

Inquiring Minds

News and notes from the Department of Clinical Investigation
Walter Reed Army Medical Center
Washington, D.C.

July 2001

Congratulations to the Bailey K. Ashford Research Award Winners!

Congratulations to the winners of the 27th Annual Bailey K. Ashford Clinical and Laboratory Research Award. This year's winners are MAJ Brennan J. Carmody (Resident, General Surgery) and MAJ David T. Ward (Resident, General Surgery).

The BKA is presented annually to the graduating trainees who have contributed the most significant research during their years of training at WRAMC. This year DCI received a record number of nominations and it was very challenging for our selection committee to determine the winners.

Finalists presented their major research findings at the BKA Symposium on 3 May in Joel Auditorium. The selection committee rated the symposium presenters, and then interviewed each finalist the following day with a winner from each category chosen.

The clinical research award winner, MAJ Brennan Carmody, conducted research on whether elevated homocysteine levels leads to increased atherosclerotic peripheral vascular disease, and if so, can it be reserved through the use of a competitive behavior, folate. Utilizing arterial specimens from consenting patients undergoing lower extremity amputation, Dr. Carmody's analysis included tritiated-thymidine incorporation and hemocytometers for cell counts. Dr. Carmody showed that indeed the effect of hyperhomocysteinemia was present on these arteries and that folate administration was protective. Dr. Carmody's work has been published in the *Journal of Vascular Surgery* (Vol 30, December 1999, pages 1121-8).

IRB Calendar

The following Institutional Review Board (IRB) meetings will be held in the months of July, August, and September 2001:

CLINICAL INVESTIGATION COMMITTEE (CIC):

10 July	14 August
17 July	04 September
07 August	11 September

HUMAN USE COMMITTEE (HUC):

24 July	28 August
31 July	18 September
21 August	25 September

INSTITUTIONAL BIOSAFETY COMMITTEE (IBC):

13 September

All meetings will begin at 1300 and will be held in the fourth floor conference room, Building 6, WRAMC.

The laboratory research award winner, MAJ David Ward, conducted research on the effects of supplementing nitric oxide synthase with its substrate, l-arginine, on development of local mucosal injury and systemic capillary leak. Previous work had shown that the lung injury that resulted from a mesenteric ischemia-reperfusion (I-R) insult was due to a decrement in nitric oxide (NO) production. Dr. Ward

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DCI Welcomes LTC Raul Marin as New Assistant Chief

The Department of Clinical Investigation is pleased to announce the addition of LTC Raul Marin, MC, effective 2 July 2001. LTC Marin will serve as Assistant Chief, DCI, and as Chief, Clinical Studies Service, DCI.

LTC Marin comes to DCI from the Department of Physical Medicine and Rehabilitation, WRAMC, where he served as Assistant Chief. Previous assignments have also included a Fellowship on Medical Research at WRAIR; Director, Ambulatory Care Clinic and Staff Psychiatrist for PM&R, WRAMC; and Chief, PM&R for the Landstuhl Regional Medical Command.

LTC Marin's current research involves the determination of low back muscle usage by MRI before and after stepper machine exercise.

LTC Marin earned his Bachelor of Arts from Gettysburg College and was awarded his Medical Degree from the University of Puerto Rico Medical School. This was followed by his transitional internship at BAMC and residency at WRAMC, where he received the Resident Research Award for PM&R.

Chemical Tracking (HMMP/HSMS) in DCI

by Diarmuid Nicholson, PhD, Research Operations Service, DCI

The Department of Clinical Investigation hazardous material (HM) and hazardous waste (HW) program became operational in May 2001. This will affect investigators with protocols that require the use of chemicals.

The Hazardous Substance Management System (HSMS) is a relational database and associated software, which tracks chemicals at WRAMC. HSMS is used to create a barcode for each chemical container; and associate the chemical container with an authorized user in a specified location. HSMS is also used to manage HW generated as part of a laboratory protocol.

Waste, for example, includes chemicals, which remain at the end of a project or mixtures generated by an instrument. The user will define the components of the waste and calculate percentages of each component, including water, in the waste. This information is used to print the WRAMC Form 2090-R; the form required to turn-in waste to the bunker behind Building 52.

Each chemical ordered must be on the Authorized Use List (AUL) and many chemicals will be on the list. However, each chemical is listed according to manufacturer and size of the container; so it is possible

to place an order for a chemical, which is not in the database. If a chemical is absent from the database, a request is made to the Garrison Environmental Office (GEO) to add the chemical to the list. The GEO will need a Material Safety Data Sheet (MSDS) for the chemical, to be able to add a new chemical to the list.

When an ordered chemical arrives in DCI, it is entered into the database, a barcode attached, and then issued to the user, who will be listed in the database by first and last initials and the last four numbers of the user's Social Security Number.

When a container with a barcode is empty, the barcode must be removed and returned to the DCI HSMS manager.

Chemicals which remain at the end of a protocol or which exceed their expiration date must be disposed of as HW and the barcodes must be removed and returned to the DCI HSMS manager; so that, the chemicals can be removed from the inventory. There is also a form to use when a chemical changes location. A chemical can be re-issued to another user in a different location, but that transaction must be recorded in the database.

Congratulations to the BKA Award Winners (cont. from page 1)

then used L-arginine to create nitric oxide, and incorporated that into the I-R model. This resulted in a protection against the lung injury effect of the I-R insult, as well as an amelioration of the intestinal effect. Dr. Ward took this idea of using L-arginine to downregulate the effects of I-R insult and developed a new model to study a way to prevent the effects of the I-R insult. A large-scale rat model was utilized in order to fully elucidate the mechanism and effect. Dr. Ward's work has been published in the *Journal of Surgical Research* (Vol 89, March 2000, pages 13-19).

The other finalists for this year's award were: CPT(P) Alexander Niven (Pulmonary & Critical Care Fellow); CPT Erik Rupard (Internal Medicine Resident); LT Daniel Tveit, USNR (Nephrology Fellow); CPT Michael Rajnik, USAF (Pediatric Infectious Diseases Fellow); CPT Ann Marie Straight (Pediatric Resident); and MAJ Jon Ben Woods, USAF (Pediatric Infectious Diseases Fellow)

All finalists were presented with an Army Commendation Medal, with the award winners (one from each category) presented with an engraved medallion and a \$750 prize at the WRAMC-NNMC graduation ceremony on 15 June.

A poster session was also included as part of the symposium to feature some of the exceptional research achievements of our graduating residents and fellows. A \$150 prize was presented to the winners that displayed the best poster presentation (one from each category). The winners for this year's poster session are CPT Steve Kent (Cardiology Fellow) for clinical research and CPT Colleen Lennard (Otolaryngology/Head & Neck Surgery Resident) for laboratory research.

DCI would like to congratulate not only the winners, but also all those nominated for this year's award. The work of these investigators represents some of the most exemplary research done at WRAMC over the past several years.



