PUBLIC HEALTH SERVICE

OFFICE OF RESEARCH INTEGRITY - DIVISION OF INVESTIGATIVE OVERSIGHT

REPORT COVER FORM

8/29/02

1. ORIGIN: CALL FROM COMPLAINANT
DATE: 8/17/01

2. STATUS: CLOSED

3. CASE NUMBER: 2001-28

4. ACCESSION NUMBER: 2352

5. TYPE OF CASE:

INQUIRY: ( ) INSTITUTIONAL: (X)
INVESTIGATION: (X) DIO-CONDUCTED: ( )
PHS INTRAMURAL: ( )

6. PERIOD OF MISCONDUCT: 1999-2000

7. DATE OF DIO CLOSURE:

8. PHS SUPPORT ( )INTRAMURAL
EXTRAMURAL (PROVIDE GRANT #S)
1 R01 CA83838-01A1

9. COMPLAINANT:
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10. RESPONDENT(S)

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RESPONDENT ATTORNEY:

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PERIOD:

13. DIO INVESTIGATIVE STAFF

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PERIOD: 8/17/01-PRESENT

NAME: JOHN KRUEGER, PH.D.

PERIOD: 8/17/01-PRESENT

NAME: KAY FIELDS, PH.D.

PERIOD: 8/17/01-8/11/02

14. LOCATIONS OF INVESTIGATIVE FILES
INSTITUTION

15. COLLATERAL CASE(S)

OFFICE/AGENCY:

CONTACT:

DISPOSITION:

16. LOCATION OF SECURED EVIDENCE

17. PUBLIC HEALTH SENSITIVITIES

19. DISTRIBUTION:
COPIES:

18. ON CONTINUATION SHEETS:
1.) List of witnesses: Name, address, phone #, position, date interviewed, and summary. 2.) Brief synopsis of allegations, scientific/medical field and impact of allegations. 3.) Analyses performed: Identify source of expertise, name of contact person, address, phone number. 4.) Issues and findings: Issue, location of claim, location of evidence and findings (for each issue) 5.) Case evaluation council action and dates. 6.) Leads identified by DRI but undeveloped and reason.

20. REPORT MADE BY: KP to ARP DATE:

21. APPROVED BY BRANCH CHIEF/SUPERVISOR:

22. INITIALS OF COORDINATOR:
DATE:

23. APPROVED BY DIRECTOR OF DRI: Alan R. Price DATE: 9/5/02

CONFIDENTIAL/SENSITIVE

SEP - 5 2002

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. Professor Helene Z. Hill, the complainant, initially alleged to Associate Professor Roger Howell, Dr. Bishayee's supervisor, that Dr. Bishayee had falsified data in October 1999. Dr. Howell included the disputed data in his National Cancer Institute (NCI), National Institutes of Health (NIH) grant application 1 R01 CA83838-01A1. In March 2001, Dr. Marek Lenarczyk, a postdoctoral fellow, raised concerns with Dr. Hill about an ongoing experiment by Dr. Bishayee. She brought forward this allegation of falsification of research to Dr. Howell, to the departmental chairman, and then to the head of the UMDNJ Newark Campus Committee[1] on Research Integrity, which conducted an inquiry between April and June 2001, concluding that both allegations did not warrant further investigation. In August 2001, Dr. Hill requested that ORI obtain and review the UMDNJ inquiry report and official's decision. In September 2001, the Division of Investigative Oversight (DIO), ORI, received from Dr. Karen Putterman, Vice President for Academic Affairs, UMDNJ, the institution's inquiry report for ORI review. In April 2002, DIO requested and received additional documentation and information from UMDNJ for review.

Summary of ORI Findings

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.

PHS Support: Data from the questioned experiment was included as Figure 7 in NCI, NIH, grant application 1 R01 CA83838-01A1, submitted in October 1999.

ORI Finding: ORI concurs with the institution that there is insufficient evidence to warrant further investigation.

PHS Issue 2: That Dr. Anupam Bishayee falsified data of an experiment done in March 2001 on the viability of "bystander cells" (which were incubated for three days in the cold in contact with cells that had incorporated tritiated-thymidine into their DNA and then were separated by fluorescence activated cell sorting).

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[1]Hereafter referred to as the "Committee."

PHS Support: The questioned research was supported by NCI, NIH, grant 1 R01 CA83838.

ORI Finding: ORI concurs with the institution that there is insufficient evidence to warrant further investigation.

PHS Relevance[2]

The questioned research was reported as preliminary data in the following NIH grant application or was supported by the subsequently awarded grant: 1 R01 CA83838-01A1 and -02, "Effects of non-uniform distributions of radioactivity" (R. Howell, Principal Investigator [P.I.]), submitted October 21, 1999, and awarded July 1, 2000, to June 30, 2005 (Attachment 2).

Background

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

Dr. Roger Howell, Dr. Bishayee's supervisor, is an Associate Professor of Radiology, UMDNJ. He was awarded a Ph.D. in Physics in 1987 from the University of Massachusetts. He is the P.I. on NCI, NIH, grant R01 CA083838, the revised 10A1-application included the first of the questioned experiments, and the subsequent grant supported the other questioned experiment on the effect of radiation on "bystander cells."

Dr. Helene Hill, the complainant, is a Professor in the Departments of Radiology, Microbiology and Molecular Genetics, and Biochemistry and Molecular Biology, UMDNJ. She was awarded a Ph.D. in Biology by Brandeis University in 1964, and she joined UMDNJ in 1981. She was a co-investigator on NCI, NIH, grant R01 CA083838 (Attachment 2, p. 2); her biographical sketch therein lists many publications on DNA damage and radiation resistence, many using *in vitro* systems and mouse melanoma cell lines.

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[2]**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."

Dr. Hill, who originally sought confidential status from ORI, called and wrote to DIO in August 2001, describing how she had originally questioned an experiment carried out by Drs. Bishayee and Howell in 1999, measuring the effects of cesium-137 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 had not been irradiated ("bystander cells") are killed by close association with irradiated cells ("the bystander effect"). Drs. Bishayee and Howell published data suggesting that the bystander effect required the formation of gap junctions between irradiated and bystander cells.[3]

However, the validity of the bystander effect on cell survival was challenged in 2000-2001 by the data of Dr. Marek Lenarczyk, a senior postdoctoral associate, who reportedly was unable to confirm the bystander effect. Dr. Hill claimed that Dr. Howell himself had been unable to replicate the key experiments presented in the CA83838 grant application and publications. Dr. Hill added that she and Dr. Lenarczyk had recently questioned another experiment performed in March 2001 by Dr. Bishayee, whom she believed was continuing to falsify data (Attachment 1). Dr. Hill stated that these allegations had been the subject of a UMDNJ inquiry, and she encouraged ORI to obtain and review the inquiry report. In September 2001, DIO requested the inquiry report as well as the attached documents from Dr. Putterman, Vice President for Academic Affairs, UMDNJ.

Institutional Inquiry: Process

The inquiry report stated that on April 10, 2001, Drs. Hill and Howell met with Dr. Elizabeth Raveché, Chairman of the Committee. Dr. Hill provided written allegations of falsification of data against Dr. Bishayee, including documentation of her observations. After consultation with Dr. Putterman, Dr. Raveché instituted an inquiry into the allegations (Attachment 3, p. 2).

Inquiry Committee

The Committee consisted of the following members, all from UMDNJ:

- Neil Cherniack, M.D., Professor, Departments of Medicine and Pharmacology and Physiology, and Associate Dean for Research and Sponsored Programs

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[3]Bishayee, A., Roa, D.V., & Howell, R.W. "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 6); and Howell, R.W. & Bishayee, A. "Bystander effects caused by non-uniform distributions of DNA-incorporated^{125}I." *Micron* 33:127-132, 2002 (Attachment 7).

- 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, School of Nursing
- Teresa Marsico, M.Ed., C.N.M., School of Health Related Professions
- Elizabeth Raveché, Ph.D., Professor of Pathology and Laboratory Medicine (Chair).[4]

Sequestration of Evidence

Dr. Raveché sequestered evidence, with the assistance of Dr. Howell (the research notebooks and available related materials) on April 10, 2001, the day she received the allegations. The materials sequestered included: 32 binders, 4 notebooks, 46 diskettes, 7 zip disks, and 38 Petri plates. Dr. Hill provided to Dr. Raveché a binder containing written allegations, narratives, diaries, photographs, copies of original data from Dr. Bishayee's notebook, and other data from Dr. Hill's records. Later, the Committee obtained additional materials: the relevant NIH grant application, publications on which the grant was based, publications appearing subsequent to funding of the grant that reported on data developed under the grant, abstracts pending presentation, and biographical sketches for the principals. These materials were stored in the Office of the UMDNJ Vice President of Academic Affairs and were reviewed by the Committee (Attachment 3, p. 3).

Allegations

The respondent, Dr. Bishayee, was informed in writing on April 12, 2001, that the Committee was considering questions about whether he falsified or fabricated data for NIH grant R01 CA83838. The inquiry focused on two specific experiments performed by Dr. Bishayee, as questioned by Drs. Hill and Lenarczyk (Attachment 3b):

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

[4]A sixth member of the Committee, 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. This was unfortunate, since Dr. Boccabella could have contributed expertise needed in the basic science and cell biology of the research at issue (see comments below under "DIO Analysis").

survivability and mutagenicity following irradiation of mammalian V79 cells with the mutant gene HPRT [sic[5]].

Allegation 2

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

On April 11, 2001, the Committee reviewed Dr. Hill's written allegation, and the members of the Committee decided to proceed with an initial inquiry.

Institutional Inquiry: Findings

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, 2001, the Committee considered additional comments of Dr. Hill and interviewed Dr. Bishayee a second time. The minutes of the Committee's meetings included summaries of the interviews. The Committee concluded that there was insufficient credible and definitive evidence of misconduct in science to warrant further investigation (Attachment 3, p. 14).

Allegation 1: The October 1999 Questioned Experiment Measuring Induction of Mutations

Drs. Bishayee and Dr. Hill had carried out a joint experiment in September 1999, which was followed immediately by a repeat experiment carried out entirely by Dr. Bishayee from September 20 to October 12, 1999. Drs. Bishayee and Hill followed a protocol for measuring mutations called "the Banbury Protocol" (Attachment 3, p. 3); it also is described in the R01 CA83838-01A1 grant application (Attachment 2, p. 34, ref. 81) as the "CHO/HGPRT mutation assay." As Dr. Hill described it, Dr. Hill performed the mutation arm of the experiment in the first run-through, while Dr. Bishayee assayed the effect of on cell viability of cesium-137 irradiation. In the second experiment, Dr. Bishayee performed both assays (Attachment 3e, p. 5).

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, 1999, the date when his experimental

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[5]DIO 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).

dishes should have been fixed and stained and the colonies counted. She found unconvincing Dr. Bishayee's explanation, that he had completed the experiment and discarded the plates and that the many large dishes left in the incubator were part of a different experiment. Dr. Hill claimed to the Committee that Dr. Howell had told her in 1999 that no other experiment involving so many plates was being done at the time (Attachment 3f, attachment 3, p. 4).

Dr. Hill noted that the dishes that provoked her questions had 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 perhaps copied from the missing Banbury Report,[6] by Dr. Bishayee (Attachment 3, p. 4). Dr. Hill immediately reported these concerns to Dr. Howell in October 1999; he reportedly did not believe her (Attachment 3, p. 4) and included the data she had questioned in the grant application (R01CA83838-01A1) that he was revising and submitting to NIH, despite Dr. Hill's objection to the experiment and her status as a "co-investigator" on this grant application. Dr. Hill did not pursue the matter further at that time.

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. The Committee found Dr. Bishayee's cell counts to be inconsistent with the expected (lethal) effects of gamma radiation from cesium-137 (Attachment 3, p. 5).[7]

The Committee met again with Dr. Bishayee and reviewed the Coulter counter measurements that he had 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. Mutations were 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 (Attachment 3, p. 5). The Committee further stated:

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[6]During the inquiry, Dr. Hill examined a library copy of the Banbury Report and concluded the 1999 data that she had questioned had not been copied from those articles (Attachment 3, p. 4); she didn't know from where Dr. Bishayee's data had come.

[7]It is not clear if the Committee decided whether Dr. Bishayee's recorded data were accurately represented by his graphs.

that the Coulter counts are not integral to the experiment in question, but are incidental data not analyzed or used in the results; they are used only as a guide to determine how to dilute the cells to get the correct number of cells for the next step and to determine when the cells had undergone a total of ten divisions (Attachment 3, p. 5).

Allegation 2: The March 2001 Questioned Experiment on the Bystander Effect

Dr. Hill alleged that Dr. Bishayee had falsified data on March 30, 2001, by substituting new hamster cell cultures for cells that were or were not radio-labeled, but became contaminated, and that he misrepresented the data he obtained as coming from cells labeled on March 26, 2001, when they had not.

Around March 26, 2001, Dr. Lenarczyk had 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 3, 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 tubes) in the cold incubator on March 28 and that they had assayed those samples for microbial contamination and obtained a positive result (Attachment 3, pp. 8-9).

Dr. Hill stated that Dr. Lenarczyk had told her that he had given new, non-contaminated V79 cells to Dr. Bishayee on March 29, 2001, 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, Dr. Hill 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. Dr. Hill concluded that Dr. Bishayee had not collected the pellets from six of the seven tubes to generate the seven cell suspensions that he claimed to have analyzed by fluorescence activated cell sorting (FACS) on March 30 (Attachment 3, p. 8).

