

Inquiring Minds

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

October 2001

Next WRAMC Research Course Set for 25 October 2001!

The next WRAMC Research Course, presented by the Department of Clinical Investigation, is scheduled for Thursday, 25 October 2001. This one-day course will be held from approximately 0800 to 1645 in Sanford Auditorium at the Uniformed Services University of the Health Sciences (USUHS) in Bethesda, MD.

The course is open to physicians, nurses, dentists, and other health care personnel who will conduct clinical, animal or laboratory research at WRAMC. The course consists of a full day of training, targeted to new investigators and to those who have not completed a Research Training Course and desire to start a research protocol. Completion of this course is required for all individuals wishing to serve as a Principal Investigator (PI) on a WRAMC research protocol and for Research Coordinators. The course is also highly encouraged for all personnel involved in research to include associate investigators, data analysts, etc.

The objective of this course is to educate WRAMC medical personnel on the ethical issues, current regulations, and design considerations in conducting medical research. Topics for this course include: an overview of DCI and resources available to investigators; elements on obtaining informed consent; commonly-made mistakes in protocol applications and how to avoid them; scientific misconduct; and publication issues. Certificates will be given at the completion of the sessions.

DCI Welcomes Dr. Marcos Rojkind & Dr. Edward Bartlett

The Department of Clinical Investigation is pleased to announce the addition of Marcos Rojkind, MD, PhD and Edward Bartlett, PhD. Dr. Rojkind will serve as Chief, Experimental Pathology, Research Operations Service and Dr. Bartlett will serve as IRB Administrator, Research Review Service.

Dr. Rojkind is a world-renowned scientist and comes to DCI from the Albert Einstein College of Medicine where he was Professor of Medicine and Pathology. His research will focus on alcohol-induced liver fibrosis.

Dr. Bartlett has a Ph.D. in public health and comes to DCI from private practice. His expertise is in risk management and research.

IRB Calendar

The following Institutional Review Board (IRB) meetings will be held in the months of October, November & December 2001:

CLINICAL INVESTIGATION COMMITTEE (CIC):

02 October	13 November
09 October	04 December
06 November	

HUMAN USE COMMITTEE (HUC):

16 October	27 November
23 October	11 December
20 November	

INSTITUTIONAL BIOSAFETY COMMITTEE (IBC):

13 December

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

Registration is available on the DCI web page or by calling Mr. Dan Rosen at (202) 782-6389. The deadline for registration is 12 October. There is no registration fee for active duty military or Walter Reed civilian investigators. Others are welcome to attend for a fee of \$60. For further information on the 25 October Research Course, see the DCI website.

DCI would like to welcome Dr. Rojkind and Dr. Bartlett to WRAMC.

Inside This Issue

IHC & ISH Available at DCI.....	2
Policy Update on Intramural Funding.....	2
October Molecular Biology Course Cancelled.....	3
Guide to Completing Informed Consent Document.....	4
Recently Approved WRAMC Protocols.....	5
Clinical Research Websites of Interest.....	6
Fiscal Year Cutoff Reminder.....	8
Recent WRAMC publications.....	8
Applying Research Ethics.....	10

Immunohistochemistry and *In-Situ* Hybridization Now Available at DCI

by Yvonne Lukes, Research Operations Service, DCI

The Immunology Section of the Department of Clinical Investigation, Research Operations Service now provides state-of-the-art automated **immuno-histochemistry (IHC)** and ***in-situ* hybridization (ISH)** using Ventana NexES/Discovery Medical Systems, to assist researchers in understanding protein and gene expression within cells and tissues. These services can be performed rapidly on a variety of cells or tissue preparations. They are effective for target hybridizations on microarrays, ISH using DNA, RNA or oligonucleotide probes and FISH, as well as for IHC procedures.

In-situ hybridization (ISH), as the name suggests, is a method of localizing and detecting specific nucleic acid sequences in morphologically preserved tissue sections or cell preparations by hybridizing the complementary strand of a nucleotide probe to the sequence of interest.

Immunohistochemical (IHC) analysis is useful for evaluating human tumors, and bacterial or viral infections using specific antibodies directed against proteins present in the tissue.

The Immunology Section is committed to providing the highest quality assistance in helping the researcher during protocol development. The average cost for IHC is approximately \$12 per slide, and for ISH approximately \$30 per slide. The cost will vary based on antibody selection, probe design and detection method. There is only a nominal cost for sectioning paraffin blocks.

For further information, contact Ms. Yvonne Lukes at (202) 782-4501 or by e-mail at Yvonne.Lukes@na.amedd.army.mil.