Developing the Background and Significance section of the WRAMC/DCI protocol application

by Gregory Fant, PhD, MPA, MSPH

As Dawson-Saunders and Trapp (1990) wrote in the chapter entitled "Reading the Medical Literature" and Friedman (1994) wrote in the chapter entitled "How to Carry Out a Study," the background and significance section of any study proposal (or protocol) is the most important and the most difficult to prepare. The "Applied Research Design Workshop" offered jointly by the Clinical Studies Service and Research Review Service, Department of Clinical Investigation, is designed to help the clinical investigator develop an over-all, research study plan that will be made part of the protocol application submitted to the Clinical Investigation Committee (CIC). The CIC is the committee of peers formed by WRAMC/DCI to review a proposed study for scientific merit and the soundness of the research study plan found in a protocol application. An early section of the WRAMC/DCI protocol application is the Background and Significance section.

Below, the reader will find some thoughts and suggestions to consider when preparing this important section of the WRAMC/DCI protocol application. These thoughts and suggestions were taken from a handout developed for the participants of the "Applied Research Design Workshop." The thoughts and suggestions may assist other clinical investigators develop a Background and Significance section for the WRAMC/DCI protocol application.

BACKGROUND AND SIGNIFICANCE:

[Statement from protocol template: *Summarize recent Literature, justify the need for conducting this project, and explain the rationale for this study. Reference your bibliography.*]

Meaning

This is the one of the most difficult sections of the research plan. The usual practice is to tell a story of the biological and medical aspects of the condition--this is not the purpose of this section.

Instead, the investigator must describe the problem

area that is the direct object of the proposed study. Be sure to indicate what prompted the interest in this problem area. Be sure to state the specific problem that will be addressed in this study.

Then, review the literature of this problem, i.e., review what is known and not known about this problem area (Friedman 1994). Be sure to review previous studies by other investigators in this problem area: What are the strengths and weaknesses of the research efforts reported by others? Synthesize the pertinent weaknesses of the previous studies into a justification for the proposed study. The weaknesses identified by the investigator developing the research plan should be addressed in the proposed study.

Hint: In notes for writing this section, construct a separate table for each study article as indicated below.

Use the content of each table for each article included in the literature review of the problem area. (Feel free to adjust this table, as necessary.) The tables will also serve to indicate what weaknesses will be addressed in the research plan. When evaluating the medical literature, refer to "Reading the Medical Literature" (ch. 15) in **Basic and Clinical Biostatistics** by Beth Dawson-Saunders and Robert Trapp (Norwalk, CT: Appleton & Lange, 1990).

In the context of the literature review, phrase the justification for this study: Why is this study needed? Then, articulate a specific research question that will be answered in this research plan. The investigator should phrase what she (or he) expects the findings to indicate about the research problem.

References:

- 1) Dawson-Saunders, Beth and Trapp, Robert. *Basic and Clinical Biostatistics*. Norwalk, CT: Appleton & Lange, 1990.
- 2) Friedman, Gary. *Primer of Epidemiology*. New York: McGraw-Hill, 1994.

Example Table 1.

Problem Area:

Article Reference:

Strengths of article	Weaknesses of article
1 st strength	1 st weakness
2 nd strength	2 nd weakness
3 rd strength	3 rd weakness

New SOP for the Handling of Data/Tissue in the Absence of Lost - Not Available Consent Forms

The WRAMC Department of Clinical Investigation (DCI), Human Use Committee, recognizes that there is an ethical as well as a legal responsibility to ensure that individuals both consent to and understand their participation in research.

Occasionally, during a chart review by the Principal Investigator, and/or an Audit Review on an approved research study it is determined that the signed consent forms of subjects enrolled in the research protocol are missing. A thorough search should be made by the principal investigator (PI) in an attempt to locate these forms since from time to time consent forms do get misplaced, either in the patient's record or get mixed with other documents.

The deviation must be reported to the Human Use Committee (HUC) by the principal investigator and the Clinical Studies Service Auditor (if an audit occurred). In the event the consent forms are not located, the HUC will then make a decision as to whether or not to allow the subjects to be re-consented.

The following are DCI guidelines to be followed for re-consenting subjects enrolled in a research protocol.

a. If the HUC recommends that the subjects be allowed to re-consent, the principal investigator provides DCI with the names and telephone numbers of the subjects to be contacted. DCI selects an employee with no involvement in the research protocol and asks this employee to contact the subjects.

b. The independent DCI employee contacts the subjects by telephone using a script (modified/adapted for individual subjects) approved by the HUC and asks the

Subjects regarding their participation in the protocol and if they recall having signed a consent form for the particular study.

c. If the subjects remember being asked to participate, and remember giving consent, they are asked if they have a copy of the original consent documents that they signed. If they are able to produce their copy of the signed original consent form, they are requested to submit the documentation to DCI/PI via mail or fax. Once the documentation is received by DCI/PI, it is then recommended to the HUC to allow the data/sample to be used by the principal investigator.

d. If the subjects remember being asked to participate and remember giving consent, but are unable to produce their copy of the original consent form, they will then be asked if they would sign a duplicate copy of the original consent form with the current date. In addition, the subjects will be asked to sign a statement documenting that they acknowledge having signed the original consent form and that they desire to sign the duplicate form and participate in the study.

e. If the subjects do not recall consenting, the independent DCI employee thanks them for their time and patience in this matter.

The findings are reported to the Human Use Committee for further recommendations. The HUC has the final decision as to whether subjects can be re-consented and whether data/samples are to be destroyed if a consent form is not available. If the HUC decides that the data/tissue be destroyed for those subjects without a consent form, a DCI auditor will arrange a date and time to complete the task with the principal investigator or his/her designee.

Molecular Biology Course for October 2001

The Department of Clinical Investigation is pleased to announce the seventh Molecular Biology Short Course for WRAMC Clinicians (Staff and GME). The course will meet on Wednesday afternoons in October (3, 10, 17, & 24 October) from 1300-1700 in the DCI laboratories.

The goal of this course is to provide clinicians with an improved understanding of common techniques associated with molecular biology to better comprehend the current literature. The format is a 1 hour didactic session followed by a 3 hour, hands on, bench top, wet DCI Molecular Biology Course for October 2001 lab in the DCI laboratories. Participants will perform RNA and

DNA extractions, PCR, restriction enzyme digests, DNA sequencing, cloning, HPLC, and many other basic bench top techniques. Each participant will receive a course book with handouts detailing each class session, pertinent articles, and directions for each wet lab. The course will be limited to 12 participants and is free of charge to WRAMC providers.

If you are interested in attending this course, or a future molecular biology course, please contact Mr. Maged Abdel-Rahim at (202) 782-7612 or via E-mail at Maged.Abdel-Rahim@na.amedd.army.mil.

Death Heightens Scrutiny of Clinical Tests

Concern About Volunteers' Safety Has Prompted Calls for New Rules, Expanded Protections

A recent article reprinted from *The Washington Post*, 25 June 2001

She noticed the cough almost immediately, began feeling short of breath and achy. Two days after her visit for a research study at the Johns Hopkins Asthma and Allergy Center -- two days after inhaling the chemical hexamethonium during what was assumed to be a low-risk test for a healthy young woman -- Ellen Roche called back, obviously concerned.

