

7 Studies Funded By Research Integrity Program

Seven research grant applications of the 25 submitted last December in response to the first request for applications (RFA) published by the Research on Research Integrity Program were funded this summer.

The RFA soliciting the second round of grant applications is posted on the ORI home page under Featured Attraction. Submission deadline is November 19, 2001. The success rate in the first round was 28 percent, which is comparable to the success rate for all NIH grants, which ranges roughly from 25 to 35 percent.

The 2-year awards were supported by the National Institute for Neurological Disorders and Stroke (NINDS), the National Institute of Nursing Research (NINR), and ORI. Total funding for the first year was approximately \$1.03 million, which doubles the \$500,000 originally committed to the program.

“The Research on Research Integrity Program has had an auspicious beginning,” Chris Pascal, Director, ORI, said. He continued, “A great deal of credit for the initial success must go to NINDS for the administrative and financial support it has provided. We look forward to the participation of NINR and other agencies in this vital program.”

The awards demonstrate the interdisciplinary nature and broad spectrum of research on research integrity. Principal investigators are in psychology, clinical psychology, sociology, pharmacology, epidemiology, and higher education/administration. The studies will investigate conflicts of interest, data sharing, clinical trials, work-strain, career course, quality assurance and organizational influences.

See **Research Topics** on page 4.

Study Addresses Incidence Of Research Misconduct

ORI has contracted with the Gallup Organization to study and answer a persistent and crucial question about research misconduct: How often does it occur?

The study, *Incidence of Research Misconduct in Biomedical Research*, is scheduled for completion in 2003. This study will initiate a longitudinal database for measuring change in the incidence of research misconduct at 5-year intervals.

The study will address the frequency of misconduct by collecting data on the (1) detection, (2) reporting, (3) investigation, and (4) verification of alleged research misconduct. The design will try to avoid the methodological flaws of previous studies by: (1) distinguishing between research misconduct and questionable research practices; (2) surveying a large representative sample of principal investigators (PI); (3) limiting reporting to a standard time period; (4) minimizing the probability that the same incidents will be reported by more than one respondent; (5) covering numerous fields of science; (6) differentiating between alleged, reported, and verified research misconduct; and (7) generating a high response rate.

The data collection will include general characteristics of institutions, departments, the accused, and the PI. No specifically identifiable information will be collected. ☺

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Data Management Guidelines Issued by British Medical Research Council

Basic policies on gathering, storing, and retaining research data were issued by the Medical Research Council (MRC) in England for all scientists supported by the MRC as part of its guidelines for good research practice.

The complete guidelines for good research practice, published in December 2000, can be accessed through the ORI web site by selecting "International" in the Resources section and clicking on the MRC link.

The guidelines state that data should be stored in a way that permits a complete retrospective audit and monitored regularly to ensure their completeness and accuracy. Primary data should be retained for 10 years from the completion of the project, but research records related to clinical or public health studies should be retained for 20 years.

The basic policies that apply to notebooks and electronic records follow:

- All raw data should be recorded and retained in indexed laboratory notebooks with permanent binding and numbered pages or in an electronic notebook dedicated to that purpose.
- Machine print-outs, questionnaires, chart recordings, autoradiographs, etc., which cannot be attached to the main record should be retained in a separate ring-binder/folder that is cross-indexed with the main record.
- Records in notebooks should be entered as soon as possible after the data are collected. Recorded data should be identified by date of the record and date of collection if the two do not coincide. Subsequent modifications or additions to records should also be clearly identified and dated.
- Special attention should be paid to recording accurately the use of potentially hazardous substances (e.g., radioactive materials) in both laboratory notebooks and any central logbooks.

- In clinical studies, consent forms should be kept securely with the raw data, and normally for the same period of time.
- Supervisors should regularly (monthly or as appropriate) review and "sign-off" notebooks of researchers to signify that records are complete and accurate. Queries should be discussed immediately with the individual who recorded the data and any resultant changes to the records should be signed by both. Authentication of data collected and recorded electronically requires special attention.
- If the data are recorded electronically, the data should be regularly backed up on disc; a hard copy should be made of particularly important data; relevant software must be retained to ensure future access, and special attention should be given to guaranteeing the security of electronic data. ☺

German University Investigating Allegation Against Cancer Researchers

The University of Gottingen in Germany is investigating an allegation of research misconduct against a researcher at that institution and another at the University of Tübingen who, according to press reports, are attempting to produce a cancer "vaccine."