Policy Update on Intramural Funding of WRAMC Protocols

The Department of Clinical Investigation would like to remind investigators of the policy regarding intramural funding of WRAMC protocols. Funding is approved by the CIC. Intramural funding is limited to \$7,500 per year for 2 years for a maximum of \$15,000 and is subject to the availability of federal funds at the time of request. As always, this funding is limited to consumable supplies and TDY travel. This policy has been amended to allow for the purchase of small equipment as follows:

1) The investigator is expected to obtain the equipment through his/her Department or through collaboration with other Departments. The investigator will provide an impact statement signed by the Department/Service Chief in question stating that the Service can or cannot support the research project by providing the equipment. If Department funds are not available, the investigator is urged to pursue extramural funding (i.e. grants, CRDAs, etc). Proof of efforts must accompany the protocol when it is presented to the CIC.

2) The necessity for equipment should be addressed in the protocol when presented to the CIC. Funds approved for supplies may be converted to the purchase of equipment. However, information required in paragraphs 1, 3 and 4 will be presented to the Research Review for administrative approval. Expenditures are restricted to the amount approved by the CIC per fiscal year. For example, if the PI is approved for \$7,500 for FY02 and he/she purchases equipment costing \$7,500, he/she forfeits access to any additional funds for supply and travel.

3) Equipment that is donated by a non-WRAMC source will be considered a gift and must follow the prescribed regulatory procedures for accepting gifts (see template on DCI web site).

4) The investigator will provide evidence that the equipment in question is essential for the successful accomplishment of the research/experiment (i.e. without this equipment, the project will not be performed).

5) The investigator will provide the CIC with a disposition plan explaining what will be done with the equipment once the protocol is complete. At DCI's discretion, any bench laboratory equipment not otherwise used for clinical practice will revert to DCI Research Laboratories at the completion of the protocol.

6) The investigator will itemize all consumable supplies as well as other budget line items listed under Paragraph 14 ("FUNDING IMPLICATIONS") of the protocol application. Please note that this policy has been in effect for several years, and the only change is with the purchase of small equipment (computers are excluded). This update will be effective after 1 October 2001. Funds approved by DCI are only for consumable supplies, travel (\$1000 maximum for travel), and now small equipment.

For further information, contact Ms. Daisy Word, Research Administration, at (202) 782-6389/7859 or fax (202) 782-3881.



FDA Faults Clinical Research at Hopkins

By Susan Levine; A recent article reprinted from *The Washington Post*, 8 September 2001

The U.S. Food and Drug Administration has found a systemic breakdown in communication and operation of the Johns Hopkins University review boards charged with oversight of clinical trials involving human subjects, according to documents released yesterday.

Agency inspectors said there was no evidence that board members' questions about research applications were ever sent to the researchers involved. It also appeared that board members with conflicts of interest in applications being reviewed did not always abstain from voting on those proposals.

"There was a systemic problem in the whole oversight scheme" said David Lepay, the FDA's senior adviser for clinical science. "We had significant concerns."

The FDA documents reflect in narrower scope the malfunction that government regulators have identified throughout the university's medical research program after a healthy young volunteer's death during an asthma study in June. In late July, that triggered a brief suspension of all of Hopkins's federally supported medical research with human participants -- 2,800 clinical trials involving more than \$300million.

The FDA and the Office for Human Research Protections are conducting inquiries into 24-year-old Ellen Roche's death. Both are part of the federal Department of Health and Human Services. The FDA's latest findings center on two institutional review boards, including the one that approved the protocol in which Roche enrolled at Hopkins's Bayview Medical Center.

Because the boards' actions were documented so poorly, the extent of the problem might not be clear even in hindsight, Lepay said. Even with meeting minutes and audiotape, inspectors could not reconstruct what happened during those boards' deliberations and resolve discrepancies, he said.

Much of the time, applications were reviewed only by individual members or subcommittees, inspectors found. They were not discussed and considered by the review boards as a whole, and dozens of applications might have been approved by a one-time vote.

Unlike the Office for Human Research Protections, which clamped harsh restrictions on Hopkins scientists even after lifting its four-day suspension, the FDA has not taken action against the university.

A final report by FDA inspectors will not be sent to agency headquarters for several weeks. Though punitive measures could be imposed, they seem unlikely given Lepay's praise yesterday afternoon for the changes university officials are implementing. In contrast to Hopkins's early denial of problems, "we do feel that Hopkins is now taking this very seriously," he said.

In a statement yesterday evening, Chi Dang, a vice dean at the university's medical school, said the FDA's findings provide guidance "to further improve our processes for conducting research involving human volunteers." The issues documented are those "that Hopkins has been reviewing and addressing throughout the summer."

Hopkins has already moved to double the number of review boards at its medical centers; strengthen training for board members and faculty in the regulations governing clinical trials; and implement a meeting review process to require full discussion and documentation by review boards.