Her symptoms were troubling enough that the staff quickly started monitoring her condition. That was May 7, and Roche's lungs already were functioning at two-thirds capacity. She was no better by May 9, when doctors admitted her to Johns Hopkins Bayview Medical Center in East Baltimore for observation.

The 24-year-old lab technician died there June 2, the university's first death of a research volunteer since 1986 and its first death ever of a healthy volunteer.

The tragedy, an "adverse event" that officials did not report publicly until mid-June, has raised anew questions about how adequately medical research participants are informed and protected during experiments. It has triggered an internal investigation, a special university review committee and probes by the federal Office for Human Research Protections and the Food and Drug Administration.

All will try to determine whether asthma researchers did anything wrong as they studied the physiological mechanics of a normal lung: whether they cut corners during the testing, for instance, or failed to fully disclose important details to Roche and other participants, or endangered their subjects from the start by using a substance that is not FDA-approved, possibly without the required permission.

Or the inquiries could find that, no matter the circumstances, the death could not have been foreseen.

"In the field of clinical investigations, the worst thing that can happen is the death, the *unanticipated* death, of a normal volunteer," said John Fletcher, professor emeritus of biomedical ethics at the University of Virginia's medical school and founder of the bioethics program at the National Institutes of Health.

"Where there's culpability, it's a life-changing and a career-changing thing. It's at least a 9 on a moral Richter scale. But we know in the total universe of human studies, these deaths are extremely rare."

Medical ethicists say the country has made great strides in the past three decades in its oversight of medical research. Institutional review boards must approve a project in advance. Scientists are expected to give research subjects truthful, clearly worded information about risk, which should be minimized as much as possible. And participants must be allowed voluntary

consent that they can withdraw at any time.

Yet since 1998, a number of serious incidents have shown continuing weaknesses in the system. Concerns about patient safety stopped clinical trials at university medical schools in Oklahoma, Alabama, North Carolina and Massachusetts. After glaring breakdowns in its gene therapy studies, which only surfaced after a teenage participant died, the University of Pennsylvania announced last year that its genetic research would no longer use human subjects.

Just last month, as Roche lay in intensive care in Baltimore, a presidentially appointed panel recommended major changes in the protections afforded participants in a range of scientific studies. Review boards often are overwhelmed by the volume and technical demands of the work they judge, the panel said; guidelines about researchers' potential conflicts of interest need strengthening, as do provisions for especially vulnerable populations such as children and mentally incompetent elderly.

Though the scale of biomedical research has exploded since 1980, the National Bioethics Advisory Commission noted that there are no statistics on how many people are involved in clinical trials or the number of adverse events. It urged that a system be created for reporting those incidents. Some members also advocated that a fund be established to compensate individuals who are hurt because of their participation.

"It's a matter of simple justice that we cover them if they end up injured," said commission member James F. Childress, who teaches bioethics at the University of Virginia. They are, he pointed out, "putting their bodies on the line for research."

Ellen Roche did so understanding that she would receive no therapeutic benefit from whatever the Hopkins scientists learned. There was a baseline investigation looking at how a normally functioning lung helps keep airways open even when they are exposed to irritants and allergens. If researchers can discover that, they can better grasp how the airways of someone with asthma begin to constrict and possibly develop a drug to prevent it.

Ten million Americans suffer from this potentially life-threatening condition. Roche did not.

Her family has not broken its silence in the weeks since she died. Perhaps she never told them why she decided to sign up for the study. Compared with the generally clear-cut motivation of a sick volunteer, a healthy person's reasons for taking part in a clinical trial can vary tremendously.

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Using a Questionnaire in a Research Project to Measure Quality

by Gregory Fant, PhD, MPA, MSPH & Anna Crane

Since the 1990s, health policy in the United States has been driven by three conceptual concerns (Kronenfeld 1993). These three concerns can be thought of as three questions and may be phrased as follows:

ACCESS-Are health services available to and accessible by those who need it?

COST-CONTAINMENT-What can be done to control the rising cost of delivering health services?

QUALITY-Are quality health services being provided to those receiving services through the health service delivery system?

This short piece will briefly explore the conceptual framework for using a questionnaire instrument in a research project to help measure quality and present an applied example. Measuring quality in the context of the delivery of health services has three components: structure, process, and outcome (Brooks, Williams, and Davis-Avery, 1976; Donabedian 1968; Donabedian, Wheeler and Wyszewianski 1982; Kronenfeld 1993). The availability of personnel, facilities, and the manner in which these are organized to deliver health services is a concern for the structural component of quality. The "content of care" or the number and types of procedures and laboratory tests ordered for a patient receiving health services reflect a concern for the process component of quality. Finally, the impact of health services on the patient is the concern for the outcome component of quality.

Assessing the outcome of health service delivery is a current topic of professional concern in addition to being of academic and applied research interest. For example, Cohen and DeBlack (1999) in **The Outcomes Mandate Case management in health care today** (St. Louis: Mosby, Inc.) discuss the role, importance, and methods of measuring quality within in context of health care case management and outcomes assessment. Additionally, Young (1998) in **Population Health Concepts and Methods** (New York: Oxford University Press) develops a theoretical framework for measuring quality--including examining health service outcomes--as an objective when evaluating a population health program. A common thread in either work is the importance of asking the recipient of health services to rate her or his experience with the health service delivery system.

One way to accomplish this task in a research project is to ask the recipient of health services to complete a questionnaire. In the context of a research project, a study may be undertaken to measure the outcome of health services provided to study participants. Research may, also, be pursued to measure the outcome of two (or more), different health treatments (or

health services) received by study participants. When deciding to use a questionnaire under these circumstances, the challenge for the investigator is to use a valid and reliable questionnaire instrument to measure the outcome of health service delivery when designing the research project.

Instead of developing an un-tested questionnaire instrument to measure the outcome, an investigator should consider using an instrument that has already been tested and proven to be valid and reliable. Several sources exist that identify valid and reliable questionnaire instruments; For example, an investigator may consult works by Ruggeri 1994; McDowell and Newell 1996; Redman 1998; Hyner, Travis, et. al. 1999; and Maruish 1999. After examining works like those cited, the investigator should obtain a complete copy of each instrument (along with validity and reliability data), study the actual instruments, and determine which instrument could measure the concept of interest in a proposed study.

Only if a valid and reliable instrument does not exist to measure the concept of interest should an investigator undertake the task of developing a new questionnaire instrument. If a new one is developed, then the instrument must be pilot tested. The validity and reliability of the new instrument must also be assessed before it can be used in a research project. Failing to pilot test a new instrument before using it in a research project invites criticism that centers around an answer to a simple question: "Where is the proof that the new instrument measures what you say it will measure?"