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, 3, 4, 5, and 7. The Helena tubes reportedly disappeared from the incubator after Dr. Howell told Dr. Bishayee that his experiment was being monitored; when Dr. Hill searched the laboratory, she could 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 (Attachment 3, p. 8).

Dr. Hill told the Committee that she concluded that Dr. Bishayee had sorted samples on March 30 using the uncontaminated cells (which he had obtained from Dr. Lenarczyk) and 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 Dr. Bishayee could see from his cloudy flasks. Dr. Hill concluded from her observations that Dr. Bishayee had not performed the experiment as planned, but had generated data by sorting and plating cells that had not been exposed, to test 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 (Attachment 3, pp. 8-9).

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 Dr. Bishayee used contaminated cells. Dr. Lenarczyk said 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, whom he trusted; she was a senior co-investigator on the grant, whereas he was relatively junior. Dr. Lenarczyk had given to Dr. Bishayee, when asked, uncontaminated new 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. He explained that special, recognizable Helena centrifuge tubes were used for aggregated cell incubations in the cold incubator and that the seven tube design was characteristic of Dr. Bishayee's experiments studying bystander effects at different levels of radiation exposure. Dr. Lenarczyk observed Dr. Bishayee working in the hood on March 30, seeing his set of tubes in the cold incubator on that day and noting that the tubes had remained there over the next few days. Dr. Lenarczyk told the Committee that he had sampled Dr. Bishayee's remaining tubes on March 30, after they should have been harvested and counted according to the usual protocol (Attachment 3, p. 9).

Dr. Lenarczyk explained that not all the digital photographs he took of the plates and tubes were dated because the camera was new and that he had learned how to set it to record dates only after he had taken the first photographs. When pressed, Dr. Lenarczyk admitted that he may have

sampled the contents of the centrifuge tubes on March 29, rather than March 30, and then incubated them overnight to test for contamination. Dr. Hill's written notes stated that they sampled two tubes on March 28 and sampled six or seven tubes on March 31 (Attachment 3e). Dr. Lenarczyk stated that he never saw Dr. Bishayee's recorded results (Attachment 3, p. 10).

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. However, 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 that Dr. Hill observed remaining in the incubator had been his, but he had been doing an experiment on a new cell line and that the remaining incubator tubes contained these other cells. Dr. Bishayee said he had no notes of his second experiment nor any written observations. 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 3, 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, but he denied using new cells for the sorting on March 30. He stated that there was nothing unusual in his getting cells from Dr. Lenarczyk, that scientists often do this (Attachment 3, p. 11). Finally, Dr. Bishayee claimed that Drs. Hill and Lenarczyk were conspiring against him because of jealousy and the conflict between Dr. Hill and Dr. Howell (Attachment 3, p. 11).

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 seven days incubation at 37° C 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.[8] Dr. Howell said that, for this particular experiment, it would have made no sense at all to substitute new cells for contaminated unlabeled bystander cells. He stated that Dr. Bishayee could not have known about the cell contamination on March 30 just by observation of the Helena tubes.[9] 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

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

[9]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.

(Attachment 3, p. 12).[10] 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. Furthermore, Dr. Bishayee reportedly had requested cells from Dr. Lenarczyk on March 29 (presumably because he had lost his flasks of V79 cells to the contamination that Drs. Hill and Lenarczyk had noticed and photographed).

Dr. Howell thought that Dr. Hill should have confronted Dr. Bishayee directly, rather than sampling his tubes. He also stated that because Drs. Hill and Lenarczyk had conducted 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 3, p. 12). Dr. Howell commented on how it made no sense to substitute uncontaminated cells for the non-radioactive, non-dyed cells (Attachment 3, p. 12). Dr. Howell had no explanation for the presence of tubes in the cold incubator after Friday, March 30. 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 had been marked on the rack and as measured by Dr. Lenarczyk) (Attachment 3, p. 13).

Dr. Howell stated that the protocol was difficult, and he acknowledged that Dr. Bishayee had experienced contamination in earlier experiments. Dr. Howell thought that the cells may have been contaminated by the phosphate buffer in which the fluorescent dye was diluted, so that only the radioactively-labeled cells had thereby become contaminated.[11] Dr. Howell had no explanation for the photographs or the observations made by Drs. Hill and Lenarczyk of Dr. Bishayee's experiment (Attachment 3, 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. The Committee could neither confirm nor disprove Dr. Bishayee's statements[12] nor confirm nor disprove the validity of the photographs (Attachment 3, p. 14). The Committee apparently thought that Dr. Hill's scenario of falsification of the experiment was not credible, and it remarked that "any such effort on Dr. Bishayee's part to fabricate the experimental results in this experiment would have been greater than simply repeating the experiment with fresh, uncontaminated cells" (Attachment 3, p. 9).

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[10]Dr. Howell did not mention that the flasks inoculated on March 26 were indicators of contamination at the start of the experiment.

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

[12]In fact, Dr. Bishayee had not denied that his flasks were contaminated nor 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, one of which Dr. Hill did not see nor photograph.

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 for 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.

2. The major evidence concerning the March 2001 experiment was the set of photographs taken by Drs. Hill and Lenarczyk.[13] The Committee considered the dating of the photographs not to be definitive and the photographs to be possibly unrelated to the experiment that Dr. Bishayee claimed to have performed on March 26 to 30. The report stated that 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[14,15] (Attachment 3, p. 14).

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

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[13]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 Dr. Bishayee did not dispute.

[14]The evidence of contamination was the testimony of what Drs. Hill and Lenarczyk observed in the flasks. They took photographs, presumably to demonstrate cloudiness due to cell detachment, bacteria, or fungi. DIO assumes that either the photographs are unclear or the Committee simply did not consider the complainants' testimonies to be truthful.

[15]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.

what they did, when they did it, and how they sampled or collected evidence regarding Dr. Bishayee's experiment[16] (Attachment 3, p. 15).

5. Drs. Hill and Lenarczyk admitted sampling ("tampering with") the tubes from Dr. Bishayee's experiment, possibly before it was completed (Attachment 3, p. 15). The Committee disapproved of this action and called their observations "secret investigations" (Attachment 3, p. 8). 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.[17]

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[18] (Attachment 3, p. 15).

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 (Attachment 3, p. 15).

Institutional Official's Decision

On July 2, 2001, Robert A. Saporito, D.D.S., Senior Vice President for Academic Affairs, wrote to Dr. Bishayee regarding the outcome of the inquiry (Attachment 3B):

> . . . the Committee unanimously concluded that there is no cause to warrant further misconduct-in-science proceedings with regard to the allegations. After reviewing the Committee's report and the minutes of the Committee's meetings, along with the attachments thereto, I have accepted the Committee's findings.

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[16]Since 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.

[17]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.

[18]The Committee evidently discounted testimony that the bystander experiment could not be repeated by Drs. Lenarczyk and Howell. If this were true, the doubt about the bystander effect would have been a substantial motive for Dr. Bishayee to falsify data showing such an effect.

DIO Analysis

DIO reviewed the Inquiry Report and its attachments as well as additional information obtained from Dr. Putterman, UMDNJ. In addition, DIO conducted additional analyses of the evidence.

Inquiry Committee Expertise

DIO questioned whether the Committee had sufficient competence to conduct adequately this inquiry. Four of the Committee members were deans whose MEDLINE citation records indicated minimal recent bench-science publications. Dr. Raveché, a pathologist, may or may not have had 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 allegations[19]).

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; e.g., when Dr. Hill questioned the counts of induced HPRT mutations in assays where colonies of surviving mutant (thioguanine-resistant) cells were evaluated, the report referred to this 1999 experiment as "irradiation of mammalian V79 cells with the mutant gene HPRT" (Attachment 3, p. 2).[20] They also naively considered it harder to substitute new cells than to restart the experiment in 2001 (Attachment 3, p. 9).

On April 12, 2001, Dr. Raveché wrote to Dr. Hill that she would be given an opportunity to comment on the report, and on June 22, 2001, Dr. Raveché notified Dr. Hill by letter of the conclusion of the Committee. However, Dr. Hill told DIO that she was not provided with a copy of the report, nor with that portion of the report that described her views as required by the PHS regulations. Perhaps as a consequence, Dr. Hill strongly objected to the decision of the inquiry, and the Committee had no opportunity to correct such factual mistakes. When UMDNJ sent the inquiry report to ORI, no comments were included from any of the principals. However, the inquiry was performed in a timely manner, and the institution was cooperative in providing additional materials to ORI.

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[19]If Dr. Raveché did so, it was an inappropriate suggestion as an alternative to a misconduct inquiry.

[20]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; Attachment 3e, pp. 12-13). For Dr. Bishayee to discard the stained culture plates (the primary data) was definitely not standard practice, especially when the technique was new to him.

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 Committee and materials sent to ORI (Attachments 1, 3d, and 3e). These included a set of data and a protocol for the two experiments carried out by Drs. Bishayee and Hill in 1999. The protocols for the evaluation of radiation effects on viability and mutation of cells were described in the grant application (Attachment 2, p. 34) as the "Banbury Protocol." The notebook materials include two graphs that show the induction of mutations (in the HPRT gene) in two sets of cell samples represented by circles and squares (Attachment 3d, pp. 1-2, page dated 9/28/99). For the experiment conducted 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) (Attachment 3d, pp. 1-2, 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 2, p. 29). The Figure 7 legend noted that all the cells had been incubated (as cell pellets) at 10° C for three days and then exposed with or without resuspension to varied doses of gamma irradiation from cesium-137. This experiment is described in the text as testing for an oxygen enhancement effect. The information agreed with the protocol contained in the material provided by Dr. Hill (Attachment 3d).

In the text of the grant application, 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 2, p. 29). This seems to match the conclusion of the graphed data from Dr. Bishayee's Experiment #2 (and Experiment #1). The data shown in Figure 7 resemble the graphed data obtained by Dr. Bishayee for Experiment #2 done in October 1999 (Attachment 3d).[21] 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 were drawn with filled squares in Figure 7, and, according to the figure legend, these were samples of cells irradiated "intact," i.e., as pellets. The second curves had filled circles; they showed slightly less killing and fewer mutations. By exclusion, they should have been the resuspended, irradiated cell samples. In the figure legend, resuspended cells were supposed to be

[21]Dr. Hill wrote: "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" (Attachment 3d, p. 2).

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 Dr. Bishayee in Experiment #2 were summarized in the text in agreement with the data in the notebook (Attachment 3d), 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 to DIO 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 Committee evidently did not notice it, or if they did notice it, they did not mention it in the report. However, the data that Dr. Hill had criticized as fabricated were used in the grant application. The contradiction between actual or stated results and its graphic presentation in the grant application may have been due to honest error or just carelessness, since it did not support the text very well.

The data for the experiment that Dr. Hill had done in September 1999 with Dr. Bishayee (Experiment #1, 09/06/99 to 9/28/99) was also submitted to the Committee by Dr. Hill (Attachment 3d, pp. 10-16). The results Dr. Hill obtained (see graph, Attachment 3d, p. 10) showed no reliable increase with dose in mutants/cell in the cells irradiated under hypoxic conditions, i.e., 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 in the text of the grant application that cells in suspension were more sensitive to the mutagenic and toxic effects of irradiation than cells left in pellets. Thus, the result obtained by Dr. Hill in the mutation arm of Experiment #1, even with rather erratic values for the (hypoxic) clustered cells, did not contradict the statements in the grant application.

Dr. Hill was not objecting to the results Dr. Bishayee claimed to have obtained as a wrong or contradictory result; her objection was that he had obtained his results by fabrication of this data (Attachments 1 and 1a). This conclusion by Dr. Hill was based 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 (Attachment 3e, p. 3 and unnumbered pages dated 10/3/99). This interpretation was reinforced for Dr. Hill by Dr. Bishayee's inability to produce the stained tissue culture plates that he claimed to have counted and by 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 for that experiment, and Dr. Howell reportedly knew of no such second experiment (Attachment 3f, pp. 1-2). Dr. Hill was distressed when Dr. Howell went ahead, despite her objections, with adding the disputed data to his 1999 grant application (original telephone call from Dr. Hill to DIO, August 9, 2001).[22]

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[22]DIO found no data on mutant induction in the two published papers cited (Attachments 6 and 7).

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 (telephone call from Dr. Hill to DIO, August 9, 2001). From the summary of the interview of Dr. Lenarczyk (Attachment 3f), it appears that this concern was not discussed with the Committee, so the Committee may not have known about this question. No details were given in the report regarding Dr. Lenarczyk's experimental system or results, and the Committee did not ask him to evaluate the 1999 data obtained with cesium-137 radiation (he had not been present in the laboratory in 1999) (Attachment 3c).

In a memo and interview with Dr. Raveché dated 5/22/01 (Attachment 3d, attachment 22), Dr. Hill questioned the reliability of the Coulter counter data recorded by Dr. Bishayee for the mutation arm of 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 ten days before plating equal numbers of cells on the selective medium to measure mutation rates (Attachment 3d).

The Committee asked Dr. Bishayee for an explanation of the cell counts that he did with a Coulter counter. Dr. Bishayee replied that he had not observed an effect on cell survival when he counted cells, but he stated during his interview that the effects on the survival and growth of irradiated cells might be delayed and not be evident when the cells were 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 its members were satisfied with Dr. Bishayee's explanation (Attachment 3, 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 three samples from each culture barely showed the variation expected from recounting the same sample (square root of N) according to a simple analysis done by DIO (Attachment 5). When Dr. Howell was asked by Dr. Putterman, as DIO had requested, about this variation, Dr. Howell claimed that he had also obtained Coulter counts that were in close agreement (Attachment 4).