Roche died of acute respiratory distress less than a month after inhaling hexamethonium. The chemical was central to a clinical trial focused on why the airways of healthy people such as Roche remain open after exposure to allergens and other irritants.

After Roche's death, Hopkins was buffeted by scathing criticism of research at its hospitals and affiliates, as well as work by a faculty member as far afield as India.

In late August, the Maryland Court of Appeals allowed lawsuits to proceed against the Kennedy Krieger Institute over a lead paint study in low-income Baltimore neighborhoods. The judges said participants in the study, which was overseen by a Hopkins board, were purposely misled about the dangers involved. After the court ruling, the Office for Human Research Protections opened a second Hopkins investigation.

Molecular Biology Course for October 2001 Cancelled

The Department of Clinical Investigation would like to announce that the Molecular Biology Course for October 2001 has been cancelled.

Unfortunately due to the power outage on the 27th of August to the 31st, the DCI laboratories suffered major set back as most of the reagents are no longer suitable for lab experiments. Also some of the laboratory's instruments require re-calibration by the manufacturers. Accordingly, the Department of Clinical Investigation is regrettably

forced to cancel the molecular biology course for October 2001.

The next Molecular Biology Course will be held in March of 2002. Further information and registration will be available on the DCI website starting January 2002.

Thank you very much for your interest in this course and DCI hopes to see you in March as a participant.

Step-By-Step Guide to Completing the Informed Consent Document

Congratulations! Your research study has been approved and you're probably eager to enroll subjects. The following information is intended to provide guidance on completing the WRAMC Informed Consent document (DA Form 5303-R). A sample consent form (ConsentForm.doc) can be downloaded on the DCI website for reference.

Informed consent for research is a process that involves a dialogue between a potential research participant and the Principal Investigator (PI) or a knowledgeable designee. This dialogue consists of an explanation of the study, potential risks and benefits, confidentiality and security of data and/or specimens, compensation, steps taken to protect the participant from risk/harm, and the participant's legal rights. The consent form serves as documentation that a dialogue between the study participant and the PI occurred and is a comprehensive summary of the information shared. Further, the consent form is an important document-verifying enrollment into a study and thus must be on file in each participant's research record as appropriate.

Depending on the circumstance, improperly completed and/or a missing consent form may exclude a participant from a study and data or samples may have to be discarded. Please note that the consent cannot be obtained by phone, mail, fax, or other electronic means.

First, some ground rules:

1. The consent form should be completed in ink, not pencil.
2. Make sure the most up-to-date version of the WRAMC approved consent form is used. The approved consent form is stamped by DCI and has the approval date and the protocol Work Unit # written in. If a consent form is revised (e.g. based on an addendum or serious adverse event), it must be re-approved. The approved, revised consent form will be re-stamped by DCI, with updated dates written in the appropriate sections. Previous versions of the consent form must not be used.
3. Surrogate Consent procedure must be approved by the HUC before it can be used. If a Surrogate Consent is being used to consent adults who are incapable of giving consent, the person acting as the surrogate must have legal authority to act on behalf of the patient. Such legal authority is evidenced by a power of attorney or court appointment as a guardian that authorizes the surrogate to approve participation in health care issues. It is not acceptable to ask the person who is accompanying a potential study subject, no matter what the relationship is, to provide consent without first establishing the legal authority of that person to act.

The following sections (4-7) provide step-by-step instructions regarding the information to fill in on the consent form:

4. Part A (1) VOLUNTEER AFFIDAVIT If the study participant is an adult (age \geq 18 years), he/she prints:

- (a) his/her name on the line following "I,"
- (b) his/her SSN on the line following "SSN"
- (c) his/her age in years on the line following "having attained full capacity to consent and having attained my"
- (d) the word "myself" on the line following "do hereby volunteer/give consent as legal representative for"

If the study participant is a minor (age < 18 years), the parent or legal guardian prints the following in Part A(1):

- (a) the name of the parent or legal guardian completing the consent form on the line following "I,"
- (b) the SSN of the parent or legal guardian on the line following "SSN"
- (c) the age in years of the parent or legal guardian on the line following "having attained full capacity to consent and having attained my"
- (d) the name of the minor who will participate in the research on the line following "do hereby volunteer/give consent as legal representative for"

5. Part A (2) ASSENT VOLUNTEER AFFIDAVIT (MINOR CHILD): If the study is approved only for adults, this section will be stamped "NOT APPLICABLE" by DCI and should be left blank.