Suppose, for example, that an investigator is interested in assessing the outcome of two, different treatments administered to study participants assigned to a case group and a reference group in a primary health care setting. The investigator decided to employ a questionnaire to measure satisfaction with the test treatment and the standard of care treatment received by study participants. The investigator consulted the work by Maruish (1999). From this work, the investigator found a questionnaire instrument that has been used to measure consumer satisfaction with primary medical care, mental health treatment, and a wide range of human service activities; the instrument is called the Client Satisfaction Questionnaire-8 (CSQ-8). (see example questionnaire instrument)

The investigator discovered, furthermore, that the CSQ-8 was developed by a group of researchers at the

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Funding For Research Proposals

by Daisy B. Word, Chief, Research Administration Service, DCI

With the coming of new interns, residents and fellows to the WRAMC GME program, this seems an appropriate time to notify new personnel and remind others of the guidelines covering research funding (intramural funding) available through the Department of Clinical Investigation.

We are fortunate to offer intramural funding for meritorious research proposals, albeit limited but available to all GME members and Walter Reed staff.

The Department of Clinical Investigation may fund up to 2 protocols per investigator per year. Each protocol may be funded up to \$7,500 per year with a cap of \$15,000 over the life of the protocol. Within the \$15,000 we earmarked \$1,000 to pay for travel when going to present the research at a scientific meeting away from Washington DC. There are no limitations in the number of protocols that can be approved if there are no costs involved or if extramural funding is received. The funds for consumable supplies must be used during the year for which it is funded.

The \$1,000 approved for travel may not be split to cover more than one trip. If the meeting costs more than the cited amount, we would like to request that the Department where the investigator is assigned absorb the funding requirement in excess of \$1,000. If that is the case, the investigator's Department fund cite should be included on the funding request form.

Unfortunately because of funding constraints we can only fund the Principal Investigator to travel on these funds. In cases where there is a change in

investigators, DCI must receive this notification in writing in advance of travel dates. Funds are not transferable to Associate Investigators or collaborators.

DCI-approved travel funds are good up to one year after end of study.

Regarding funding for animal studies where other institutions are involved:

-Consult with the administrative office of the institution to determine cost of animals, housing and care, supplies and any other hidden costs.

-Where government facilities are utilized (e.g. WRAIR, USUHS, AFIP), have the facility administrator provide a completed MIPR form (DD448) and provide it to DCI. Information should include the institution's account number, POC name, mailing address, fax and telephone numbers, an invoice with a breakdown of costs, and any other information deemed pertinent.

-When non-governmental facilities are utilized, the PI should provide the DCI with a statement of work (SOW) stating the nature of the collaboration, what services will be provided by WRAMC and which to be rendered by the other institution, an invoice on the institution's letter head itemizing all costs to be borne by WRAMC and signed by an official. In addition we need a justification as to why government facilities are not being used.

For further information contact Ms. Daisy Word at Research Administration at (202)782-6389 or fax (202) 782-3881.

Gene Therapy is Performed in Bid to Halt Alzheimer's

A recent article reprinted from *The New York Times*, 11 April 2001

Six days ago, a woman in the early stages of Alzheimer's disease entered a California hospital, had a small hole drilled through her skull and was injected with millions of her own cells, in what researchers said was the first time gene therapy had been tried on an Alzheimer's patient.

The researchers who announced the experiment yesterday at a news conference held at the University of California at San Diego, where the surgery took place, said it was also the first time that doctors had tried to prevent progressive cell loss in a neurodegenerative disease.

The 60-year-old patient, who asked to remain anonymous, was discharged from the hospital last Saturday and is recovering well at home, said Dr. Mark Tuszynski, a neurologist at the university who led the research.

"We hope to learn within the next three months if the procedure is working," Dr. Tuszynski said in a telephone interview. "But this is just one patient. It may take years before we know if it works in a large number of people."

Dr. William Mobley, the chairman of the neurology department at Stanford University, who is familiar with the research, called the procedure "a very important first step" toward finding a novel way to treat Alzheimer's disease.

"The work is being done very carefully," Dr. Mobley said. "Their logic is very good."

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Recently Approved Protocols at WRAMC

Congratulations to the following principal investigators on their recently approved protocols.

Armed Forces Institute of Pathology

01-92005E: Arsenic Determination by ICP-MS
PI: LT John W. Ejnik, MSC, USNR 25 April 2001

Department of Allergy-Immunology

01-33001: In Vitro Gamma-Interferon Response to MTB Antigens in BCG-Vaccinated Individuals and Those with Equivocal PPD Skin Test Compared to Negative and Positive Control Subjects
PI: MAJ Rohit Katial, MC 26 April 2001

01-33002: Suppression of Ragweed Wheal Response by Montelukas: A Double-blind Study
PI: CPT Kirk H. Waibel, MC 6 April 2001

Department of Clinical Investigation

01-92003: Hepatitis C Virus Infection: Mechanism of Disease Progression
PI: COL Maria H. Sjogren, MC 4 May 2001

Department of Medicine

Endocrinology Service

01-13001: A Comparison of the Effects of Rosiglitazone and Metformin on Markers of Inflammation and Carotid Plaque Burden in Patients with Type 2 Diabetes Mellitus. Cardiovascular Effects of Hypoglycemic Medications in Diabetes - CHD Study
PI: CPT Derek J. Stocker, MC 9 April 2001

01-13008E: A Cross-Sectional Examination of the Relationship Between Coronary Artery Calcium Scores and Serum TSH in Patients Undergoing Non-Contrast Electron Beam Computed Tomography (EBCT) at the Walter Reed Army Medical Center (WRAMC)
PI: CPT Vineeth Mohan, USAF, MC 13 April 2001

Gastroenterology Service

01-14004: The Timing of Liver Enzyme Elevation and Hepatitis C Seroconversion in a Cohort of United States Military Gulf War Veterans
PI: COL Kent Holtzmuller, MC 31 May 2001

General Medicine Service

01-10006E: Electively Induced Amenorrhea Through the Use of Birth Control Pills
PI: 2LT Nicole Powell-Dunford, USAR 22 March 2001

01-10007E: Osteoporosis risk and management in a primary care clinic
PI: LTC Jeffrey L. Jackson, MC 20 April 2001

Hematology-Oncology Service

01-15005: CALGB 79804: Issues of Survivorship Among Breast Cancer Survivors
PI: LTC Joseph J. Drabick, MC 30 May 2001

01-15006: CALGB 89904: A Randomized Phase II Study of Gemcitabine/Cisplatin, Gemcitabine/Docetaxel, Gemcitabine/Irinotecan, or Fixed Dose Rate Infusion Gemcitabine in Patients with Metastatic Pancreatic Cancer
PI: LTC Joseph J. Drabick, MC 12 June 2001

01-1504: CALGB 59901: A Phase II Study of 506U78 in Patients with Previously Systemically Untreated Cutaneous T-Cell Lymphoma or With Refractory or Relapsed Non-Cutaneous Peripheral T-Cell Lymphoma
PI: LTC Joseph J. Drabick, MC 18 April 2001

Infectious Disease Service

01-88000E: The impact of ethnicity and cytochrome P450 2D6 and 2C19 polymorphisms on clinical response to efavirenz in a cohort of HIV-1 infected military subjects
PI: COL Naomi Aronson, MC 23 May 2001