In contrast (as shown in Attachment 5A), DIO noted that Dr. Hill had obtained highly variable Coulter counts in Experiment #1 (she even switched to counting cells with a hemocytometer instead). 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); but Dr. Hill stated that she expected to see in Dr. Bishayee's Experiment #2 a ten-fold reduction in cell count. The very small variation in Dr. Bishayee's recorded Coulter counts is striking (Attachment 5A).

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 expertise in mutagenesis. Dr. Howell, on the other hand, was trained as a physicist, and his experience with cell culture was minimal as judged by his publications (Attachment 2, pp. 5-6). DIO questions why the Committee dismissed the testimony and judgment of Dr. Hill in this matter, since she had 20 years of experience and many publications in this field of research. The Committee may have accepted Coulter count data that appears by comparison to have been too precise to represent accurately reported data.

According to Dr. Hill's written allegation, she reacted to the first incident in October 1999 where she suspected that Dr. Bishayee had fabricated data by informing Dr. Howell (Attachment 3e, unnumbered pages dated 10/23/99). He appears to have taken no action other than to inform Dr. Bishayee (who then disposed of the plates in the incubator) and to retain the questioned preliminary data (which was inaccurately graphed: the clusters and resuspended cell data were mislabeled in Figure 7) in his grant application (Attachment 2, p. 29). The Committee did not appear to take seriously Dr. Hill's allegation about the 1999 experiment in simply accepting the explanation of Dr. Bishayee (Attachment 3, p. 6). His explanation that the plates were in the incubator for a second experiment was not supported by any evidence, but the Committee did not pursue this question with Dr. Bishayee (Attachment 3e, pp. 6-12) or Dr. Howell (Attachment 3e, pp. 12-14).[23]

DIO also conducted an additional analysis (Attachment 5B), entering into a spreadsheet for evaluation the raw numbers that were recorded by Dr. Bishayee as his Coulter count data for September 24 and 29 and October 1 and 4, 1999 (Attachment 5). DIO observed an unusual "reuse" of two numbers, 56 and 72, and a high frequency of 1's, 2's and 9's in the right-most terminal (ones) place of these three-digit numbers. The numbers are questionable as to whether they could represent the output of an unbiased counting device, such as the Coulter counter (Attachment 5B).

However, given the absence of proper controls for this analysis, DIO does not find this evidence or the above inadequacies in the inquiry report sufficient to warrant further investigation in this case. As noted by the Committee, the Coulter counts were not data that was reported as results; they were only used as guides for the implementation of the protocol. From the available evidence, DIO cannot resolve whether the Coulter counts were actually fabricated, and this issue for DIO remains unresolved.

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[23]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 application, and could establish to what extent Dr. Bishayee's Coulter counts usually varied. According to Dr. Hill, Dr. Lenarczyk was measuring mutagenesis in this laboratory (telephone call to DIO, August 9, 2001), but he was not asked what results he obtained or whether he was able to replicate Dr. Bishayee's experimental data (Attachment 3g, pp. 1-5).

PHS Issue 2

> That Dr. Anupam Bishayee falsified data of an experiment done in March 2001, on the viability of "bystander cells" (which were incubated for three days in the cold in contact with cells that had incorporated tritiated-thymidine into their DNA and then were separated by fluorescence activated cell sorting).

The experiment that provoked Dr. Hill's allegation in 2001 involved radiation from tritiated thymidine incorporated into cellular DNA.[24] Dr. Lenarczyk mentioned his concerns about Dr. Bishayee's ongoing experiment to Dr. Hill, and Dr. Lenarczyk provided a fresh cell culture to Dr. Bishayee on March 29, 2001(Attachment 3e, p. 2). Dr. Lenarczyk observed 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 (Attachment 3e, pp. 1-2). He and Dr. Hill decided to monitor carefully what Dr. Bishayee did with the experiment that was underway. They observed the flasks in the tissue culture room and samples in the incubators. Dr. Hill took notes on what they saw; Dr. Lenarczyk took photographs of the flasks and tubes to document their observations (Attachment 3e). Then Dr. Hill compared what they observed with the results that Dr. Bishayee recorded in his notebook, wrote out her concerns (Attachment 3e), and went to talk with Dr. Howell, the head of the research project and the P.I. on the grant that was supporting Drs. Bishayee and Lenarczyk. Drs. Howell and Hill went together to talk to their chairman, Dr. Baker, who sent them to discuss the matter with Dr. Raveché (Attachment 3, pp. 1-2).

However, the Committee was skeptical about the photographs offered by Dr. Hill, citing the lack of definitive dating of the photographs as a reason to doubt that the plates or tubes photographed were relevant to the experiment that Dr. Bishayee performed (Attachment 3, p. 8). However, Dr. Bishayee had not claimed to have any other plates in the incubator or any other experiment using plates underway, so the central issue to DIO was the set of small centrifuge tubes for the purported experiment. Dr. Bishayee did not claim that he was using any alternative incubator, nor did he have any notes to show that he had prepared more than one set of tubes or to show that he was actually doing a second experiment that Drs. Hill and Lenarczyk could have mistaken for the bystander effect experiment in question. The Committee appeared to imply that the photographs were falsified, rather than just interpreted incorrectly by Dr. Hill (Attachment 3, pp. 14-15).[25] However, the veracity of the photographs was not disputed by Dr. Bishayee; he was

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[24] DIO notes that the radiation (beta particle decay) from tritiated thymidine is much less penetrating than the gamma irradiation of cesium-137, so tritium might not be expected to penetrate far enough from its location in the DNA in one cell's nucleus to cause mutations in an adjacent cell's nucleus.

[25]The Committee stated Drs. Hill and Lenarczyk had "interfered" or "tampered" with Dr. Bishayee's experiment, clearly disapproved of their "secret investigation" and appeared to be accusing them of producing falsified photographs (Attachment 3, pp. 10 and 15). If Drs. Hill and Lenarczyk sampled the tubes as they claimed, after the cell sorting had started, DIO found 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 fact, their claim that they observed radioactivity in the Helena tubes (Attachment 3e, p. 3b) seems to DIO to favor their identification of those tubes as belonging to the "bystander" tritiated-thymidine experiment, since

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 (Attachment 3g, pp. 6-9). Dr. Lenarczyk's observations supported the idea that Dr. Bishayee was trying to grow the new human cell line, and it was not growing well, certainly not well enough to generate a set of cell pellets, so it was then simply discarded.

Dr. Bishayee's explanation of a second set of tubes could not be confirmed; 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. DIO notes that mammalian cells do not grow at 10°C, and their growth, unlike that of 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 he did not explain how he evaluated growth without any recorded measurements, had no protocol, gave no coherent explanation of what he might have been measuring in pellets of the other cell line, and provided no information that would account for the second set of tubes. He also did not describe what he intended to measure and why he had not done so. Therefore, DIO does not find Dr. Bishayee's claim for a second experiment to be supported or credible.

The Committee members did not explain why they chose to believe Dr. Bishayee's account of his experiment, rather than the observations and photographs of the complainants, who were members of the same laboratory. Stripped of the extraneous details, Dr. Bishayee's basic claim was that he had harvested seven tubes of cold-incubated cells and subjected them to FACS sorting on March 30, whereas Drs. 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 during the next week. Neither Dr. Hill nor Dr. Lenarczyk observed two sets of Helena tubes in the cold incubator, and Dr. Bishayee did not inform the Committee what he had done with the cells that he got from Dr. Lenarczyk.

The major evidence concerning Dr. Bishayee's questioned March 2001 experiment was the set of photographs taken by Drs. Hill and Lenarczyk.[26] The Committee's report 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 on March 26 to 30; the date of the photographs claimed by Dr. Hill could not be reconciled by the Committee 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 (Attachment 3, pp. 10, 13, and 14).

Nonetheless, this evidence does not appear to DIO to be sufficient alone to warrant further investigation. DIO does not have adequate evidence available to resolve whether the claims for this research were fabricated, and this issue remains unresolved.

Dr. Bishayee implied that the second experiment did not involve radiolabeled cells.

[26]DIO considers the major evidence of falsification of research to be the recorded observations of the two witnesses/complainants, their apparent 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.

Possible Pattern of Behavior by Dr. Bishayee

DIO found similar alleged behaviors by Dr. Bishayee in both PHS Issues 1 and 2. In both instances, he claimed to be doing another, unrecorded experiment, to have substituted samples or data in failed experiments, and to have discarded samples when their authenticity was challenged. If he had retained the fixed, counted plates as the primary data in PHS Issue 1, he could readily have supported his experimental data (the plates could have been recounted). Likewise, if he had not discarded the disputed set of six Helena tubes left in the cold incubator in PHS Issue 2, he could have demonstrated the absence of tritium-label or even the human (rather than hamster) origin of the cells, and thus he would have had evidence to disprove the allegation. Dr. Bishayee's actions in discarding crucial evidence after being accused of fabricating or falsifying data are questionable.

It is also striking that Dr. Howell, Dr. Bishayee, and the laboratory protocol and notes on the experiment did not reveal in what way the experiment was primarily concerned with the radioactively-labeled cells, rather than the bystander cells. The FACS separations 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 co-incubation was not discussed in the report. However, Dr. Howell's proffered explanation, for the contamination of only the fluorescent cells by a dye solution, was incorrect; incubation of a mixture of contaminated fluorescently-labeled cells with uncontaminated non-radioactive cells as mixed cell pellets for three days could not have yielded uncontaminated, separated, non-tritiated cells (there was 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 its 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. Thus, 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 if he had restarted the experiment on March 30. If the arrangement for use of central FACS facility was inflexible or if Dr. Howell would have been reluctant to have his grant were charged twice by the facility if the experiment had to be rescheduled, there could have been pressure on Dr. Bishayee to continue the experiment, despite the contamination. Carrying on with fresh cells would have been easier than starting over, but it would not have given any information about the bystander effect or the effects of exposure of any of the cells to the decay of tritiated thymidine.

DIO Recommendation

While DIO would normally recommend in such a case that further investigation by a committee with expertise in cell biology, cell culture, or related research on mammalian cells be carried out,

given the weaknesses in the UMDNJ inquiry in this case, DIO does not find sufficient new evidence that would warrant such a recommendation. While it remains unresolved whether the bystander effect was ever reproducible in Dr. Howell's laboratory, as reported in two publications (Attachments 6 and 7), in the absence of additional evidence of their falsification, this question would not be a PHS issue of scientific misconduct. Thus, DIO recommends that ORI decline to pursue this case further.

ORI Conclusion

ORI concurs with the institution that there is insufficient evidence, on either PHS issue, to warrant further investigation.

Attachments

1. Allegation letter to DIO, ORI, from Dr. Hill, August 23, 2001, and
   a. Letter to DIO from Dr. Hill, December 12, 2001

2. NIH grant application 1 R01 CA83838-01A1 (selected pages)

3. Inquiry Report from UMDNJ, with selected attachments:
   a. Transmittal letter from Dr. Putterman to DIO, September 7, 2001
   b. Report Attachment B, official's decision letter, July 2, 2001
   c. Report Appendix C, Summaries of Meetings of April 11 and May 9, 2001
   d. Report attachment 1a (Attachment 22), memo and data from Dr. Hill
   e. Report attachment 1b, Introduction and records from Dr. Hill
   f. Report attachment I, Summary of Meeting of April 17, 2001, with attachments 2 to 8 from Dr. Hill
   g. Report attachment J, Summary of Meeting of April 27, 2001 (& photos)
   h. Report attachments 20 and 21

4. Letter from Dr. Putterman to ORI regarding additional information, April 19, 2002

5. Analysis of data by DIO:

   A. Coulter count data 3/26/01
   B. Coulter count data 9/24/99 to 10/4/99

6. Bishayee, A., Rao, D.V., and Howell, R. W. "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

7. Bishayee, A., Hill, H.Z., Stein, D. Rao, D.V. and Howell, R. W. "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, 2001

Allegation letter to DIO, ORI, from Dr. Hill, August 23, 2001, and

a. Letter to DIO from Dr. Hill, December 12, 2001.

Attachment 1

Helene Z. Hill, Ph.D.
3 Silver Spring Road
West Orange, NJ 07052-4317
Tel/Fax: 973-736-0738
hzhill@home.com

Thursday, August 23, 2001

Dr. Kay Fields
Division of Investigative Oversight
Office of Research Integrity
5515 Security Lane
Suite 700
Rockville, MD 20852

Dear Dr. Fields,

As per our conversation last week, I am sending you material regarding scientific misconduct at the New Jersey Medical School. I believe that the acts observed by myself and my colleague, Dr. Marek Lenarczyk, constitute misconduct in science as defined in our University policy 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'. I believe that the findings of the initial investigation of 'insufficient definitive evidence' for scientific misconduct were in error. I present to you the material that I provided to the Committee and I also relate that in the aftermath, the key experiments cannot be replicated and the person that I accused of misconduct was forced to resign and has been black-balled from obtaining jobs in the relevant field.

The grant in question is R01CA83838, Roger W. Howell, Ph.D., Principal Investigator, 'Effects of non-uniform distributions of radioactivity', total costs requested for 5 years $1,358,075. I am listed as a co-Investigator on this grant.

