97 (1999) (Attachment 3), cited in grant application 1 R01 CA83838-01A1, pp. 2, 26 and p. 48 (as ref. 66) (Attachment 1).

³¹ Bishayee, A., Hill, H.Z. Stein, D. Rao, D.V. and Howell, R. W. (2001) "Free-radical initiated and gap junction-mediated bystander effect due to nonuniform distribution of incorporated radioactivity in a three-dimensional tissue culture model," *Radiat. Res* 155: 335-344 (Attachment 4), also reported in grant application R01 CA83838-02, p. 6. (Attachment 2)



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produce any data, and it is not clear whether he was referring to a bystander effect of incorporated tritium, or other types of radiation.

The inquiry report did not consider the broader allegation that the bystander effect of tritium had been fabricated by Dr. Bishayee, because others in the lab could not reproduce it. DIO examined the paper published in 1999, which was a presentation of data showing the bystander effect on cell survival in cells exposed (in cell pellets) to cells containing incorporated tritiated thymidine. The paper also presented data supporting the Howell lab's explanation that the bystander effect (decrease in viability of cells not containing radioactive label) depended on the formation of gap junctions, since lindane, a chemical that blocks gap junction "communication," markedly reduced the effect (i.e. the killing of bystander cells in the clusters). (Bishayee et al., 1999) The original data shown in the grant application was Figure 2 (Attachment 1, p. 26)- "Survival of V79 cells as a function of cluster activity of 3HTdR" (tritiated thymidine). It displayed three curves: a curve showing a rapid decrease with time of the surviving fraction when 100% of the cells are labeled, a two-slope curve of greater survival (at equivalent dose of radioactivity) when only 50% of the cells are labeled (middle curve), and a curve with a shallow slope when only 10% of the cells are radiolabeled. In the accompanying text, it was stated that the two component nature of the curve when 50% of the cells are labeled was "shown better in Attachment #1 (in the appendix) ref. 66, the paper by Bishayee et al., (1999) (Attachment 2). In the text of the grant, it was stated, "the second component (of the curves) indicates that cells continue to be killed even though they are not significantly irradiated. This suggests that a bystander effect is responsible for killing of unlabeled cells." (Attachment 1, p.26).

In the grant and in the paper, the data appears to be from only two experiments.

Similar data was presented in the second paper, where more evidence was shown for a bystander effect of tritiated thymidine and elimination of the effect by lindane and by dimethylsulfoxide, a hydroxyl radical scavenger (Attachment 3, Bishayee et al., 2001). The authors (who included Dr. Hill) concluded that the bystander effect in clustered (hypoxic) cells may be initiated by free radicals and mediated through gap junctions. The number of experiments reported in this paper was between 2 and 5 for each condition where the bystander effects was claimed to exist (50% or 10% labeling of cells) (Attachment 3, Bishayee et al., 2001, Table 1, p. 338).

It does not seem unreasonable for the inquiry committee, before dismissing the allegations, to have asked to see the data for the 2 or 4 experiments in the latter paper that were the basis for the claim of a bystander effect when 10% or 50% of the cells were labeled, respectively, and to examine the experimental data of Dr. Lenarczyk, in which he did not observe a bystander effect. Instead, the committee totally ignored the claim of Dr. Hill, that both Dr. Lenarczyk and Dr. Howell could not reproduce the bystander effect claimed by the laboratory on the basis of experiments done by Dr. Bishayee, or else the committee was not aware of this allegation.

The allegation- that no one can repeat the basic observation of the bystander effect of tritium- would seem to call for verification of the data in this paper wherever a killing curve was claimed to have a second component (referred to as A2 in the Table 1. (Attachment 3, p. 338). It would



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be helpful to have the institution determine whether Dr. Howell attempted to repeat the bystander effect himself, and what result he obtained.

The committee recommended that Dr. Putterman ask Dr. Howell to take corrective actions to improve the conduct of research and the environment in his laboratory. Dr. Hill alleged to ORI that Dr. Howell's subsequent actions were to exclude Dr. Hill from the departmental laboratories, stop his collaboration with her, to not renew Dr. Lenarczyk's appointment, and to force Dr. Bishayee to leave the laboratory. (Attachment 5, p.)

DIO asked Dr. Putterman to look into the question of whether Dr. Howell demanded Dr. Bishayee's resignation immediately after the inquiry, because it seemed so much at odds with Dr. Howell's testimony about Dr. Bishayee's abilities and productivity. Dr. Putterman stated that Dr. Bishayee had resigned, but he claimed it was because he was uncomfortable with Dr. Hill in the laboratory, and he went back to India. He then returned to UMDNJ in the winter, 2001-2002, and took a position in a different department. Dr. Putterman stated that Dr. Howell had not written a letter of recommendation for Dr. Bishayee, but said it was not needed since his new job was also at UMDNJ. Dr. Putterman prevented Dr. Hill's exclusion from the departmental laboratories.