Nephrology Service

01-11012E: A multidisciplinary approach to achieving target lipid goals in chronic hemodialysis patients
PI: Rebecca A. Viola, RPh., DAC 13 April 2001

Pulmonary & Critical Care Medicine Service

01-17010E: Evaluation of the Accuracy of a Clinical Diagnosis of Idiopathic Pulmonary Fibrosis
PI: CPT Donald Helman, MC 23 May 2001

01-17011E: Outcomes for patients with sarcoidosis requiring lung transplantation
PI: MAJ Andrew Shorr, MC 31 May 2001

Department of Neurology

01-71001: Assessing States of Unconsciousness by Actigraphy
PI: LTC Michael B. Russo, MC 11 May 2001

Department of Nursing

01-75003: Improving Adherence in a Coronary Disease Reversal Program with Web-Based Technology
PI: MAJ Debra Spencer, AN 30 March 2001

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Recently Approved Protocols at WRAMC (continued from page 9)

Department of Obstetrics and Gynecology

01-43002: GOG 0179: A Randomized Phase III Study of Cisplatin vs. Cisplatin Plus Topotecan vs. MVAC in Stage IVB, Recurrent or Persistent Carcinoma of the Cervix
PI: MAJ Larry G. Maxwell, MC 31 May 2001

01-43004: GOG 0182: A Phase III Randomized Trial of Paclitaxel and Carboplatin Versus Triplet or Sequential Doublet Combinations in Patients with Epithelial Ovarian or Primary Peritoneal Carcinoma
PI: MAJ Larry G. Maxwell, MC 13 June 2001

01-44002: The Comparison of the Effectiveness of Burch Colposuspension Versus Suburethral Sling in the Management of Primary Genuine Stress Urinary Incontinence
PI: LTC Ernest G. Lockrown, MC 6 April 2001

Department of Ministry & Pastoral Care

01-91001E: The Use of a Common Factors Approach in Multicultural Ministry and Pastoral Care Among Chaplains at Walter Reed Army Medical Center
PI: CPT John C. Wheatley, Chaplain Corps 18 May 2001

Department of Pathology

01-48003: Oxidative and Nitrosative Stress in Carcinogenesis of Colitis-Associated Malignancies
PI: LTC Aizen Marrogi, MC 24 May 2001

Department of Pediatrics

01-65001: An Archival Fixed-Tissue Thyroid Tissue Bank
PI: COL Gary Francis, MC 10 June 2001

01-66001a: POG 9905: ALinC 17 Protocol for Patients with Standard Risk Acute Lymphoblastic Leukemia (ALL) - A Pediatric Oncology GROUP Phase III Study
PI: LTC Glenn E. Edwards, MC 5 June 2001

01-66001b: POG 9906: ALinC 17: Protocol for Patients with Newly Diagnosed High Risk Acute Lymphoblastic Leukemia (ALL) - Evaluation of the Augmented BFM Regimen: A Phase III Study
PI: LTC Glenn E. Edwards, MC 5 June 2001

01-66001c: POG 9904: ALinC 17 Treatment for Patients with Low Risk Acute Lymphoblastic Leukemia: A Pediatric Oncology Group Phase III Study
PI: LTC Glenn E. Edwards, MC 6 June 2001

Department of Pharmacy

01-36004E: A prospective evaluation of the impact of an adverse drug event teaching session to interns on the frequency of adverse event reporting
PI: LTC Michael Riel, MC 8 June 2001

Department of Physical Medicine and Rehabilitation

01-96007E: Assessment tools used for resident evaluations by program directors in Physical Medicine and Rehabilitation
PI: LCDR Sean Kelly, MC, USN 4 June 2001

Department of Psychology

01-7301: Computer Automated Neuropsychological Assessment of U.S. Army Aviators
PI: MAJ Mark R. Baggett, MS 30 April 2001

Department of Radiology

01-4501: Intraoperative Staging of Lung Cancer Using the Gamma Probe and Tc-99m Depreotide
PI: MAJ Robert S. Bridwell, MC 14 May 2001

Department of Surgery

General Surgery Service

01-20003: A Prospective Randomized Phase III Study Comparing Radiofrequency Ablation Versus Cryosurgical Ablation for the Treatment of Malignant Liver Tumors
PI: LTC George E. Peoples, MC 30 March 2001

01-20004: A Randomized, Double Blind, Multi-Center, Comparative Phase III Study of Intravenous BMS-284756 Follow-up... Intravenous Piperacillin/Tazobactam With or Without Oral moxicillin/Clavulanate Follow-up in the Treatment of Complicated Skin and Skin Structure I
PI: LTC George Peoples, MC 7 May 2001

01-2002: A Prospective, Randomized, Double Blind, Multicenter Trial Assessing the Safety and Efficacy of Sequential (Intravenous/Oral) BAY 12-88093 (Moxifloxacin) 400mg Every 24 Hours Compared to Intravenous Poperacillin/Tazobactam 3.375 grams Every 6 Hours Follo
PI: LTC George Peoples, MC 16 April 2001

01-20004E: The Learning Curve of Transrectal Ultrasound
PI: MAJ Brennan Carmody, MC 4 April 2001

Organ Transplant Service

01-26002E: Post Kidney Transplant Humoral Rejection: A Retrospective Study of Presenting Features and Response to IVIG
PI: LTC Sidney J. Swanson, MC 1 May 2001

(Continued on page 14)

U.S. Oversight Urged for Human Research

System of Review on Safety and Ethical Issues Is Overloaded, Panel Reports

A recent article reprinted from *The Washington Post*, 16 May 2001

Many Americans who participate in scientific studies are not protected by the government system meant to ensure that research is conducted safely and ethically, according to a major report approved yesterday by a presidentially appointed commission.

Government oversight should be expanded to cover all studies on humans in the United States, according to the report by the National Bioethics Advisory Commission (NBAC). Researchers who conduct human studies and members of ethics committees that approve them should be trained and certified, and a new, independent federal office should be established to oversee all research involving human participants, the report recommends.

No figures are available on how many studies on humans are conducted annually in this country. However, data on biomedical research show explosive growth in the last two decades. Federal spending for health research increased from \$6.9 billion to \$13.4 billion between 1986 and 1995, and industry spending tripled -- from \$6.2 billion to \$18.6 billion -- during the same period. Between 45,000 and 50,000 U.S. researchers are thought to participate in conducting clinical studies in humans.

With the increase in human studies, there has been growing concern that the system for monitoring research safety and ethics is overloaded and inadequate. Numerous government agencies, congressional committees and private organizations have addressed the issue in reports and hearings. Many of the changes recommended in the NBAC report, entitled "Ethical and Policy Issues in Research Involving Human Participants," would require congressional action.

The report notes that government protections do not cover participants in some kinds of medical studies, such as privately funded research conducted in fertility clinics, weight loss clinics and doctors' offices.

"You've got a system that doesn't cover everyone [and] a system that doesn't extend to the private sector," said Eric M. Meslin, executive director of the NBAC.

The report says that federal oversight of human research should cover all participants who "are exposed to manipulations or interventions," who interact with researchers, or who can be identified from the data collected. That definition would make some additional studies subject to approval by Institutional Review Boards (IRBs), committees charged with determining whether studies are ethically acceptable.