If, after you review the material that I provide and that the University will provide you, and you agree with me, I ask that the inquiry be reopened and proceed to the second – investigative – phase as described in our University guidelines for misconduct.

During your initial investigation of this matter, I prefer to remain anonymous.

Thank you for your patience with me. I have every hope that we will eventually get to the truth of this matter.

Sincerely yours,
Helene Z Hill
Helene Z. Hill, Ph.D.

Table of Contents

Attachment 1a

askORI

From: @home NetMail [hzhill@home.com]
Sent: Wednesday, December 12, 2001 11:21
To: askORI
Subject: ATTN Dr Kay Fields

Re: DIO 2352

Dear Dr. Fields,

You asked me to verify the Figures in the two papers that contained data that could not be reproduced (Bishayee, et al., Rad Research 152: 88-97, 1999; Bishayee, et al., Rad Research 155: 335-344, 2001). These would, indeed, be Figures 3 and 6 in the earlier paper and 2A in the more recent paper. Also, Figure 7 in Dr. Roger Howell's grant application depicts the data in the 1999 experiment that I believe to have been fabricated.

As far as I know, the experiment that was repeated many times without showing a bystander effect only involved incubating 50% radio-labeled cells with non-labeled cells in the absence of any modifiers such as lindane and DMSO. The results did not show a rapid decline in survival to 50% followed by a slower decline. They showed a rapid decline to about 50% and then little or no further killing. The other conditions -- +/- lindane, +/- DMSO would only be relevant if there were a bystander effect and a decline in survival after 50% in the master experiment.

Dr. Marek Lenarczyk should have the data from the experiments that he did. I am sure that he would be glad to talk with or correspond with you. His email address is mlenarczyk@pzh.gov.pl.

I would like to ask you if you could send me a copy of the first letter that I received about the misconduct before the investigation began that says that I would get a copy of the report. As I told you, I could not find my copy and have no idea where it can be. Also, would you be able to send me a copy of the report. I am sure I would have some observations about it that might be useful.

Along those lines, I have thought about what both Drs. Anupam Bishayee and Howell said about a second experiment and a second cell line. As you can see from the plan of the lab, quarters are small and Marek and Anupam spent most of their time together in the inner lab. If there had been a second experiment, Marek would certainly have known about it. Roger's routine, which I never knew to vary, was such that cells were harvested for rolling on either Monday or Thursday and they rolled overnight to be harvested on Tuesday or Friday. They then incubated at 10.5 degrees until the next Friday or Monday. We know that there was no experiment started on Thursday, March 29 because my notes show that the rollers were empty in the morning before Anupam came in. Furthermore, if Anupam had processed cells for a new experiment which appeared in the 10.5 degree incubator at the very time that the previous experiment would have disappeared from the same incubator, he would have had to be a miracle worker because he had plenty to do that whole morning getting cells ready for the FACS. There was no protocol for such an experiment at the time that we copied pages from the notebook to make our report and there is no evidence for such an experiment in the radioactivity record. We know that the tubes that remained in the incubator were radioactive because we counted them later (see notes from March 31). The second cell line would almost certainly have been AG1522 which Anupam was growing in a T175 flask in his incubator. The flask was not contaminated but on Friday, the day the putative experiment would have gone into the 10.5 degree incubator, that flask was in the trash. I remember looking at the cells. They had not been trypsinized but were floating in sheets. They had apparently overgrown and detached - a common problem with human fibroblasts. Furthermore, at the time that Anupam told Marek that he was working with clusters, those very clusters were still sitting in the incubator.

It is clear to me that scientific misconduct occurred over the time of this experiment. Contaminated cells cannot give rise to uncontaminated cells so Anupam must have made a substitution. Clean cells were available to him from Marek. I am sad to say that Roger must have dissembled before

the committee. He knew perfectly well that there was no second experiment (he also used that as an excuse to me after the experiment in 1999). Even sadder to say, I think that the committee must have realized that as well. I now believe that what we are looking at here is not just scientific misconduct but cover up.

I used to think that scientists were special, high-minded people who devoted their lives to seeking the truth. Many I have known are that way, but too many are not.

Sincerely yours,

Helene

CONFIDENTIAL/SENSITIVE
ORI 2001-28
Attachment 2

NIH grant application 1 R01 CA83838-01A1 (selected pages)

AA

Form Approved Through 02/28/01
OMB No. 0925-0001

Department of Health and Human Services
Public Health Service

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s carefully. NOV 1 - 1
...character length restrictions indicated on sample.

& NAME: HOWELL, ROGER W
APPL NO:1 R01 CA83838-01A1 COUNCIL: 05/00
DUAL: RCVD:11-01-99
IRG: RAD

1. TITLE OF PROJECT *(Do not exceed 56 characters, including spaces and punctuation.)*
Effects of nonuniform distributions of radioactivity

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT [X] NO [ ] YES *(If "Yes," state number and title)*
Number: Title:

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR — New Investigator [ ] YES

3a. NAME *(Last, first, middle)*	3b. DEGREE(S)	3c. SOCIAL SECURITY NO.
Howell, Roger W.	Ph.D.	*Provide on Form Page KK.*

3d. POSITION TITLE
Associate Professor

3e. MAILING ADDRESS *(Street, city, state, zip code)*
Department of Radiology, MSB F-451
UMDNJ - New Jersey Medical School
185 S. Orange Ave.
Newark, NJ 07103

3f. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Radiology

3g. MAJOR SUBDIVISION
New Jersey Medical School

3h. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: 973-972-5067
FAX: 973-972-6474

E-MAIL ADDRESS: rhowell@umdnj.edu

4. HUMAN SUBJECTS	4a. If "Yes," Exemption no. or IRB approval date	Full IRB or Expedited Review	4b. Assurance of compliance No.	5. VERTEBRATE ANIMALS	5a. If "Yes," IACUC approval date	5b. Animal welfare assurance no.
[X] No [ ] Yes			M1466-01NR	[X] No [ ] Yes		A3158-01

6. DATES OF PROPOSED PERIOD OF SUPPORT *(month, day, year-MM/DD/YY)*		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD		8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT	
From	Through	7a. Direct Costs ($)	7b. Total Costs ($)	8a. Direct Costs ($)	8b. Total Costs ($)
07/01/00	06/30/05	175,000.	259,075.	875,000.	1,358,075.

9. APPLICANT ORGANIZATION
Name: UMDNJ - New Jersey Medical School
Address: 185 South Orange Avenue
Newark, NJ 07103-2714

10. TYPE OF ORGANIZATION
Public: → [ ] Federal [X] State [ ] Local
Private: → [ ] Private Nonprofit
Forprofit: → [ ] General [ ] Small Business

11. ORGANIZATIONAL COMPONENT CODE: 01

12. ENTITY IDENTIFICATION NUMBER: 1221775306A2
DUNS NO. *(if available)*

Congressional District: 10

13. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE
Name: Mr. Richard Wagner
Title: Manager, Grants and Contracts
Address: 30 Bergen Street
Newark, NJ 07103-3000

Telephone: (973)972-6456
FAX: (973)972-3425
E-Mail: grants_newark@umdnj.edu

14. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Name: Neil S. Cherniack, M.D.
Title: Director of Research & Clinical Affairs
Address: UMDNJ - New Jersey Medical School
185 South Orange Avenue
Newark, NJ 07103-2714

Phone: (973)972-4568
FAX: (973)972-3585
E-Mail: cherniac@umdnj.edu

15. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE:
I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

SIGNATURE OF PI/PD NAMED IN 3a. *(In ink. "Per" signature not acceptable.)*
R. G. Howell

DATE: 10/21/99

16. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE:
I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Service terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 14. *(In ink. "Per" signature not acceptable.)*

DATE: 10/21/99

AA

DESCRIPTION: State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This description is meant to serve as a succinct and accurate description of the proposed work when separated from the application. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

There are numerous factors that determine the biological response of tissues that contain radioactivity such as radiosensitivity, distribution of radioactivity, type and number of radiations emitted by the radionuclide, biokinetics of the radionuclide, repair time, etc. Traditionally, the mean absorbed dose to the tissue is calculated to correlate the biological response with mean absorbed dose. However, nonuniform activity distributions in tissue at the multicellular and subcellular levels result in nonuniform doses and therefore have made it difficult to adequately correlate biological response with mean absorbed dose. This is an important problem in diagnostic and therapeutic nuclear medicine. In the case of diagnosis, the risk of the radiation insult can in principle be drastically underestimated and potentially lead to increased risk of inducing cancer. In contrast, patients can be over- or under-treated in radionuclide therapy of cancer. Over-treatment or under-treatment in radionuclide therapy of cancer can have very adverse consequences in the final outcome for the patient. While calculation of absorbed dose at the cellular level has been advocated as a means to address this problem, this has largely remained a theoretical exercise. We hypothesize that the biological response of tissues containing incorporated radionuclides can be correlated with absorbed dose when calculated at the cellular level. To test our hypothesis, a novel in vitro multicellular cluster model will be used which allows tight control over variables. Multicellular clusters will be assembled with mammalian cells containing radioactivity and the cell survival fraction as a function of cluster activity will be determined for several different radiopharmaceuticals which emit alpha particles, beta particles, or Auger electrons. Different percentages of the cells will be labeled with the different radiochemicals to ascertain the impact of nonuniform distributions of radioactivity at the cellular and subcellular levels. By controlling the percentage of cells labeled, this model will also be used to ascertain the role of bystander effects in the biological effects of incorporated radioactivity. These data and cellular dosimetry calculations will be used to develop a theoretical model to predict response based on cellular absorbed dose and bystander effects. The outcome of this research is expected to have a major impact on understanding and predicting the biological response of tumor and normal tissue to nonuniform distributions of radioactivity.

PERFORMANCE SITE(S) *(organization, city, state)*

UMDNJ - New Jersey Medical School
Newark, NJ

KEY PERSONNEL. See instructions on page 11. *Use continuation pages as needed* to provide the required information in the format shown below.

Name	Organization	Role on Project
Roger W. Howell, Ph.D.	UMDNJ - New Jersey Medical School, Radiology	Principal Investigator
Helene Z. Hill, Ph.D.	UMDNJ – New Jersey Medical School, Radiology	Co-Investigator
Dandamudi V. Rao, Ph.D.	UMDNJ - New Jersey Medical School, Radiology	Co-Investigator
Anupam Bishayee, Ph.D.	UMDNJ - New Jersey Medical School, Radiology	Res. Teaching Specialist

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Anupam Bishayee, Ph.D.	Research & Teaching Specialist

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR CONFERRED	FIELD OF STUDY
Jadavpur University, Calcutta, India	B.Pharm.	1989	Pharm. Tech.
Jadavpur University, Calcutta, India	M.Pharm.	1991	Biochem. Pharmacol.
Jadavpur University, Calcutta, India	Ph.D.	1996	Tumor Biol.

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

Ph.D. Thesis: Biological and biochemical role vanadium in the chemoprevention of neoplastic transformation against chemically-induced hepatocarcinogenesis in rats.

Professional Experience:

Feb. 1997-present Research & Teaching Specialist, UMDNJ - New Jersey Medical School

Awards:

1991 Award of Senior Research Fellowship from CSIR, India
1994 "Young Scientist" Award from National Science Council, Canada
1995 Award of Research Associateship from CSIR, India
1995 "Younger Scientist" Award from Indian Chemical Society
1999 "Young Investigator" Award from Indo-American Society of Nuclear Medicine, Los Angles

Bibliography:

A. Chapters or articles in books

. Chatterjee, M. and Bishayee, A.: Vanadium - a new tool for cancer prevention. In, Vanadium in the Environment, Part 2: Health Effects (edited by Nriagu, J.O.). John Wiley and Sons Inc., New York, pp. 347-390 (1998)

2. Bishayee, A. and Chatterjee, M.: Antitumour potential of vanadium against chemically induced hepatocarcinogenesis : reflection in hepatic drug detoxification. In, Proceedings of the XVIth International Cancer Congress (edited by Rao, R.S., Deo, M.G. and Sanghvi, L.D.), Monduzzi Editore S.p.A., Bologna, pp. 3071-3076 (1994)

B. Articles

. Goddu, S.M., **Bishayee, A.**, Bouchet, L.G., Bloch, W.E., Rao, D.V., Howell, R.W.: Marrow toxicity of ^{33}P- versus ^{32}P-orthophosphate: implications for therapy of bone pain and bone metastases. *Journal of Nuclear Medicine* - accepted (1999)