The clinical research involves treating kidney cancer patients with a vaccine composed of tumor cells fused with immune cells. Regression of secondary tumors was reported in an article last year.

The allegations assert that a photo in another paper submitted for publication purportedly showing the fused tumor cells had been downloaded from the Internet. In addition, the investigation is looking into charges of patient endangerment. Recruitment into the study has been suspended. ☺

RCR Instruction Listserv Provides Discussion Forum

A new listserv designed to promote discussion and networking among researchers, research administrators, and responsible conduct of research (RCR) instructors has been initiated.

The listserv is administered through the National Institutes of Health server and managed by ORI, and presently has over 110 members. It is hoped that members will use the listserv to (1) exchange ideas and strategies for developing RCR educational programs and materials, (2) share information about existing educational resources, and (3) discuss general issues concerning the responsible conduct of research.

To join the listserv, send an e-mail to the list manager at rclist@osophs.dhhs.gov requesting information on how to join. Instructions for joining will be sent in response. ☺

Research Conference Proceedings Available

Proceedings from the first Research Conference on Research Integrity held last November are expected to be available in October on the ORI web site under Breaking News on the home page and under Research in the Programs section.

Entitled *Investigating Research Integrity: Proceedings of the First ORI Research Conference on Research Integrity*, the publication contains 42 papers organized in 3 sections: Normative and Environmental Issues; Teaching; and Research Theory and Methods.

A limited number of printed, soft bound copies of the proceedings will be published. Conference attendees will be sent a copy. Others may request a copy from ORI while the supply lasts.

The second Research Conference on Research Integrity will be held in the Washington metropolitan area in November 2002. Further information will be posted on the ORI web site as it becomes available. ☺

Successful E-Submission of Annual Report; Problems Addressed

Converting the Annual Report on Possible Research Misconduct to an electronic format was successful, but some problems developed that are being addressed by the software designer and ORI.

“We expected some problems to occur with the Calendar Year (CY) 2000 report because it was the system shakedown,” John Butler, Assurance Program Manager, said. “It was a learning experience for everyone. Fortunately, we all are quick learners. Submission of the CY 2001 report should be almost effortless for most institutions.”

One of the more frequent problems encountered in filing the CY 2000 report concerned use of the identification number and password to access the system. The instructions for filing the report will be revised to address these and other problems.

Institutions using Macintosh® computers had difficulties accessing the system. The system software is being examined for compatibility with the Macintosh® operating system, and software revisions may be needed to accommodate these users.

The software package also will be revised to provide an institution with an automatic acknowledgment that its Annual Report was received by ORI. Many institutional officials called ORI to verify receipt of the report.

Although the electronic format reduces the effort involved in filing the Annual Report, the format does not seem to increase the response rate or the accuracy of the reports. The number of incomplete reports, however, did decline from 54 to 39.

The CY 2000 Annual Report produced a response rate of 77 percent, compared with 84 percent for CY 1999. Annual Reports for CY 2000 were not submitted by 861 institutions; their assurance was withdrawn making them ineligible to receive PHS research or research training support. ☺

Conflict of Interest Conference Attracts Major Stakeholders

Representatives from five countries, including the United States, will discuss conflicts of interest in research during the *International Conference on Conflict of Interest and Its Significance in Science and Medicine* in Warsaw, Poland, on April 5-6, 2002.

American speakers include J.B. Martin, Dean of the Medical Faculty, Harvard University; J. Cohen, President, Association of American Medical Colleges; N. Hasselmo, President, Association of American Universities; J.M. Drazen, Editor-in-Chief, New England Journal of Medicine; C.D. de Angelis, Editor-in-Chief, Journal of American Medical Association; M.F. Marshall, Chairperson, National Human Research Protections Advisory Committee, and L.J. Rhoades, Associate Director, ORI. See <http://surfer.iitd.pan.wroc.pl/events/conferenceApril2002.html>.

Research Topics

(from page 1)

Grant titles, principal investigators, and institutions for the awards follow:

- *Management Decisions in Financial Conflicts of Interest*. Lisa Bero, University of California-San Francisco.
- *Research Integrity in Pharmacological Clinical Trials*. William Gardner, University of Pittsburgh.
- *Quality Assurance and Data in Clinical Trials*. Yuan Min, Johns Hopkins University.
- *Work-Strain, Career Course and Research Integrity*. Brian Martinson, Health Partners Research Foundation, Minnesota.
- *Data Sharing and Data Withholding among Trainees in Science*. Eric Campbell, Massachusetts General Hospital.
- *Organizational Influences on Scientific Integrity*. Michael Mumford, University of Oklahoma.
- *Perceived Organizational Justice in Scientific Dishonesty*. Gerald Koocher, Children's Hospital, Boston.