Besides biomedical research, the report advocates requiring some degree of IRB review for studies in many other fields, including anthropology, psychology, political science, history, business and law. Although many studies in these fields are reviewed by IRBs, others are exempted. Research using surveys, interviews and educational tests is now often exempted from IRB approval.

Except for health-related studies, research funded by industry generally is not regulated by the federal government. The commission recommends extending federal protections to adult human subjects in all privately funded research. (The report does not discuss research on children or on adults who are not mentally competent to give informed consent.)

Even when research is sponsored by the government, it is treated inconsistently depending on which federal agency pays for it, according to the report. Eighteen federal agencies protect human subjects under a set of 1991 regulations collectively known as the "Common Rule," but at least 69 other federal agencies and departments, some of which conduct research, are not covered by the Common Rule.

"There's a huge universe of research not regulated by the Common Rule," Meslin said. The report recommends that at least 25 percent of an IRB's members should be non-scientists and that at least 25 percent should "represent the perspective of the participant." It says researchers should be required to disclose financial conflicts of interest that might affect their objectivity.

It also recommends setting up a system for reporting adverse events that occur during human studies. No mechanism now exists for compensating people injured by participating in research.

The report acknowledges that the nation's 3,000 to 5,000 IRBs are overwhelmed by the volume of research they must consider. It suggests that their workload could be lightened by designating a single "lead" IRB to make decisions on studies involving multiple hospitals or sites. Dozens of IRBs are often required to sign off on a single study.

(Continued on page 16)



Clinical Research Websites of Interest

[DCI Biometrics \(www.wrampc.amedd.army.mil/departments/dci/biometrics.htm\)](http://www.wrampc.amedd.army.mil/departments/dci/biometrics.htm): This is a newly developed website by the Biometrics Section of the Research Review Service at DCI. This site provides WRAMC investigators with an overview of the Biometric Section, contact information, statistical links, and other valuable information.

[Cell Biology Laboratory Manual \(www.gac.edu/~cellab/\)](http://www.gac.edu/~cellab/): This is a 15-chapter manual that provides an online data source for cell biology laboratories including detailed protocols and a listing of other useful cell biology-related Internet sites.

[FDA Consumer Magazine Special Research Issue \(www.fda.gov/fdac/special/newdrug/ndd_toc.html\)](http://www.fda.gov/fdac/special/newdrug/ndd_toc.html): Article entitled From Test Tube to Patient: New Drug Development in the US.

[Centerwatch Clinical Trials Network \(www.centerwatch.com\)](http://www.centerwatch.com): This site offers a wealth of information related to clinical trials, such as a listing of more than 41,000 industry- and government-sponsored clinical trials as well as new drug therapies recently approved by the FDA.

[BioMed Central \(www.biomedcentral.com\)](http://www.biomedcentral.com): BioMed Central publishes peer reviewed research across all areas of biology and medicine, with immediate, barrier-free access for all. BioMed Central offers fast, efficient online publishing of research articles in all areas of biomedical research with full peer review and no barriers to access of any kind.

[Public Responsibility in Medicine and Research \(www.primr.org\)](http://www.primr.org): PRIM&R addresses a broad range of issues in research, clinical practice, ethics, and the law. Topics include the ethical and procedural issues surrounding the operation of IRBs and IACUCs, healthcare ethics committees, scientific integrity, and conflict of interest.

[Hardin Meta Directory of Internet Health Sources \(www.lib.uiowa.edu/hardin/md/index.html\)](http://www.lib.uiowa.edu/hardin/md/index.html): A great directory of internet health resources with subjects listed by disease and medical specialty.

[Medical Glossary \(www.ama-assn.org/insight/gen_hlth/glossary/index.htm\)](http://www.ama-assn.org/insight/gen_hlth/glossary/index.htm): This site offers help with terms that may be used in research and an informed consent document.

New York Times Article (From Page 8)

That logic is based on 20 years of exploring the changes that accompany normal aging of the human brain and the disease processes that lead to dementias like Alzheimer's disease, Dr. Tuszynski said. Both conditions share certain biological mechanisms. For example, higher brain regions where language, memory and other cognitive functions reside are nourished by a chemical substance made in a small clump of cells, the nucleus basalis, found deep in the brain just under each frontal lobe. About the size of a human thumb nail, the nucleus basalis makes a substance, acetylcholine, which is sent to target cells all over the brain.

Acetylcholine modulates the excitability of distant neurons, increasing or decreasing their electrical activity depending on the amount of the chemical supplied by the nucleus basalis. When a cell in a distant area gets particularly excited and needs more acetylcholine, it sends a signal, called nerve growth factor, back to the nucleus basalis telling it to make more.

In Alzheimer's disease, some still mysterious process kills cells throughout higher brain regions and the nucleus basalis does not get the nerve growth factor it needs to prod it into making more acetylcholine. Without acetylcholine, higher brain areas that control things like memory, attention, personality and the ability to navigate through space can be severely impaired.

The gene therapy experiments are designed to fix this

state of affairs by putting a source of nerve growth factor back into the nucleus basalis. First, researchers took skin cells from the Alzheimer's patient and inserted the gene that makes nerve growth factor. By adding substances that promote gene expression, they turned her skin cells into tiny nerve growth factor pumps.

Then Dr. Hoi Sang U, the neurosurgeon on the team, injected two and one-half million cells that produce nerve growth factor next to the patient's right nucleus basalis. The new cells are expected to produce enough nerve growth factor to bring atrophied cells back to life.

In aged monkeys, the same procedure not only stopped cells from dying, it also revived them from their atrophied state, Dr. U said. "They got plump. And their many target cells made new connections."

Whether the therapy will restore memory loss in Alzheimer's patients is not known, Dr. Tuszynski said. The hope is that it will at least slow the disease process. The patient, a former teacher from Oregon, will be tested in coming weeks and months to see if her right hemisphere regains any function or if it maintains function compared with the untreated side of her brain.

Dr. Tuszynski said a second patient would receive genetically engineered cells in three months, again on one side of the brain. If no harm is detected, six more patients will receive the engineered cells in both sides of the brain.

Using a Questionnaire in a Research Project.... (From Page 7)

identified a few sources that have reported the findings of valid and reliable questionnaire instruments for measuring the outcome component of quality and suggested how a valid and reliable instrument could be modified for use in a research study.

Citations:

- 1) Brooks, O, and K. Williams, A. Davis-Avery. "Quality assurance today and tomorrow: forecast for the future." *Annals of Internal Medicine* 85 (1976): p. 809-817.
- 2) Cohen, E, and V. De Back. *The Outcomes Mandate case management in health care today*. St. Louis: Mosby, Inc., 1999.
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- 5) Kronenfeld, J. *Controversial Issues in Health Care Policy*. Newbury Park, CA: SAGE Publications, 1993.
- 6) Larsen, D. and C. Attkisson, W. Hargreaves, and T. Nguyen. "Assessment of client/patient satisfaction: development of a general scale." *Evaluation and Program Planning* 2 (1979): p. 197-207.
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- 8) McDowell, I. And C. Newell. *Measuring Health*, second edition. New York: Oxford University Press, 1996.