2. **Bishayee, A.,** Beguinot, L., Bishayee, S.: Conformational analysis of the phosphorylated epidermal growth factor receptor. *Bioscience Reports - in press* (1999)
3. **Bishayee, A.,** Roy, S., Chatterjee, M.: Characterization of selective induction and alteration of xenobiotic biotransforming enzymes by vanadium during diethylnitrosamine-induced chemical rat liver carcinogenesis. *Oncology Research* 11, 41-53 (1999)
4. **Bishayee, A.,** Rao, D.V., Howell, R.W.: Evidence for pronounced bystander effects caused by nonuniform distributions of radioactivity using a novel three-dimensional tissue culture model. *Radiation Research,* 152, 88-97 (1999)
5. **Bishayee, A.,** Beguinot, L., Bishayee, S.: Phosphorylation of tyrosine 992, 1068, and 1086 is required for conformational change of the human epidermal growth factor receptor C-terminal tail. *Molecular Biology of the Cell, 10, 525-536* (1999)
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8. Sarkar, A., Basak, R., **Bishayee, A.,** Basak, J. and Chatterjee, M.: β-Carotene inhibits rat liver chromosomal aberrations and DNA chain break after a single injection of diethylnitrosamine. *British Journal of Cancer,* 76, 855-861 (1997)
9. **Bishayee, A.,** Karmakar, R., Mandal, A., Kundu, S.N. and Chatterjee, M.: Vanadium-mediated chemoprotection against chemical rat hepatocarcinogenesis : reflection in haematological and histological characteristics. *European Journal of Cancer Prevention,* 6, 58-70 (1997)
10. **Bishayee, A.,** Banik, S., Marimuthu, P. and Chatterjee, M.: Vanadium-mediated suppression of diethylnitrosamine-induced chromosomal aberrations in rat hepatocytes and its correlation with induction of hepatic glutathione and glutathione S-transferase. *International Journal of Oncology,* 10, 413-423 (1997)
11. Banerjee, K.K., **Bishayee, A.,** Marimuthu, P.: Evaluation of cyanide exposure and its effect on thyroid function of workers in a cable industry. *Journal of Occupational and Environmental Medicine,* 39, 258-260 (1997)
12. Mandal, A., **Bishayee, A.** and Chatterjee, M.: *Trianthema portulacastrum* affords antihepatotoxic activity against carbon tetrachloride-induced chronic liver damage in mice : reflection in subcellular levels. *Phytotherapy Research,* 11, 216-221 (1997)
13. **Bishayee, A.,** Mandal, A. and Chatterjee, M.: Prevention of alcohol carbon tetrachloride-induced signs of early hepatotoxicity in mice by *Trianthema portulacastrum* L. *Phytomedicine,* 3, 155-161 (1996)
14. **Bishayee, A.** and Chatterjee, M.: Inhibitory effect of vanadium on rat liver carcinogenesis initiated with diethylnitrosamine and promoted by phenobarbital. *British Journal of Cancer,* 71, 1214-1220 (1995)
15. **Bishayee, A.** and Chatterjee, M.: Inhibition of altered liver cell foci and persistent nodule growth by vanadium during diethylnitrosamine-induced hepatocarcinogenesis in rats. *Anticancer Research,* 15, 455-462 (1995)
16. Sarkar, A., **Bishayee, A.** and Chatterjee, M.: Beta-carotene prevents lipid peroxidation and red blood cell membrane protein damage in experimental hepatocarcinogenesis. *Cancer Biochemistry Biophysics,* 15, 111-125 (1995)
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18. **Bishayee, A.,** Sarkar, A. and Chatterjee, M.: Hepatoprotective activity of carrot (*Daucus carota* L.) against carbon tetrachloride intoxication in mouse liver. *Journal of Ethnopharmacology,* 47, 69-74 (1995)
19. **Bishayee, A.** and Chatterjee, M.: Mechanism of anti-stress activity of *Mikania cordata* root extract in albino mice. *International Journal of Pharmacognosy,* 33, 215-221 (1995)

20. **Bishayee, A.,** Banerjee, K.K. and Chatterjee, M.: Alterations in hepatic drug metabolizing enzyme activities following administration of human placental extract in rats. *European Review for Medical and Pharmacological Sciences,* 17, 19-16 (1995)
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31. **Bishayee, A.** and Chatterjee, M.: Carrot aqueous extract protection against hepatic oxidative stress and lipid peroxidation induced by acute carbon tetrachloride intoxication in mice. *Fitoterapia,* 64, 261-265 (1993)
32. Mandal, P.K., **Bishayee, A**. and Chatterjee, M.: Stimulation of tissue repair by *Mikania cordata* root extract in carbon tetrachloride-induced liver injury in mice. *Phytotherapy Research,* 7, 103-105 (1993)
33. Mandal, P.K., **Bishayee, A**. and Chatterjee, M.: Stimulation of hepatic protein synthesis in response to *Mikania cordata* root extract in carbon tetrachloride-induced hepatotoxicity in mice. *Italian Journal of Biochemistry,* 41, 345-351 (1992)
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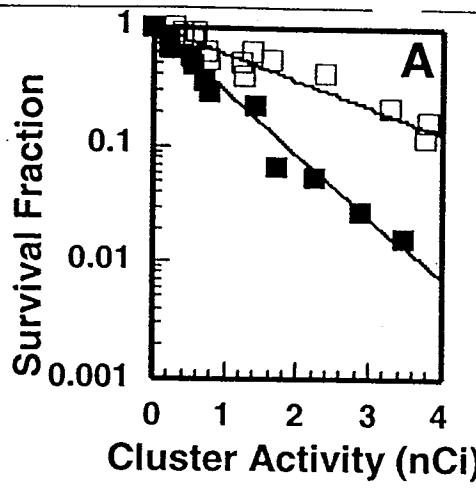
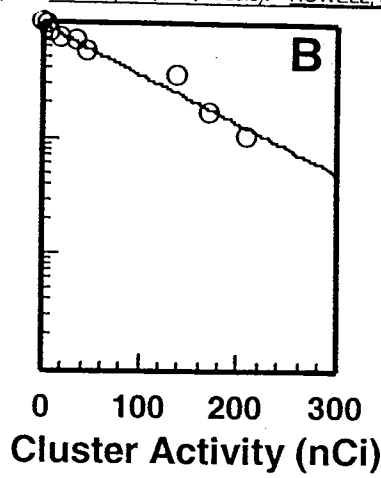


Figure 1A. Survival of V79 cells as a function of cluster activity of ^{210}Po-citrate. 100% (■) and 10% (□) of the cells were radiolabeled.
Figure 1B. Survival of V79 cells as a function of cluster activity of ^{131}IdU. 10% (O) of the cells were radiolabeled.



Studies for ^{3}HTdR are shown in Fig. 2 for 10%, 50% and 100% labeling of the cells. The 100% labeling data in Fig. 2 can be least squares fit to a single exponential response where a mean lethal cluster activity of 2.44 kBq is obtained (*66*). In contrast, the 50% and 10% labeling cases require fits to a two-component exponential function:

$$S = (1\text{-}a)\exp(-A/A_1) + a\exp(-A/A_2) \qquad (C.1)$$

These fits result S(50%) = 0.33 exp(-A/0.81) + 0.67 exp(-A/11.8) and S(10%) = 0.13 exp(-A/0.39) + 0.87 exp(-A/19.8), where the cluster activity A is in kBq (*66*). These results are indeed curious because beta particles emitted by ^{3}H have a spectrum of energies from 0-18.6 keV (*73*) with ranges in water from 0-7 μm. The mean energy is only 5.7 keV which has a range of 1 μm in water. The electrons must travel a minimum of 2 μm (range of 10 keV electron) just to get from the perimeter of the nucleus of a labeled cell to the perimeter of a nucleus of an unlabeled cell which presumably contains the primary radiosensitive targets. Since the electrons emitted by decays occurring randomly throughout the nucleus, nearly all of them will have to travel substantially more than 2 μm to reach the cell nucleus of an unlabelled cell. Given that very few of the beta particles emitted are in excess of the minimum requirement of 10 keV, the cross-dose received by cells in the cluster is negligible. This is supported by the calculations of Goddu et al. (*26*) that show that the cross-dose for electrons in this energy range is negligible when the radioactivity is localized in the cell nucleus. Therefore, in the absence of bystander effects, we should expect to see essentially no killing of unlabeled cells. At high cluster activities, this should translate into a 50% and 10% survival fraction in the case of 50% and 10% labeling, respectively. The first components of the fits indicate that about 50% and 10% of the cells are killed at low cluster activities, however, the second component 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.

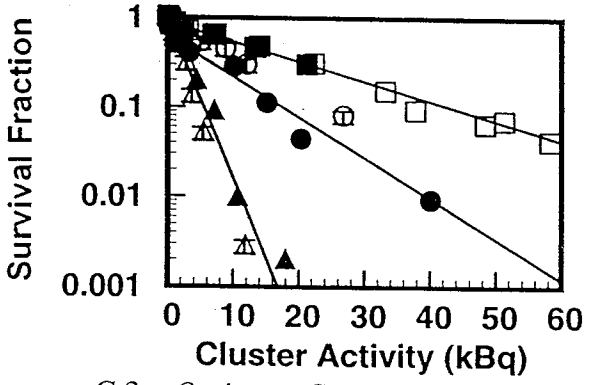


Figure 2. Survival of V79 cells as a function of cluster activity of ^{3}HTdR. Data are shown for experiments where 10% (■,□), 50% (●,O) or 100% (▲,△) cells were radiolabeled in multicellular clusters which were maintained at 10.5°C for 72 h and then the survival fraction was determined compared to unlabeled cells. A clearer view of the two-component nature of the 50% case can be seen in Fig. 3 of Attachment #1 (*66*).

C.2e. *Optimum Concentration and Impact of the Gap-Junction Inhibitor Lindane.* To assess the impact GJIC on the biological response, it was necessary to determine the optimal concentration of lindane, a known inhibitor of GJIC (*14*). Multicellular clusters were prepared wherein 50% cells were labeled with a fixed activity concentration of ^{3}HTdR (148 MBq/ml). The clusters were maintained at 10.5°C for 72 h in the presence of 20-

irradiated clusters were subsequently ..isassociated and processed for surviva. .action. Figure 6 shows the dose response curves for V79 multicellular clusters exposed to chronic and acute ^{137}Cs gamma irradiation at 10.5°C. The shouldered dose response curves are characteristic of the response of mammalian cells to radiations with low linear energy transfer (LET). It is clear that the response of the multicellular clusters is dependent on the e rate. The chronic dose rates are similar to the dose rates encountered with incorporated radionuclides, ...erefore, the α and β coefficients for the chronic irradiation can be taken as representative of the coefficients one would expect for the response to cross-dose from low-LET radiations emitted by the radionuclides.

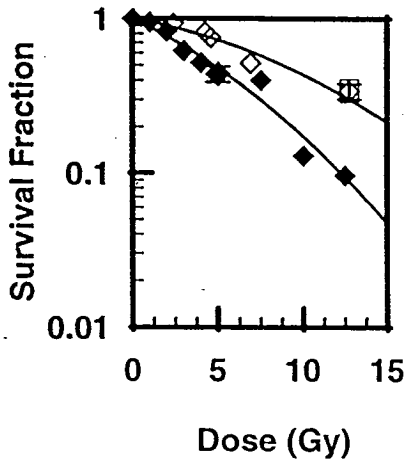


Figure 6. Survival of V79 cells following acute (◆) and chronic (◇) irradiation of multicellular clusters with ^{137}Cs gamma rays. Irradiations were carried out under the same conditions as those maintained in the radionuclide studies. A least squares fit of the data to the linear-quadratic model ($SF = Exp(-\alpha D - \beta D^2)$) yielded the following:

$SF(chronic) = Exp(-4.4 \times 10^{-2} D - 3.9 \times 10^{-3} D^2)$
$SF(acute) = Exp(-1.18 \times 10^{-1} D - 5.6 \times 10^{-3} D^2)$

where the α and β coefficients are in Gy^{-1} and Gy^{-2}, respectively

C.2i. *Mutagenesis and Survival Studies with External Gamma Rays: The Question of Hypoxia in the Clusters.* In this experiment, the protocol used in the above acute gamma ray experiment was followed except that immediately prior to irradiation, cells in half the tubes were resuspended to replace depleted oxygen while the cells in the remaining tubes were continued as pellets. Cells in all tubes were plated to evaluate colony-ning ability. Fig. 7A shows that the cells that remained in clusters were somewhat more resistant to killing acute gamma irradiation relative to those that had been resuspended. Curve fits to the linear quadratic model resulted in $\alpha(susp) = 0.24\ Gy^{-1}$, $\beta(susp) = 0.0022\ Gy^{-2}$, $\alpha(pellet) = 0.12\ Gy^{-1}$, and $\beta(pellet) = 0.0070\ Gy^{-2}$. Fig. 7B shows that the same is true for induction of mutations at the HPGRT locus. Least squares fits to the number of mutants per cell plated F yield: $F(susp) = 3.9 \times 10^{-5}$ per Gy and $F(pellet) = 2.5 \times 10^{-5}$ per Gy. For this latter arm of the experiment, the Banbury Protocol was followed (*81*). The oxygen enhancement ratio (OER) for survival as about 1.4, and for mutation was approximately 1.6.

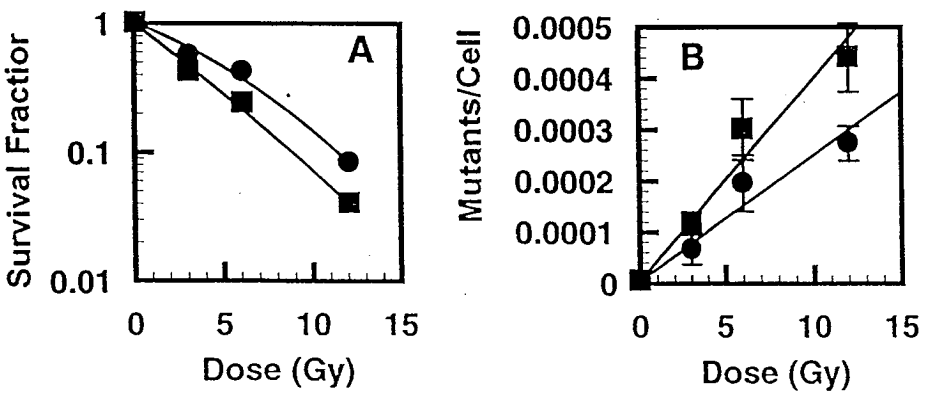


Figure 7. Response of V79 cells following acute irradiation with ^{137}Cs gamma rays at 10.5°C when clusters are maintained at 10.5°C for 72 h and then irradiated intact (■) or after dissociating (□). Two endpoints are examined: A) cell survival, and B) mutations at the HGPRT locus.