DIO recommendation:

It is recommended that an investigation, independent of the former committee, be carried out, with input from persons engaged in cell biology, cell culture or related research on mammalian cells. It is also recommended that the allegation that Dr. Howell knows that the data for the bystander effect could not be repeated in his own laboratory, be evaluated by the second committee. It seems very possible that Dr. Howell failed to pay sufficient attention to the lack of verifiable primary data of Dr. Bishayee in 1999, included questionable data in a grant application, has failed to have questioned preliminary experiments on mutation rate repeated, and that he retaliated in terms of their employment against Dr. Bishayee, Dr. Lenarczyk, and Dr. Hill. A thorough examination of the data underlying the bystander effect, and a determination of the results (if any) of Dr. Howell's alleged attempt during the inquiry to repeat the key experiment should be examined, together with his actions as a supervisor of Dr. Bishayee and Dr. Lenarczyk.

ORI Conclusion

ORI (or just KLF) does/does not concur with the institution's determination that there was insufficient evidence to warrant an investigation. DIO urges that the institution be encouraged to go forward with a more thorough investigation, and to include persons with more cell biology expertise on the committee.



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Attachments

1. Grant application 1 R01 CA83838-01A1 (selected pages) (pp. 2,26,48)
2. Grant application 2 R01 CA83838-02. (selected pages) (p.6) (biographical sketch of Dr. Lenarczyk.)
3. Bishayee, A., Rao, D.V., and Howell, R. W. (1999) "Evidence for pronounced bystander effects caused by nonuniform distributions of radioactivity using a novel three-dimensional tissue culture model." *Radiat. Res.* 152: 88-97 (questioned data, figures 3 & 6) Article cited in grant application as showing bystander effect.
4. Bishayee, A., Hill, H.Z., Stein, D. Rao, D.V. and Howell, R. W. (2001) Free-radical initiated and gap junction-mediated bystander effect due to nonuniform distribution of incorporated radioactivity in a three-dimensional tissue culture model, *Radiat. Res* 155: 335-344. (Grant-supported research containing questioned data- Figure 3).
5. Request for a review of the Inquiry, Letter to ORI dated August 23, 2001, with attachments.
6. Inquiry Report from UMDNJ, with selected attachments.
7. Letter from Dr. Putterman regarding additional information. April 19, 2002.
8. Analysis of data by DIO.
- (9. Summary of Information regarding experience of inquiry committee)- CEC only



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ORI 2001-28

Attachment 1

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Attachment 2

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Attachment 3

CONFIDENTIAL/SENSITIVE

ORI 2001-28

Attachment 4

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Attachment 5

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Attachment 6

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Attachment 7

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Attachment 8

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Attachment 9



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2001-28 UMDNJ

Analysis of digits 8/2/02 JD:

Issue: Dr. Bishayee was accused of falsifying an experiment that he carried out between 9/24/99 and 10/11/99. The data he recorded were either cell counts done on cells in suspension with a Coulter counter or colony counts on tissue culture plates (on 10/11/99).

These data are found in the CEC package, attachment 6 (inquiry report) attachment 6E (p 3 and handwritten on pp 7-9).

DIO copied these numbers (Coulter counts columns A-D); colony counts columns G & H. from the data provided to the inquiry committee by the complainant.

Comparable data that is (relatively) unquestioned are the Coulter counts for the immediately preceding experiment done 9/10/99 and 9/17/99 (columns E & F) and colonies (columns I, 9/27/99) where the Coulter counts were done by the complainant.

JD ran these numbers through the Mosimann program and came up with the following results:

Operator	Bishayee	Bishayee	Bishayee	Hill	Hill	Hill	Hill
Date	9-10/99	same	same	9/10 & 9/17/99	same	same	same
Type of data	Coulter	same	same	Coulter	same	same	same
Column of numbers	A-D	A-D	A-D	E&F	same	same	same
# valid numbers	120	120	240	62	62	124	62
digit examined	10's	1's	10's & 1's	10's	1's	10's & 1's	100's
probability	0.01	1X 10 ⁽⁻⁷⁾	2X 10 ⁽⁻⁵⁾	0.82	0.025	0.05	0.53

Interpretation: The distribution of non-significant numbers in Dr. Bishayee's Coulter count data for the questioned experiment of Sept-October 1999 was very significantly improbable to be random sampling.

Dr. Hill's comparable data was not in all cases close to random, but least probable was 0.02 (1/50).

See accompanying data sheets showing numbers in data columns A-F, and program printouts of digit counts

H:\FILES\0-2001-28UMDNJ\digit analysis.wpd



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