9) Young, K. *Population Health concepts and methods*. New York: Oxford University Press, 1998.

Note:

1. If an investigator would like to use the CSQ-8 in research, please contact the authors of the instrument (see below):

Internet contact information: saawww.ucsf.edu/csq -

This web page contains an electronic order form. The site includes an email address, as well. The web page, also, contains reliability and validity scores and numerous additional statistics. The web page is very comprehensive and an excellent reference tool.

Contact person and mailing information:

Clifford Attkisson, Ph.D.
University of California, San Francisco
Student Academic Affairs
500 Parnassus Avenue, MU200W
San Francisco, CA 94143

2. Dr. Fant acknowledges Ms. Anna Crane who was responsible for finding the CSQ-8 and assisted in writing this piece. Ms. Crane is a research assistant in the Department of Child and Adolescent Psychiatry (Bldg 6) at Walter Reed Army Medical Center. Ms. Crane received a bachelor's degree in psychology (William and Mary, 2000). Beginning this Fall 2001, Anna Crane will begin her studies as a Ph.D. student in Clinical Psychology (concentration, child clinical psychology) at Ohio University in Athens, OH. Dr. Fant, also, acknowledges COL Ryo Chun, MC, USA, for agreeing to share the CSQ-8 with the Walter Reed research community.

Recent WRAMC publications

Congratulations to the following WRAMC investigators on their recently published papers. This list was compiled from a recent MEDLINE search of the literature. Listed articles have been cleared through DCI and the WRAMC Public Affairs Office. If you have recently published, and we have not included your publication, please let us know so we may list your publication in the next issue of the newsletter.

Abbott KC, Oliver III JD, Hypolite I, Lepler LL, Kirk AD, Ko CW, Hawkes CA, Jones CA, Agodoa LY. **Hospitalizations for bacterial septicemia after renal transplantation in the united states.** *Am J Nephrol*. 2001 Mar-Apr;21(2):120-7.

Kent SM, Markwood TT, Vernalis MN, Tighe JF Jr. **Cleft posterior mitral valve leaflet associated with counterclockwise papillary muscle malrotation.** *J Am Soc Echocardiogr*. 2001 Apr;14(4):303-4.

Choma TJ, Chwirut D, Polly Jr DW. **Biomechanics of long segment fixation: hook patterns and rod strain.** *J Spinal Disord*. 2001 Apr;14(2):125-32.

Brietzke SE, Mair EA. **Injection snoreplasty: How to treat snoring without all the pain and expense.** *Otolaryngol Head Neck Surg*. 2001 May;124(5):503-10.

Lennard CM, Patel A, Wilson J, Reinhardt B, Tuman C, Fenton C, Blair E, Francis GL, Tuttle RM. **Intensity of vascular endothelial growth factor expression is associated with increased risk of recurrence and decreased disease-free survival in papillary thyroid cancer.** *Surgery*. 2001 May;129(5):552-8.

Fincher RK, Wong RK, Osgard EM. **Oral preparations for flexible sigmoidoscopy.** *Gastrointest Endosc*. 2001 May;53(5):698-9.

Norton SA. **On First Looking Into Pernkopf's Atlas (Part 1).** *Arch Dermatol*. 2001 May;137(5):549-551.

Feuerstein IM, Brazaitis MP, Zoltick JM, Barko WF, Vaitkus MA, Combs JJ, Burger LM, Blanck RR. **Electron beam computed tomography screening of the coronary arteries: experience with 3,263 patients at Walter Reed Army Medical Center.** *Mil Med*. 2001 May;166(5):432-42.

Belmont Jr CP, Taylor CK, Mason CK, Shawen CS, Polly Jr LD, Klemme LW. **Incidence, Epidemiology, and Occupational Outcomes of Thoracolumbar Fractures among U.S. Army Aviators.** *J Trauma*. 2001 May;50(5):855-861.

(Continued on page 14)

Recent WRAMC Publications (continued from page 13)

Byrd JC, Shinn C, Willis CR, Flinn IW, Lehman T, Sausville E, Lucas D, Grever MR. **UCN-01 induces cytotoxicity toward human CLL cells through a p53-independent mechanism.** *Exp Hematol.* 2001 Jun;29(6):703-708.

Mitchell JP, Dennis GJ, Rider LG. **Juvenile dermatomyositis presenting with anasarca: A possible indicator of severe disease activity.** *J Pediatr* 2001 Jun;138(6):942-5.

Criswell MA, Sinha CK. **Hyperthermic,**

supersaturated humidification in the treatment of xerostomia. *Laryngoscope* 2001 Jun;111(6):992-6.

Abbott KC, Yuan CM, Batty DS, Lane JD, Stiles KP. **Transjugular biopsy in patients with combined renal and liver disease: making every organ count.** *Am J Kidney Dis* 2001 Jun;37(6):1304-7.

Leek MR, Summers V. **Pitch strength and pitch dominance of iterated rippled noises in hearing-impaired listeners.** *J Acoust Soc Am.* 2001 Jun;109(6):2944-54.

Recently Approved Protocols at WRAMC (continued from page 10)

Ophthalmology Service

01-23001: Telemedical Examination of Eyelid Lesions: Correlation of Remote Diagnosis with in Person Clinical Exam and Pathologic Analysis
PI: CPT Eric D. Weichel, MC 14 May 2001

Orthopaedic Surgery Service

01-24005: Prospective Cohort Analysis of Hip Arthroscopy in Young Active Adults with Two Years Follow-up
PI: MAJ Romney C. Andersen, MC 13 June 2001

Otolaryngology-Head & Neck Service

01-32003: Palatal Sclerotherapy with Sotradecol as a Treatment for Obstructive Sleep Apnea Syndrome
PI: CPT Scott E. Brietzke, MC 11 May 2001

01-32004: Treatment of Snoring with Palatal Stiffening Injection Sclerotherapy Using Ethanol
PI: CPT Scott E. Brietzke, MC 11 May 2001

01-3202: Does Oral Steroid Therapy After Tonsillectomy Decreaswe Postoperative Pain and Morbidity? A Prospective, Double Blinded, Placebo Controlled Analysis
PI: CPT Andrew Battiata, MC 6 April 2001

Urology Service

01-28002: A Pilot Study to Evaluate the Safety and Feasibility of Thermal Ablation with ThermoRods™ for Residual Prostate Cancer Following External Beam Radiation Therapy
PI: COL David G. McLeod, MC 24 May 2001

01-2857-98a: Outcome Comparison of Radical Prostaectomy Pathologic Specimens
PI: COL Judd W. Moul, MC 15 June 2001

01-2871-98a: Characterization of Novel Prostate Specific Gene, PCGEM1
PI: COL David McLeod, MC 12 April 2001

01-2871-98b: The Use of Transformed Prostate Cell Lines CPDR7, CPDR8 and CPDR9 to Evaluate the Capacity of T Lymphocytes to Recongnized Prostate-derived Antigens
PI: COL David McLeod, MC 3 May 2001