This experiment demonstrates that, after the 72 h incubation, hypoxia is present in the clusters. However, it appears to be uniform throughout the pellet since differentially hypoxic populations would result in a two- or more component exponential response to uniform irradiation. This is an important point because ferential hypoxia would make data interpretation difficult. The OER is substantially less than 2.5 to 3.0, the ...aximum range expected for anoxia (Ref. (*82*), pg. 135) so the clusters are not completely hypoxic. In fact,

agents such as lindane. Survival studies will be carried out with all three cell lines, while mutation studies will be selectively carried out with the wild-type WBs which are HGPRT$^+$.

D.3 Experimental Methods and Design

D.3a. *Survival of Cells in Multicellular Clusters.* As indicated in Specific Aims 1 and 2, the cell survival fraction of multicellular clusters will be ascertained for each radiochemical under conditions where either 1%, 10%, 50% or 100% of the cells are labeled with the radiochemical. The procedures for labeling the cells and assembling the multicellular clusters is described in detail in Section C.2c. Briefly, cells in suspension will be labeled in several different tubes containing different concentrations of the radiochemical to achieve various activities per cell (e.g. mBq/cell). After washing the cells free of extracellular activity, the activity per cell will be determined and the remaining labeled cells will be mixed with unlabeled cells to obtain the desired % labeling and $4x10^6$ cells in 400 µl of culture medium. The cell suspension will be transferred to a sterile 400 µl microcentrifuge tube, capped, and centrifuged gently at 1000 rpm for 5 min to form a close-packed multicellular cluster. The tubes will then be transferred to a 10.5°C environment for three days (72 h) to accumulate radioactive decays. This temperature was selected based on our earlier studies that showed the cells maintain their plating efficiency and do not divide (*71*). This is one additional element of control over the radiobiology of the cluster in that the distribution of activity in that the cluster remains fixed because the cells do not divide. After three days, the cells will be gently removed from the tubes, vortexed, resuspended in 2 ml of culture medium, and gently passed through a 21 g needle several times to break up cell clumps. Aliquots of the cell suspension will be taken to determine the cluster activity and the average activity per cell (e.g. mBq/cell). The cluster activity will simply be the total activity in the tube of suspended cells. The activity per cell will be determined using well established procedures (*1, 72*). Finally, the cells will be washed three times with wash medium, serially diluted, seeded into culture dishes, and placed in an incubator at 37°C, 5% CO_2, 95% air. After one week, the colonies will be washed with 0.9% saline, fixed with methanol, stained with crystal violet, and scored (> 50 cells constitutes a colony). After ensuring the absence of chemical toxicity which is not expected for these high specific activity radiochemicals, the survival fraction compared to untreated controls will initially be plotted as a function of the total activity in the cluster and the cellular uptake in the labeled cells (see Section D.4). This will be repeated for each radiochemicals in Specific Aims 1 and 2. These studies will be carried out for the V79 cells and for the WB^r and aB1 cells (see Section D.3e.2 for rationale) as indicated in Table 1 in the Timeline. These studies will provide information on the lethality of nonuniform distributions of radioactivity which is an important topic in therapeutic nuclear medicine both in terms of eliminating tumor cells as well as dose limiting organ toxicity.

D.3b. *Mutation of Cells in Multicellular Clusters.* Mutagenesis will be followed according to the Banbury Protocol (*81*). After the 72 h incubation at 10.5°C, 10^6 cells will be plated from each experimental condition examined in Specific Aims 1 and 2 and allowed to undergo 10 cell divisions in culture medium to allow for mutant expression. The resulting cells will be challenged with 6-thioguanine (Sigma Chemical Co.) to evaluate mutations at the HGPRT locus. This will be achieved by plating $2x10^5$ cells into five 100 mm culture dishes in culture medium containing reduced fetal calf serum (5%) and 10 µM 6-thioguanine. The resulting mutant colonies will be stained and scored as per methods described above. Plating efficiency will be determined for each data point by plating 200 cells into 60 mm culture dishes containing the same culture medium without 6-thioguanine. Controls will consist of clusters assembled with unlabeled cells or 100% labeled cells which have also been incubated at 10.5°C. The resulting data will be used to calculate the number of mutants per cell plated according to the Banbury Protocol. These studies will be carried out with the V79 cells and the wild type WBs cells. No mutagenesis studies will be carried out with the WB^r and aB1 populations since they are HGPRT$^-$. If the bystander effect involves nuclear interactions, then there should be more mutants in the mixed population than one would predict based on the mutation frequencies observed in the 0% and 100% cases. If, on the other hand, the bystander effect does not involve nuclear interactions, the mutation frequency should be close to the predicted value and one would have to conclude that the lethal bystander effect is the result of cell membrane or cytoplasmic interactions. Perhaps more importantly, these data will provide information on the risk of exposure to nonuniform distributions of radioactivity. This is of considerable importance to radiation protection.

Inquiry Report from UMDNJ, with selected attachments:

a. Transmittal letter from Dr. Putterman to DIO, September 7, 2001
b. Report Attachment B, official's decision letter, July 2, 2001
c. Report Appendix C, Summaries of Meetings of April 11, May 9, June 7, 2001
d. Report attachment 1a (Attachment 22), memo and data from Dr. Hill
e. Report attachment 1b, Introduction and records from Dr. Hill
f. Report attachment I, Summary of Meeting of April 17, 2001, with attachments from Dr. Hill
g. Report attachment J, Summary of Meeting of April 27, 2001 and photographs from Dr. Hill's original allegations to UMDNJ & ORI
h. Report attachments 20 and 21

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CONFIDENTIAL

June 22, 2001

TO: Robert A. Saporito, D.D.S.
Senior Vice President for Academic Affairs

FROM: Elizabeth Raveché, PhD.
Professor, Department of Pathology & Laboratory Medicine, NJMS
Chair, Newark Campus Committee on Research Integrity

RE: **REPORT OF INITIAL INQUIRY BY NEWARK CAMPUS COMMITTEE ON RESEARCH INTEGRITY**

Enclosed is the report of an initial inquiry conducted by the Newark Campus Committee on Research Integrity in response to an allegation of scientific misconduct. This report is sent to you for your consideration of this matter and decision pursuant to the University Policy on Misconduct in Science (#00-01-20-60:00).

Enclosure

CONFIDENTIAL

June 21, 2001

REPORT OF INITIAL INQUIRY INTO ALLEGATIONS OF POTENTIAL MISCONDUCT IN SCIENCE AGAINST ANUPAM BISHAYEE, PH.D.

In accordance with the University Policy on Misconduct in Science (#00-01-20-60:00) (Appendix A), the Newark Campus Committee on Research Integrity is constituted to receive reports or allegations of misconduct in science and conduct initial inquiries for the Newark Campus.

Current members of the Committee were nominated by their Deans and appointed by the Senior Vice President for Academic Affairs. Committee membership is as follows: Anthony V. Boccabella, Ph.D., J.D., Professor, Department of Anatomy, Cell Biology & Injury Sciences, UMDNJ-New Jersey Medical School (representing UMDNJ-Graduate School of Biomedical Sciences); Neil Cherniack, M.D., Professor, Departments of Medicine and Pharmacology & Physiology, UMDNJ-New Jersey Medical School; Daniel Fine, D.D.S., Professor, Department of Oral Pathology, Biology & Diagnostic Sciences, UMDNJ-New Jersey Dental School; Anthony Forrester, Ph.D., R.N., Professor, UMDNJ-School of Nursing; Teresa Marsico, M.Ed., C.N.M., UMDNJ-School of Health Related Professions; and Elizabeth Raveché, Ph.D., Professor, Department of Pathology & Laboratory Medicine, UMDNJ-New Jersey Medical School (Chair of the Committee). Dr. Boccabella did not participate in the proceedings because he was absent during the first meeting and therefore was excused from the remaining meetings.

In the following report, asterisks (*) denote that pertinent documents are to be found in the attachments to the minutes of the Committee's meetings which are in Appendix C of this report.

CHRONOLOGY OF ACTIVITIES

On April 9, 2001, Dr. Stephen Baker, Chair of Radiology at UMDNJ-New Jersey Medical School, informed Dr. Elizabeth Raveché, Chair of the Newark Campus Committee on Research Integrity, that Dr. Helene Z. Hill, Professor in the Department of Radiology, suspected a Research Associate, Anupam Bishayee, Ph.D. of possible research misconduct in research conducted under NIH Grant RO1#CA83838. Dr. Roger Howell,

Associate Professor in the Department of Radiology, is P.I. on this grant. Dr. Raveché indicated to Dr. Baker that the complainant, Dr. Hill, would need to contact her directly in order to make a formal allegation of scientific misconduct.

On the following day, April 10, 2001, Dr. Raveché met with Dr. Hill who was accompanied by Dr. Howell. In that meeting, Dr. Hill alleged that Dr. Bishayee had fabricated and/or falsified and/or plagiarized data during two experiments. The first experiment took place in September/October 1999 and involved survivability and mutagenicity following irradiation of mammalian V79 cells with the mutant gene HPRT. The second experiment took place during March 26-30, 2001 and was concerned with the "bystander" effect of radioactive mammalian cells. These experiments and details of Dr. Hill's allegations concerning them are described in the following sections of the report, as well as in the attachments to the Committee meeting minutes (Appendix C).

Following this meeting with Dr. Hill on April 10, 2001, Dr. Raveché sequestered the original data in question on the same day. With the assistance of Dr. Howell, the pertinent materials were identified and removed from his laboratory to Dr. Raveché's office, including 32 binders, 4 notebooks, 46 diskettes, 7 zip disks and 38 petri dishes, the latter from Dr. Bishayee's March 26-30, 2001 experiment. In addition, Dr. Hill gave Dr. Raveché a binder containing her written allegations which consisted of narratives, diaries, photographs, copies of Dr. Bishayee's original data from his lab book, Dr. Hill's original data from similar experiments, and the experimental protocol(*).

The Newark Campus Committee on Research Integrity was convened the next day, April 11, 2001, and performed a preliminary assessment of the allegations. The Committee considered Dr. Hill's oral statements to Dr. Raveché of April 10, 2001 as related by Dr. Raveché, as well as Dr. Hill's written allegations, copies of which were distributed to the Committee(*). The Committee voted unanimously that (1) the allegations met the definition of misconduct in science under PHS regulations and University policy; and (2) there was adequate information for an initial inquiry to proceed. The Committee immediately commenced the initial inquiry, the official start date of which was therefore April 11, 2001.

The Committee first discussed whether any of its members had a conflict of interest or bias as described in the University policy, Section V.D.3. Each member stated that he or she did not have such conflict of interest or bias and therefore would remain on the Committee for the initial inquiry. Dr. Raveché was requested to prepare formal written notifications of

the commencement of an initial inquiry to the respondent, Dr. Bishayee, the complainant, Dr. Hill, Dr. Russell Joffe, Dean of UMDNJ-New Jersey Medical School, and Dr. Karen Putterman, Vice President for Academic Affairs, UMDNJ, pursuant to University policy (Appendix B). The Committee then reviewed the six circumstances under which the ORI must be immediately notified of an allegation of misconduct in science, as set forth in the University policy Section V.H. The Committee decided that none of these conditions pertained to the current case and therefore ORI did not need to be notified at this time.

The Committee decided which individuals it would interview at its next meetings and which additional materials it would review. The individuals to be interviewed were Dr. Hill, Dr. Bishayee, Dr. Howell and Dr. Marek Lenarczyk, a postdoctoral fellow working for Dr. Howell who, according to Dr. Hill, helped her observe and investigate Dr. Bishayee's March 26-30, 2001 experiment by taking photographs, culturing Dr. Bishayee's experimental materials for contamination, and testing these materials for radioactivity. The additional materials that were gathered and reviewed by the Committee included the grant in question, all publications on which the grant was based, all publications appearing subsequent to receipt of the grant which reported on data developed under the grant, all abstracts pending presentation, and the CVs of Drs. Bishayee, Hill and Howell.

The Committee met again on April 17, 2001 to interview Dr. Hill, the complainant. On April 27, 2001 the Committee interviewed Dr. Howell, Dr. Bishayee, and Dr. Lenarczyk. The Committee met to discuss the evidence and testimony on May 9, 2001. The Committee met for the last time on June 7, 2001 to consider additional comments submitted by Dr. Hill to Dr. Raveché on May 22, 2001 during a private meeting with her, and to interview Dr. Bishayee a second time. The Committee finalized its conclusions and recommendations at its June 7, 2001 meeting.

The minutes of all Committee meetings are in Appendix C.