For further information, contact Mary Scheetz, Ph.D., Program Officer, at 301-443-5300. E-mail: mscheetz@osophs.dhhs.gov.

ORI Emphasizing Education and Prevention of Research Misconduct

The year 2000 was a busy and productive year for ORI, involving several significant policy issues and changes in program emphasis, according to the *ORI Annual Report - 2000*, which is expected to be released in September.

New Departmental policies have ORI concentrating on assessing and referring allegations to institutions, conducting oversight reviews of institutional inquiries and investigations, and providing advice and rapid technical assistance. ORI opened 26 new cases and closed 27 cases in 2000, with 7 cases resulting in sustained findings of misconduct or PHS administrative actions, and 15 institutions using ORI's new rapid response technical assistance program.

A long-awaited Notice of Proposed Rulemaking to establish standards for protecting whistleblowers or others who cooperate with a research misconduct investigation was published in November 2000, drawing 43 public comments. Analysis of public comments and drafting of revisions is ongoing.

In preparation for release of the PHS Policy on Instruction in the Responsible Conduct of Research (RCR), ORI added a new RCR resource section to its web site, supported an on-line resource for RCR instruction hosted by the University of California-San Diego, and worked with NIH to create a grant program to encourage development of new RCR materials. Although implementation of the policy was delayed, ORI co-sponsored four national conferences, developed new instructional materials, and initiated an effort to create a community of RCR instructors.

ORI held a highly successful first research conference in 2000 and worked with NIH to launch a new research grant program on research integrity. ORI commissioned the Institute of Medicine to prepare a report on conceptual issues related to assessing integrity in research environments so that ORI can begin planning a longitudinal database for tracking efforts to foster research integrity by institutions and PHS. Copies of the report are available upon request or from ORI's web site <http://ori.hhs.gov>.

Statistical Forensics: Check Rightmost Digits for Uniform Distribution

Numbers are often recorded beyond the repeatability of the experimental procedure. When counts or measurements are recorded to higher precision than can be repeated in replications of an experiment, the rightmost digits of the recorded numbers have little biological meaning. Consider a count of radioactivity for a biological preparation, for example, 5179. In a recount of the sample, or in a replication of the assay, it is unlikely that the *rightmost* digits will be the same. Thus, with three repetitions, 5179, 5118 and 5134 could be expected.

The rightmost digits of these three numbers differ. Thus xx **79** differs from xx **18**, and, in turn, both differ from xx **34**.

In large samples of numbers, such rightmost digits often occur with the same frequency, like lottery digits where each of the digits 0, 1, 2, ..., 9 has the same expectation. Statistically speaking, rightmost digits are approximately *uniformly distributed* in many circumstances.

In one ORI case, the respondent's notebook contained fabricated counts as well as un-fabricated counts. For the fabricated counts the radioactive spots on the experimental sheets had not been excised and hence could not have been counted in the scintillation counter. The un-fabricated counts were supported by counter tapes.

Investigators from ORI's Division of Investigative Oversight (DIO) compared rightmost digits of fabricated and un-fabricated counts. The fabricated digits differed significantly from uniform. The un-fabricated digits did not so differ. (The respondent accepted voluntary exclusion from receiving Federal funds for 3 years.)

In another case, one column of a published table of numbers was not supported by notebook data. DIO investigators found that the rightmost digits of the unsupported column differed significantly from uniform. The rightmost digits of the supported columns did not

so differ. (The paper was retracted, and in a related Department of Justice settlement, the Government recovered over \$1 million from two universities.)

To succeed in fabricating data, the fabricator must make the *leftmost* digits exhibit the desired biological magnitudes. Rightmost digits, given little thought, may be subject to personal preferences of the moment, and hence not uniform. Even when instructed to "make up" numbers with uniform digits, many subjects appear unable to do so. (See "Data Fabrication: Can people generate Random Digits?" J.E. Mosimann, C.V. Wiseman and R.E. Edelman, *Accountability in Research*, 4, 31-55, 1995).

In cases of scientific misconduct, un-scientific details, like rightmost digits, are worthy of attention.☺

Conference Proposals Due February 1

ORI is seeking proposals from institutions, professional associations, and scientific societies that wish to collaborate with ORI in developing a conference or workshop on promoting research integrity or handling scientific misconduct allegations.