01-28007E: Analysis of Prostate Cancer Detected With Increasing Number of Biopsy Cores Taken: Are These Tumors Clinically Significant
PI: LCDR John Taylor, MC 4 April 2001

Deployment Health Clinical Center

01-89007E: Using Existing Public-Access Data from Epidemiologic Catchment Area Studies to Estimate the Prevalence of Psychiatric Conditions in Military Populations
PI: LTC Charles Engel, MC 26 March 2001

Fort Knox, KY - Ireland Army Community Hospital

01-81000E: Most effective antiemetic in preventing nausea and vomiting in surgery
PI: MAJ Samuel Weber, AN 23 May 2001

01-81001E: Attention Deficit/Hyperactivity Disorder: ADHD and medical Illness and Injury in Children, and the Identification of Birth Characteristics Associated with ADHD
PI: COL John A. Richman, MC 30 March 2001

Landstuhl Regional Medical Center

00-8502: Tele-Psychiatry in the Division: A Study of Diagnostic Reliability and Cost Benefits using Desktop VTC
PI: CPT Brett J. Schneider, MC 16 April 2001

Washington Post Article (From Page 5)

Scientific curiosity or simple altruism? A commitment to advancing an area of research or the need to make some extra money? Had Roche completed the seven- to nine-visit schedule specified in the research protocol that Hopkins posted on its Web site after her death, she would have been paid \$365. Medical ethicists say that amount does not seem enough to coerce or unduly influence a volunteer's decision.

In keeping with her family's wishes, university officials have released no personal information about the young woman, a 1998 graduate of Frostburg State University. She lived in Reisterstown, northwest of Baltimore, in a two-story town house only a few miles from her father and stepmother. Just up from their house is Franklin High School, where a counselor remembers Roche as a quiet, involved student who was honored her senior year for academic accomplishments.

Roche worked at the university's allergy and asthma center. But she did not report directly to the principal investigators on the study, which is part of a \$1.55 million grant from the National Heart, Lung and Blood Institute. Hopkins officials would not detail her employment or any other involvement in research projects. Workers and students are never solicited directly, they said; instead, fliers advertising a research trial are posted on campus.

The two-page "clinical investigation consent form" that Roche and eight other people signed explained the purpose of the project, its procedures and risks. During their first several half-hour visits, according to the form, they would inhale methacholine, a substance that usually causes mild coughing, shortness of breath and tightness in the chest. It is commonly used in doctors' offices to determine if a patient has asthma.

By a sixth visit, lasting up to four hours, study subjects would receive two substances, methacholine and either hexamethonium or a placebo. Hexamethonium was commonly prescribed during the 1950s for hypertension and to minimize bleeding during surgery. It later was supplanted by other drugs and taken off the market in the 1970s.

"This is capable of stopping some nerves in your airways from functioning for a short period," the consent form explains. It may reduce blood pressure "and make you feel dizzy, especially when you stand up. This effect may last up to three hours. During the visit you receive hexamethonium, you will be connected to a heart monitor and we will measure your blood pressure very often. You will also have an IV . . . placed only as a precaution."

The protocol application submitted to Hopkins' review board last summer by Alkis G. Togias, an associate professor, specified that participants would inhale up to 1,000 mg of the chemical during each of four visits.

Based on published research from the 1980s, Togias wrote, "This dose . . . has been shown to be both safe and efficacious." He explained that a laboratory preparation would make the compound 99.6 percent pure.

Records show that the university is checking whether the chemical or the equipment used for Roche's test became contaminated. Two other volunteers who inhaled hexamethonium experienced little or no adverse reaction.

In the wake of Roche's death, Solbert Permutt, the pulmonary specialist overseeing this project alerted asthma specialists across the country to research from the late '50s linking hexamethonium -- albeit in higher doses over longer time -- to dramatic lung changes leading to individuals' deaths.

And last Tuesday, the director of the National Heart, Lung and Blood Institute suggested that lung investigators temporarily curtail research using the compound.

Hopkins suspended its experiment after Roche fell ill. In his warning letter, Permutt described how her symptoms "rapidly progressed" to acute respiratory distress syndrome, a dangerous medical enigma caused by acute injury to the lung. For three desperate weeks, doctors struggled to save Roche as her failing lungs precipitated a cascade of critical events ending with the shutdown of her kidneys.

"It is with deep regret that I report the death of the subject," Chi Van Dang, Hopkins' vice dean for research, informed the U.S. Office for Human Research Protection on June 6.

Results of Roche's autopsy, conducted at Hopkins, have not been released. In a statement Friday, the university announced that the findings of its special review committee will be sent to federal officials by July 13. Its statement disclosed that "some problems" relating to procedural issues and the review board have been discovered.

The impact of this case ultimately may be felt far beyond Baltimore.

"I worry about many people in clinical trials or other human research hearing about this and panicking," said Ruth Faden, executive director of the Phoebe R. Berman Bioethics Institute at Johns Hopkins. "Biomedical research, to succeed, really does depend on the confidence of the public."



Attention DCI Employees! Don't Forget Your BMAR!

All DCI personnel must be up to date in their BMAR training. BMAR on-line is available at:

<http://160.151.186.9/walterreed/>

Your userid & password are the first four letters of your last name and the last five numbers of your SSN. The BMAR course assignments will appear under "My Course" tab. Click on the course link to take a course.

DCI personnel are reminded to print off their evaluation sheets after they complete the training. These sheets certify that you have completed the course.

The online BMAR takes approximately 2½ - 3 hours to complete, with a test at the end to test your knowledge of the covered material.

BMAR is still given didactically. The next didactic versions of BMAR will be given on 11 & 25 July, 8 & 22 August, and 12 & 26 September in Joel Auditorium.

The following DCI personnel have birthdays in the months of July, August, and September:

Janet Kapur (04 July)
Vicki Miskovsky (13 July)
David Jackson (03 August)
Deborah Kessler (22 August)
Jessie Martin (24 August)
Elena Morris (28 August)
Greg Rose (01 September)
Diarmuid Nicholson (09 September)
Guy Durant (14 September)
Robin Howard (16 September)
SGT Tarvin Smith (29 September)



Washington Post Article (From Page 11)

Federal appropriations for research programs should include separate funding for oversight to protect human participants, the report states. Most government agencies spend only 1 percent to 2 percent of their human research budget on such oversight, and the National Institutes of Health -- the biggest sponsor of such research -- spends less than 0.05 percent.

Sidney M. Wolfe, director of Public Citizen Health Research Group, a consumer organization, said the recommendations did not go far enough to ensure that study participants understand the risks and to prohibit financial conflicts of interest among researchers.

Sen. Bill Frist (R-Tenn.), chairman of the Senate subcommittee on public health, plans to hold a hearing next Wednesday to discuss ways to strengthen

protection of research participants. "This report is an important part of our national response to improving protections for individuals participating in clinical trials," he said in a statement.

The NBAC was established by President Bill Clinton in 1995 to advise the White House on bioethical issues related to human research.

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