DESCRIPTION OF SEPTEMBER/OCTOBER 1999 EXPERIMENT AND ALLEGATION

This experiment used V79 HPRT mutant cells and investigated their survivability and mutagenicity following irradiation using the "Banbury protocol" as published in Mammalian Cell Mutagenesis, Banbury Report No. 28, M.M. Moore et al., editors, 1987. There are two arms to these experiments, a survival arm followed by a mutagenesis arm. During Dr. Hill's interview with the Committee on April 17, 2001, she reported that on September 6, 1999,

Dr. Bishayee began one such experiment jointly with Dr. Hill, with Dr. Bishayee performing the survival part and Dr. Hill the mutagenesis part. Dr. Hill went on to say that on September 20, 1999, Dr. Bishayee initiated another one of these experiments, this time doing both parts himself. She described her concerns about the mutagenicity part of Dr. Bishayee's September 20, 1999 experiment. Dr. Hill explained that on October 11, 1999, following ten days of incubation, the plated cells were ready to be fixed and stained and the colonies counted. Dr. Hill said Dr. Bishayee told her he was going to stain the plates that day (October 11). The next day, October 12, 1999, Dr. Hill said she became suspicious when she found a set of dishes of the number and type that would be used under this protocol still in the incubator. She said she examined the plates under a microscope, and found no colonies or even dead cells which she said would be expected in this type of experiment. Dr. Hill reported that she had questioned Dr. Bishayee on October 13, 1999 about these dishes she found in the incubator, and he had told her they were for a different experiment. However according to Dr. Hill, the P.I., Dr. Howell, later told Dr. Hill that there was no other experiment going on in the lab at that time that used this kind of dish. Dr. Hill also said that on October 14, 1999, the day after she questioned Dr. Bishayee about the dishes and what experiment they were for, the dishes disappeared from the lab and she could not find them in the trash. Dr. Hill concluded from these occurrences that Dr. Bishayee had fabricated the mutation data from this experiment, or that he may have plagiarized the experimental results from the Banbury publication that had also disappeared from the laboratory at the same time.

Following Dr. Hill's interview with the Committee on April 17, 2001, a copy of the Banbury publication was obtained from the library and shown to Dr. Hill on April 26, 2001 by Dr. Sheila Eder, Director of Institutional Research in the UMDNJ Office of Academic Affairs. Dr. Hill reviewed it in Dr. Eder's presence and stated she could not find any data that Dr. Bishayee had plagiarized(*).

Dr. Hill told the Committee she reported her suspicions to Dr. Howell shortly after her observations about Dr. Bishayee's September/October 1999 V79 mutant experiment. She said that Dr. Howell did not believe her. She did not take the issue further because, she stated to the Committee, she was not "absolutely certain" she was correct since she was unfamiliar with and had difficulty using the particular microscope with which she examined the dishes in question. In her April 17, 2001 interview with the Committee, Dr. Hill also said that Dr. Bishayee might have been merely sloppy rather than dishonest.

On May 22, 2001, Dr. Hill met with Dr. Raveché separately to provide the Committee with additional comments about this experiment(*). At that time, she told Dr. Raveché she went back and reviewed Dr. Bishayee's survival data, including the Coulter cell counts of September 24 and 27, and October 1 and 4, 1999, and graphed his survival and mutagenicity results. Dr. Hill told Dr. Raveché that she believed his Coulter counts after irradiation do not show the expected difference between the controls and the irradiated cells, i.e., the irradiated cells should be expected to have lower counts than the controls due to cell death or damage from the irradiation making it impossible for the cells to divide normally. Dr. Hill showed Dr. Raveché her own data from the same protocol she had carried out on September 6, 1999 which she said do show this difference(*). Dr. Hill concluded that, with these Coulter readings three days after irradiation, Dr. Bishayee could not have gotten the experimental results he did, which appear to be valid and as predicted for this experiment.

At its meeting of June 7, 2001, the Committee reviewed both Dr. Hill's testimony of April 17, 2001 concerning this experiment and her additional comments discussed with Dr. Raveché on May 22, 2001. The Committee reviewed the steps in the protocol that was followed by Drs. Hill and Bishayee in September/October 1999 and the specific techniques involved. They noted that high variability in counting cells using Coulter methodology is the norm, and that Coulter counts can be thrown off by technical flaws such as failure to adequately disperse the cells, the presence of bubbles, etc. The Committee also noted the fact that the Coulter counts are not integral to the experiment in question, but are incidental data not analyzed or used in the results; they are used only as a guide to determine how to dilute the cells to get the correct number of cells for the next step and to determine when the cells had undergone a total of ten divisions. The Committee did agree, however, that the pattern of Coulter counts in Dr. Bishayee's experiment showed inconsistent effects of irradiation compared to the non-irradiated controls.

Therefore the Committee interviewed Dr. Bishayee a second time on June 7, 2001 concerning his September/October 1999 experiment. Dr. Bishayee explained that plating for survival is done on day zero of exposure (irradiation) and the plates are read seven days later. In his running of the experiment, Dr. Bishayee stated that September 24, 1999 was day zero (day of irradiation). Dr. Bishayee confirmed this by pointing to his records in his notebook(*). Therefore the Coulter counts on September 24, 1999 would not be expected to show any significant difference between controls and irradiated tubes. Dr. Bishayee reviewed with the Committee the Coulter counts for September 27, 1999, the

actual day three, at which time such differences might be present. He and the Committee noted that except for tubes five and ten whose counts appear too high for the highest radiation-dose tubes, the expected difference in counts was in fact observed (tubes three and four had lower counts than tubes one and two, and tubes eight and nine lower than tubes six and seven). The Committee agreed with Dr. Bishayee that the counts in tubes five and ten, although not fitting the expected pattern, were within experimental error. In addition, Dr. Bishayee explained to the Committee why even on day three one might not necessarily see survival effects of irradiation (because, for example, cell death or damage might not occur right away but be delayed and appear later in an exponential fashion). Survival effects are known to occur for sure by day seven which is why the plates prepared on day zero are read seven days later for survival.

The Committee was satisfied with Dr. Bishayee's explanation of his running of this protocol and the data he had recorded in September/October 1999.

DESCRIPTION OF MARCH 26-30, 2001 EXPERIMENT AND ALLEGATION

This was one of a series of experiments on the bystander effect of radioactive thymidine incorporation into mammalian cells performed under Dr. Howell's NIH grant RO1#CA83838. At the time of these experiments, Dr. Lenarczyk had joined Dr. Howell's lab as of April 2000.

Dr. Hill stated to the Committee at her interview on April 17, 2001 that Dr. Lenarczyk told her he had also become suspicious of Dr. Bishayee's work, and she had shared with him her concerns about the September/October 1999 experiment. This led to their teaming up to observe and investigate the experiment conducted by Dr. Bishayee from March 26, 2001 through March 30, 2001. Their investigations of Dr. Bishayee's experiment were without his knowledge and were also kept secret from Dr. Howell. Drs. Hill and Lenarczyk secretly tested Dr. Bishayee's incubating test tubes for bacterial or yeast contamination, and attempted to monitor the number and location of the test tubes during the experiment, documenting and photographing their findings. Following is a description of the activities of Drs. Hill and Lenarczyk and their conclusions.

Dr. Hill told the Committee that Dr. Lenarczyk, working near Dr. Bishayee at the beginning of his March 26-30, 2001 experiment, had told her he thought that Dr. Bishayee's two cell culture T175 flasks were contaminated based on visual inspection of them (cloudiness).

Dr. Hill and Dr. Lenarczyk subsequently recovered Dr. Bishayee's flasks from the trash and photographed them to show contamination. Dr. Hill submitted as evidence to the Committee photographs she said were Dr. Bishayee's flasks(*). According to Dr. Hill, Dr. Lenarczyk also told her that despite this contamination, he saw Dr. Bishayee proceed with his experiment using cells from one of the T175 flasks which Dr. Lenarczyk had observed to be contaminated. Dr. Hill told the Committee that this behavior by Dr. Bishayee would call into question the validity of any of his experimental results.

The Committee asked Dr. Hill how she could know that the cells from these flasks were really contaminated and, if so, were actually used by Dr. Bishayee for his experiment. Dr. Hill responded that that was her hypothesis. Dr. Raveché asked Dr. Hill for the evidence that Dr. Bishayee's experiment was contaminated since gross contamination could not be observed in helena tubes. In particular, Dr. Raveché asked when she had observed Dr. Bishayee's two allegedly contaminated T175 flasks in the 37 degree incubator. Dr. Hill responded that the two T175 flasks were in the 37 degree incubator on Wednesday, March 28, 2001 rather than the one flask that would have been expected to remain following initiation of the experiment. Dr. Hill indicated that to her this meant that Dr. Bishayee split and reseeded the material from the single T175 flask to make the two T175 flasks observed on Wednesday, March 28. It remained unclear to the Committee, even after several specific questions about this to Dr. Hill, exactly when she had observed Dr. Bishayee's single T175 flask to be contaminated. Dr. Hill also stated that Dr. Bishayee asked Dr. Lenarczyk for cells on Thursday night, March 29, 2001. Dr. Hill believes that Dr. Bishayee substituted the cells he received from Dr. Lenarczyk on March 29 in his own experiment.

Dr. Hill continued her testimony to the Committee by stating that she and Dr. Lenarczyk began to secretly monitor and photograph Dr. Bishayee's experiment after they suspected he had proceeded using contaminated material. Their photographs of helena tubes in the 10.5 degree incubator, which they believed to be those of Dr. Bishayee's experiment, were also submitted to the Committee(*).

During these secret observations, Dr. Hill said she noticed that six of the original seven tubes were not removed from the 10.5 degree incubator on the day she believed Dr. Bishayee had supposedly harvested his cells. Dr. Hill said she found the seventh tube, which would have contained radioactive substances, empty in the non-radioactive trash in the lab. Drs. Hill and Lenarczyk tested the tubes they found remaining in the 10.5 degree

incubator for radioactivity, and concluded that Dr. Bishayee had used the contents of the discarded seventh tube to add radioactive aliquots to the other six tubes that were then measured in the FACS laboratory. Dr. Hill explained to the Committee how Dr. Bishayee might have achieved his experimental results from a single aliquot from tube #7, the missing tube. However Drs. Hill and Lenarczyk did not test the discarded seventh tube for radioactivity.

Dr. Hill stated that she and Dr. Lenarczyk, acting on the hypothesis that Dr. Bishayee had used contaminated cells for the March 26, 2001 experiment, secretly sampled the material from Dr. Bishayee's helena tubes later on during his experiment, cultured the samples on sterile media, and grew bacteria. In addition to sampling Dr. Bishayee's tubes for contamination, Drs. Hill and Lenarczyk also sampled for radioactivity cells from all of Dr. Bishayee's tubes remaining in the 10.5 degree incubator. All the tubes subsequently disappeared from the lab after Dr. Bishayee was told Drs. Hill and Lenarczyk were watching him, and Dr. Hill could not find them anywhere, even in the trash.

The photographs presented to the Committee showed helena tubes in a radioactive-labeled rack in an incubator with numbered labels but no investigator name. Some of the photographs were taken with a digital camera indicating a date(*).

On Friday, March 30, 2001, Dr. Hill believed Dr. Bishayee sorted samples that he got from Dr. Lenarczyk and not from the material original to the experiment, which was instead left in the 10.5 degree incubator.

From these secret investigations, Dr. Hill told the Committee she concluded that Dr. Bishayee fabricated and/or falsified the data from this experiment because he could not have obtained any valid results otherwise under the circumstances in which the experiment was observed by Drs. Hill and Lenarczyk to have been conducted (presumably contaminated original culture flasks, helena tubes left in the incubator after they were supposed to have been harvested, the seventh tube missing from the incubator and found in the trash, the complete disappearance of all tubes after Dr. Bishayee was alerted, Dr. Bishayee asking Dr. Lenarczyk for fresh cultures on March 29).

The Committee asked Dr. Hill how Dr. Bishayee could have gotten any results from his experiment if Dr. Hill's hypothesis about Dr. Bishayee was correct. Dr. Hill believes that Dr. Bishayee could have figured out how many cells to plate of those he received from Dr.

Lenarczyk on March 29, 2001 in order to get 1 percent survival, the expected result. The Committee noted that any such effort on Dr. Bishayee's part to fabricate the experimental results in this experiment would have been greater than simply repeating the experiment with fresh, uncontaminated cells.

The Committee interviewed Dr. Lenarczyk on April 27, 2001 about the March 26-30, 2001 experiment. Dr. Lenarczyk stated that the experiments measuring cell survival rates cannot be validly completed if carried out with contaminated cell material. In the case of the experiment started by Dr. Bishayee on Monday, March 26, 2001, Dr. Lenarczyk believes that Dr. Bishayee had used contaminated cells.

Dr. Lenarczyk explained to the Committee that by Friday, March 30, 2001, he was sure that the experiment was contaminated. Since he had no reason to check on Dr. Bishayee's cells before that, he couldn't say for certain that the experiment was begun with contaminated material. But on Friday, March 30, 2001, Dr. Lenarczyk observed that Dr. Bishayee's cells were still in helena tubes in the 10.5 degree incubator when, according to the protocol, they should have been taken out by that time. In addition, Dr. Lenarczyk said that Dr. Bishayee had asked Dr. Lenarczyk for new cells on Thursday, March 29, 2001, and that this aroused his suspicions because of the long-standing problem of contamination in the lab which he ascribed to Dr. Bishayee's poor technique. He wondered why Dr. Bishayee was asking for cells on Thursday, when the cells for the experiment should be removed from the tubes on Friday. When the Committee asked whether Dr. Bishayee might not have been following a different protocol, Dr. Lenarczyk answered that he thought the fact that the cells were in helena tubes indicated that the experiment was looking for bystander effect and was using that protocol.