ORI intends to hold four to six regional conferences or workshops each year in strategic locations around the country. The amount of funding available generally ranges from \$5,000 to \$20,000.

February 1, 2002, is the next target date for the receipt of applications. Proposal instructions and an application form are available on ORI's web site, <http://ori.hhs.gov>, by calling 301-443-5300, or sending an e-mail to askori@osophs.dhhs.gov

CASE SUMMARIES

David R. Jacoby, M.D., Ph.D., Harvard Medical School (HMS) and Massachusetts General Hospital (MGH): Based on the HMS and MGH investigation report and additional analysis by ORI in its oversight review, the U.S. Public Health Service (PHS) found that Dr. Jacoby, former Instructor, Department of Neurology, MGH, engaged in 15 acts of scientific misconduct by plagiarizing and falsifying research data taken from another scientist's experiment in a published journal article for use in a program project grant application submitted to, and funded by, the National Institutes of Health (NIH).

Specifically, Dr. Jacoby plagiarized an image of a Southern blot analysis of genomic DNA that appeared as Figure 3A in Balagué, et al., "Adeno-Associated Virus Rep78 Protein and Terminal Repeats Enhance Integration of DNA Sequences into the Cellular Genome." *J. Virology* 71:3299-3306, 1997. Dr. Jacoby first falsified the image using computer software to misrepresent the image as data from his own experimental analysis of clonal cell lines. His falsified image supported his claim that the transgene DNA had integrated into the cell genome at a specific site. These plagiarized and falsified results were reported in (1) appendix material supporting an NIH grant; (2) three presentations by his supervisor to colleagues at MGH; and (3) an NIH grant application for continuation of his Clinical Investigator (CI) Award.

During the institutional investigation in 1998, Dr. Jacoby presented another falsified image in which he altered the locations of three major bands. He then used the different band locations as "evidence" of the differences between Figure 3A and the data purportedly from his own experiment by presenting the falsified image: (1) to the Chief of MGH's Neurology Service; (2) to a scientist assisting the Inquiry Committee; and (3) to the Inquiry Committee as data from his own independent experiment.

After the institution concluded that Dr. Jacoby had engaged in scientific misconduct, Dr. Jacoby forged the signature of the institutional official for the MGH Grants and Contracts Office and knowingly included

false and material information on his NIH non-competing renewal application for a CI Award he submitted to NIH on or about August 1, 2000.

Dr. Jacoby's falsifications gave NIH reviewers inaccurate information for their evaluation of the progress made by the research group at MGH and substantially hindered the progress of the PHS-funded research project. His falsifications also induced NIH to conditionally approve research funds for Dr. Jacoby's CI grant at a time when he was no longer conducting research. Accordingly, PHS further found that Dr. Jacoby engaged in a pattern of dishonest conduct that demonstrates a lack of present responsibility to be a steward of Federal funds.

Dr. Jacoby entered into a Voluntary Exclusion Agreement with PHS in which he voluntarily agreed for 5 years beginning June 12, 2001: (1) to exclude himself from any contracting, subcontracting, or involvement in grants and cooperative agreements with the U.S. Government; and (2) to exclude himself from serving in any advisory capacity to PHS.

Kuie-Fu (Tom) Lin, D.V.M., Medical University of South Carolina (MUSC): Based on the MUSC investigation report and additional analysis by ORI, the PHS found that Dr. Lin, a former graduate student, Department of Biochemistry and Molecular Biology at MUSC, engaged in scientific misconduct in research supported by the National Heart, Lung, and Blood Institute (NHLBI), NIH, grants R01 HL29397, "Regulation and Function of Renal Kallikrein," and R01 HL56686, "Gene Therapy in Experimental Hypertension and Renal Diseases." The PHS found that Dr. Lin (A) falsified research on the expression and effect of the human atrial natriuretic peptide (ANP) gene in rats reported in *Hypertension* 26:847-853, 1995; (B) falsified research on the expression and effect of the human adrenomedullin (ADM) gene in rats reported in *Hypertension Research* 20:269-277, 1997; and (C) falsified research on the expression and effect of the human ANP gene in rats reported in *Human Gene Therapy* 9:1429-1438, 1998. All three of the questioned papers described gene therapy

CASE SUMMARIES (Continued)

models in which the introduced gene lowered blood pressure in hypertensive or salt-sensitive rats. Dr. Lin's falsifications greatly enhanced the apparent expression and effects of the introduced ANP and ADM genes in the experimental rats.