Dr. Lenarczyk went on to say that when he went to the 10.5 degree incubator on Friday, March 30, 2001, to remove his own tubes, he observed Dr. Bishayee's tubes still there with one tube missing. He had seen earlier in the week that Dr. Bishayee had started with seven tubes, the expected number, in the 10.5 degree incubator. Dr. Lenarczyk said he had seen Dr. Bishayee sitting in the hood on Friday morning, March 30, 2001 at 10 or 11 a.m. While he didn't check what Dr. Bishayee was doing, he assumed that he was processing cells from that week's experiment.

Dr. Lenarczyk began to think that "something was going wrong" and took samples of the tubes remaining in the 10.5 degree incubator. Dr. Lenarczyk stated that he sampled the tubes on Friday, March 30, 2001 because he believed Dr. Bishayee had already concluded the experiment when he saw him working in the hood that morning.

The Committee asked why Dr. Lenarczyk didn't ask Dr. Bishayee about what was going on. Dr. Lenarczyk replied that he chose not to speak to Dr. Bishayee, but to talk to Dr. Hill since he was living in her house.

The Committee asked Dr. Lenarczyk when it was that he started taking pictures. Dr. Lenarczyk responded that he didn't remember. Dr. Lenarczyk said that the camera was new and he had to learn how to set it to record dates. Therefore not all the photographs submitted to the Committee were dated.

The Committee was concerned with inconsistencies in Dr. Lenarczyk's remarks concerning the dates the photographs were taken and the manipulation during the experiment of the tubes purported to be those of Dr. Bishayee by Drs. Hill and Lenarczyk.

The Committee was also concerned that actions by Dr. Hill and Dr. Lenarczyk may have interfered with Dr. Bishayee's experiment. If cultures from the sampled 6 tubes were allowed to grow for a day to prove contamination, then the samples must have been drawn by Drs. Hill and Lenarczyk on Thursday, March 29, 2001. If so, this seems like it would have interfered with Dr. Bishayee's experiment. Dr. Lenarczyk said that he might have taken samples that Thursday, but was not sure.

The Committee wondered whether there could have been scientific misconduct if Dr. Bishayee had used contaminated cells but then admitted to a contamination problem by reporting in his lab book that half of the petri dishes were contaminated and half were not. (The petri dishes were in the Committee's possession and demonstrate this pattern of contamination reported by Dr. Bishayee in his lab book.) The Committee asked Dr. Lenarczyk if he was aware of Dr. Bishayee's recorded results, and he responded that he never saw the results. The Committee considered whether there could be alternative explanations for the presence of the tubes in the 10.5 degree incubator on Friday , March 30, 2001, including that these tubes might have been from a different experiment.

The Committee interviewed Dr. Bishayee on April 27, 2001 about his March 26-30, 2001 experiment. Dr. Bishayee told the Committee that this experiment was only partly successful in that half the plates were lost to contamination. However he denied that he knew that his original cultures in the T175 flasks were contaminated at the time the experiment was initiated. He described the course of the experiment, and said he had removed his tubes from the 10.5 degree incubator on March 30, 2001. Dr. Bishayee also informed the Committee that he had been conducting tests at the same time of a new cell line to observe its growth and cluster size characteristics prior to beginning bystander experiments with it. He also placed these tubes in the 10.5 degree incubator sometime during March 26 to March 30, 2001, but did not have consistent recollections of exactly when or how many tubes there were, or when he discarded them, and he did not make notes in his lab book of his observations of the new cell line. Dr. Bishayee explained that he did not record his observations of the new cell line because he was not collecting data on it but rather just physically observing the cells for their growth characteristics.

The Committee showed Dr. Bishayee during his first interview the photographs Dr. Hill and Dr. Lenarczyk had secretly taken of helena tubes in the 10.5 degree incubator(*). Dr. Bishayee said he thought the tubes in the photographs were his because he thought he recognized the numbering on the tubes' labels. However he could not explain why there were only six tubes in the rack, when the photos could have been taken, or why the racks changed in location within the incubator from one photo to the next. Dr. Bishayee denied ever removing only one tube from the rack during this experiment. Dr. Bishayee also did not remember why he had asked Dr. Lenarczyk for new cells on March 29, 2001, but denied using these new cells for the sorting on March 30, 2001. He pointed out to the Committee that investigators often ask colleagues within their labs for cells, and there was nothing unusual in his request to Dr. Lenarczyk.

Dr. Bishayee told the Committee that he felt he was the victim of a conspiracy against him, that these allegations could be the result of jealousy, and that he had had "problems" with Dr. Hill over the past two years because, he believed, Dr. Howell did not want to incorporate Dr. Hill's work into his grant. He also described fights with Dr. Lenarczyk and a conflict of interest on Dr. Lenarczyk's part stemming from his living in Dr. Hill's house which created an obligation to her.

The Committee interviewed Dr. Howell about these experiments on the same day, April 27, 2001. Dr. Howell said that there were certain details of the experiment that neither Dr. Hill nor Dr. Lenarczyk would have known. According to Dr. Howell, Dr. Hill and Dr. Lenarczyk believed that both populations of cells (radioactive and bystander) at the point of plating were contaminated because they thought all Dr. Bishayee's original cultures were contaminated at the start of his experiment. However, this would be hard to know from looking at the contents of the helena tubes because these were incubated in the cold (at 10.5 degrees), under which conditions bacterial and cell growth is minimal. Contamination would not be known for sure until after the seven days of growth in petri dishes at 37 degrees. In fact, while the plated petri dishes of dyed (irradiated) cells were found to be contaminated after seven days and could not be counted, the undyed (bystander) plated cells grew and were in fact counted in Dr. Howell's presence.

The Committee asked Dr. Howell how he could be sure of the origin of the cells plated in the petri dishes, and whether something improper could have been done to get the end results. Dr. Howell responded that this was possible, but if someone were going to improperly manipulate experimental material, he or she would not falsify the "wrong" population of cells. He went on to explain that each experiment focuses on either the radioactive dyed cells or the bystander undyed cells. The amount of radioactivity used varies according to the focus of the experiment. The experiment in question focused on the radioactive cells which was different from previous experiments. Drs. Hill and Lenarczyk were unaware of this change in focus. Dr. Howell said it would make no sense for Dr. Bishayee to substitute new uncontaminated cells for the non-radioactive cells because they were not the focus of the experiment.

Dr. Raveché told Dr. Howell that Dr. Hill had said that Dr. Bishayee's experiment was contaminated and that Dr. Bishayee knew that already on Friday, March 30, 2001. Dr. Howell responded that Dr. Bishayee would have no way of knowing that just from observing the helena tubes; the only way would have been if he had plated the cells at the beginning of the experiment.

When Dr. Howell was asked for his comments about the sampling of the tubes by Dr. Lenarczyk during Dr. Bishayee's experiment, he responded that he didn't understand why Drs. Hill and Lenarczyk didn't confront Dr. Bishayee directly with their questions about his experiment.

Dr. Howell also had no explanation for the Committee as to why Dr. Bishayee would have allegedly left the tubes in the 10.5 degree incubator after they were supposed to have been removed for the conclusion of the experiment.

In an attempt to account for there being only 6 tubes in the 10.5 degree incubator, Dr. Howell stated that they could have been the new cell line tubes that Dr. Bishayee was testing at the same time as his bystander experiment. However the rack shown in the photographs had a radioactive label.

Dr. Howell stated that Dr. Bishayee had a good record of producing work, that Dr. Hill had not produced original research in years, and that Dr. Lenarczyk has been non-productive in his 9 months as a postdoctoral fellow. Dr. Howell noted that this experimental protocol is very difficult and there is pressure to publish. There are a number of steps that are prone to contamination. Dr. Howell told the Committee that Dr. Bishayee had "one complete, two failed and one half-contaminated" experiment under this protocol.

Dr. Raveché asked if Dr. Howell could explain the surprising fact that only half the experimental tubes were contaminated following plating. Dr. Howell stated that it could have had something to do with the dye. He knew that the dye was sterile but the phosphate buffer used with the dye could have been contaminated. After 30 minutes in the dye, the cells are washed, mixed with the unlabeled cells and then chilled. The bacteria would remain dormant and not infect the unlabeled cells.

The Committee asked Dr. Howell to comment on the same set of photographs reviewed by Dr. Bishayee(*), and to respond to the observations made by Drs. Hill and Lenarczyk about Dr. Bishayee's experiment. Dr. Howell had no explanation for the photographs nor for Drs. Hill's and Lenarczyk's stated observations of Dr. Bishayee's experiment.

Following its interviews with Drs. Hills, Lenarczyk, Bishayee and Howell concerning Dr. Bishayee's March 26-30, 2001 bystander effect experiment, the Committee found no apparent explanation to account for the photographs if they were taken as and when stated by Dr. Hill, and if Dr. Bishayee's testimony about his conduct of the experiment was truthful. No other evidence was available to either prove or disprove Dr. Bishayee's statements or confirm the validity of the photographs.

CONCLUSIONS AND RECOMMENDATIONS

On May 9, 2001 and again in June 7, 2001, the Committee reviewed the evidence and the interviews, and unanimously voted that there was insufficient credible and definitive evidence of misconduct in science to warrant further investigation. This conclusion was based upon the following considerations:

- With regard to Dr. Hill's allegation of falsification/fabrication/plagiarism by Dr. Bishayee in his September/October 1999 experiment under the "Banbury protocol," the Committee found insufficient evidence to substantiate this allegation from its examination of Dr. Bishayee's notebooks(*), from Dr. Hill's testimony about her observations of unlabeled plates she found in the incubator, and from her statements following her review of the published data in Banbury Report No. 28(*). The Committee was also satisfied with Dr. Bishayee's explanation of his September/October 1999 experiment with regard to the pattern of Coulter counts and their relevance to the successful running of the experiment.

- With regard to Dr. Hill's allegation of falsification/fabrication by Dr. Bishayee in his March, 2001 bystander experiment, the major physical evidence was the photographs taken by Drs. Hill and Lenarczyk(*). These photographs could not be dated definitively and could not be related definitively to the experiment that Dr. Bishayee said he performed from March 26-30, 2001. There was insufficient evidence to reconcile the purported date of the photographs and what Dr. Hill believed they demonstrate about Dr. Bishayee's experiment of March 2001 with the testimony of Dr. Bishayee that he conducted the experiment as recorded in his lab book and obtained the results as recorded therein(*). Therefore the Committee was unconvinced that the photographs credibly proved that the experiment Dr. Bishayee actually carried out was different from that recorded in his lab book.

- The evidence that Dr. Bishayee's March 26-30, 2001 experimental materials were contaminated from the inception of his experiment was insufficiently credible to support the complainant's contention that Dr. Bishayee could not have obtained the data he recorded from the experiment he actually carried out.

- The testimony of the complainant, Dr. Hill, conflicted with that of Dr. Lenarczyk as to dates, their observations of Dr. Bishayee's helena tubes, and what they did when with Dr. Bishayee's experimental materials in their attempt to collect evidence of misconduct in the March 26-30, 2001 experiment.

- Dr. Hill and Dr. Lenarczyk admitted to tampering with Dr. Bishayee's March 26-30, 2001 experiment, possibly before it was completed.

- Although the Committee discussed possible motivations for Dr. Bishayee's alleged actions, it could discern no reason for Dr. Bishayee's falsification, fabrication or plagiarism of the data for his experiments of September/October 1999 or of March 26-30, 2001.

After hearing all the testimony, the Committee was very concerned that serious problems regarding interpersonal relationships, communication and oversight of research existed in Dr. Howell's lab. Therefore, the Committee voted unanimously to recommend that the Senior Vice President for Academic Affairs ask Dr. Howell to take corrective actions to improve the conduct of research and the environment in his lab.

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REGISTERED MAIL, RETURN RECEIPT REQUESTED

April 12, 2001

Anupam Bishayee, Ph.D.
Research Associate III
Division of Radiation Research
Department of Radiology
UMDNJ-New Jersey Medical School
185 South Orange Ave., MSB F-451
Newark, New Jersey 07103

Dear Dr. Bishayee:

Information about possible fabrication and/or falsification of research data that may constitute misconduct in science as defined by the Federal government and University policy has been received by the Newark Campus Committee on Research Integrity. At the Committee's meeting on April 11, 2001, the Committee voted to open an Initial Inquiry to determine whether this information warrants further investigation. The information involved questions about whether you falsified and/or fabricated data for NIH grant RO1 #CA83838, Dr. Roger Howell, Principal Investigator. You are the respondent in this case. Under the University's policy, a copy of which is enclosed, you are hereby notified of this proceeding. You will be given the opportunity to be heard and will be expected to cooperate fully in this and any subsequent proceedings. Unreasonable refusal to supply relevant material or other uncooperative behavior shall constitute violation of the University policy. Pursuant to University policy, confidentiality will be maintained to the extent possible and permitted by law.

If you have any questions, please do not hesitate to call me at (973)972-5240.

Sincerely yours,

Elizabeth Raveché

Elizabeth Raveché, Ph.D.
Chair, Newark Campus Committee on Research Integrity
Professor, Pathology and Laboratory Medicine, UMDNJ-New Jersey Medical School

Enclosure: University Policy on Misconduct in Science

bc: Patterman, Klajnman

Inquiry Report from UMDNJ, with selected attachments:

a. Transmittal letter from Dr. Putterman to DIO, September 7, 2001