Dr. Lin stated that he made honest mistakes and deeply regrets his unintentional errors in data handling. Dr. Lin entered into a Voluntary Exclusion Agreement with PHS in which he voluntarily agreed: (1) to exclude himself for 3 years beginning June 12, 2001, from any contracting, subcontracting, or involvement in grants and cooperative agreements with the U.S. Government and from serving in any advisory capacity to PHS; and (2) to submit letters of correction or retraction to *Hypertension* 26:847-853, 1995; and *Hypertension Research* 20:269-277, 1997.

Raghootama S. Pandurangi, Ph.D., University of Missouri--Columbia (UMC): Based on the UMC investigation report and additional analysis by ORI, PHS found that Dr. Pandurangi, a former Research Assistant Professor at UMC, engaged in scientific misconduct by plagiarizing and falsifying research data taken from a journal article published by other scientists for use in supplementary materials of a research grant application submitted to NIH. PHS found that he plagiarized the images of data and related text in supplemental material he submitted with an NHLBI, NIH, grant application and its supplement.

Dr. Pandurangi entered into a Voluntary Exclusion Agreement with PHS in which he voluntarily agreed: (1) to exclude himself from any contracting, subcontracting, or involvement in grants and cooperative agreements with the U.S. Government for 1 year, beginning July 17, 2001; (2) that for an additional 3 years after the exclusion, any institution that submits an application for PHS support for a research project on which Dr. Pandurangi's participation is proposed or which uses him in any capacity on PHS supported research, must concurrently submit to PHS and ORI (a) a plan for supervision of his duties during; and (b) a certification that the data provided by him is based on actual

experiments or are otherwise legitimately derived; and (3) to exclude himself from serving in any advisory capacity to PHS for 4 years, beginning July 17, 2001.

Ayman Saleh, Ph.D., University of Pittsburgh (UP): Based on the UP inquiry report and additional analysis by ORI, PHS found that Dr. Saleh, former postdoctoral research associate, School of Medicine, UP, engaged in scientific misconduct in research supported by NIH. PHS found that Dr. Saleh falsified: (a) data for a manuscript which purported to show Western blots of rabbit Bcl-2 and tubulin; the blots were actually obtained from different experiments by another researcher; (b) the label on a Western blot for Bcl-2 that he presented to the inquiry committee as evidence that he had conducted the experiment at issue; the blot was actually from a different experiment by a coworker; (c) data for a laboratory figure purported to represent a rabbit PARP cleavage blot; the data was from another experiment, and the antibody to PARP was not available to Dr. Saleh at that time; (d) Western blot data on pcasp-9 and p37/p35 for a manuscript on Hsp27; the data represented experiments that could not be performed because the cell lines were unavailable at the time; and (e) Figure 2b, the panel that shows a Western blot of Casp-9(WT) in a publication by Srinivasula, et al., "A conserved XIAP-interaction motif in caspase-9 and Smac/DIABLO regulates caspase activity and apoptosis." *Nature* 410(6824):112-116, 2001. The experiments examined the regulation of programmed cell death (apoptosis), a process that is important to a better understanding of cancer. Figure 2b in the *Nature* paper represented a control experiment that confirmed the association of an X-linked gene to a particular type of apoptosis.

While neither accepting nor admitting to the findings of scientific misconduct, Dr. Saleh entered into a Voluntary Exclusion Agreement with PHS in which he voluntarily agreed for 3 years beginning on May 3, 2001, to exclude himself from any contracting, subcontracting, grants and cooperative agreements with the U.S. Government; and from serving in any advisory capacity to PHS.

UPCOMING MEETINGS

November 16-17, 2001
**Training for Responsible Conduct of
Research**, Birmingham, AL

April 16-17, 2002
**Conflicts of Interest and Research
Misconduct**, St. Louis, MO

May 2-3, 2002
Promoting Integrity in Clinical Research,
Cleveland, OH

June 19-22, 2002
**Symposium on Research Responsibility and
Undergraduates**, New London, CT

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ORI NEWSLETTER

The ORI Newsletter is published quarterly by the Office of Research Integrity, Office of the Secretary of Health and Human Services, and distributed to applicant or awardee institutions and PHS agencies to facilitate pursuit of a common interest in handling allegations of misconduct and promoting integrity in PHS-supported research.

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