If the study is open to minors, the minor may complete this section if he/she is of an age (usually >13 yrs) and has the cognitive capacity where assent is appropriate. For this section, the minor prints:

- (a) his/her name on the line following "I,"
- (b) his/her SSN on the line following "SSN"
- (c) his/her age in years on the line following "having attained full capacity to consent and having attained my"
- (d) the word "myself" on the line following "do hereby volunteer for"

6. Pg 2 of the Consent Form (DA Form 5303-R): The consenting subject should check and initial the box "I do" or "I do not" regarding his/her consent for the inclusion of the consent form in his/her outpatient medical record.

7. Signature blanks found on page 2 and all subsequent pages of the Consent Form are completed as follows:

- (a) SIGNATURE OF VOLUNTEER is completed by the consenting adult or assenting minor who will be participating in the research; this block may be initialed on subsequent pages.

(Continued on page 11)

Surgeon 'made up research results'

By Adam Fresco; A recent article reprinted from *The Times*, 28 June 2001

A PROFESSOR involved in vital research into a new drug for the treatment of blood circulation disease made up results from the study using the name of a dead patient, an inquiry was told yesterday.

Dr Peter Longthorne, a monitor for Schering Health Care Limited, told the General Medical Council's professional conduct committee that the case of the deceased patient confirmed its fears that data supplied from Ralph Kester, 65, a vascular surgeon at the St James's University Hospital in Leeds, was fraudulent and compromised the safety of the three-year trial.

Dr Longthorne told the committee there had been escalating concern about the validity of the results

emanating from the study. It emerged that patient TP, whom the professor had recorded as having visited the laboratory on six occasions between March 7 and August 8, 1994, had died on February 20 of that year, it was said.

Cross-examined by Mr James Turner QC, barrister for the professor, Dr Longthorne denied demanding that "heads must roll" when he met Professor Kester and in reporting him to the GMC, Scherings had been merely trying to preserve the integrity of the internationally important drugs trials, he added.

Professor Kester, of Roundhay, Leeds, denies serious professional misconduct. The hearing continues.

Recently Approved Protocols at WRAMC

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

Department of Clinical Investigation

01-92006E: Effect of Age on Disease Progression in Chronic Hepatitis C
PI: COL Maria H. Sjogren, MC 27 June 2001

01-92004: Interleukin-6 and Tumor Necrosis Factor-Alpha Role In Alcoholic Liver Cirrhosis
PI: Marcos Rojkind, M.D. 11 September 2001

Department of Medicine

Endocrinology Service

01-13003: The Avandia Worldwide Awareness Registry (AWARe): Comparison of Avandia and Actos in "Real World" Medical Practice
PI: COL Robert A. Vigersky, MC 23 August 2001

01-13004: Pilot Study: Recombinant TSH Stimulation of Radioactive Iodine Uptake in Hyperthyroidism
PI: MAJ Victor J. Bernet, MC 21 September 2001

01-13005: Determination of Thyroid Nodule Malignancy with 18F-FDG Coincidence Imaging and Tc-99m Depreotide Scintigraphy
PI: MAJ Roy W. Langley, MC 6 September 2001

Gastroenterology Service

01-14001: Association of Helicobacter pylori Infection with Coronary Heart Disease Detected by Electron Beam CT
PI: CPT Roger D. Polish, MC 26 July 2001

01-14002: An Efficacy and Safety Study of Intravenous

Pantoprazole in the Prevention of Recurrent Peptic Ulcer Bleeding After Successful Hemostasis (Sponsored Study by Wyeth-Ayerst Research)
PI: CPT Peter M. Dunaway, MC 9 July 2001

01-14003: Effect of Complete Intraesophageal Acid Ablation Upon Cellular Markers of Proliferation, Differentiation, and Apoptosis in Long-Segment Barrett's Esophagus
PI: CPT Peter M. Dunaway, MC 12 July 2001

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01-14001: Association of Helicobacter pylori Infection with Coronary Heart Disease Detected by Electron Beam CT
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PI: CPT Peter M. Dunaway, MC 9 July 2001

01-14003: Effect of Complete Intraesophageal Acid Ablation Upon Cellular Markers of Proliferation, Differentiation, and Apoptosis in Long-Segment Barrett's Esophagus
PI: CPT Peter M. Dunaway, MC 12 July 2001

General Medicine Service

01-10008E: Can medical students accurately self-assess using descriptive, standard vocabulary?
PI: LTC Paul A. Hemmer, USAF, MC 20 June 2001

(Continued on page 7)

Gene-Based AIDS Test Hits Market

By Lauran Neergaard; A recent article reprinted from *The Washington Post*, 27 September 2001

WASHINGTON -The government has approved the first gene-based test to tell quickly whether an HIV patient's virus is mutating to make a particular drug therapy fail, important to know so the person can switch AIDS medications.

Visible Genetics Inc.'s Trugene is one of the most complex genetic test systems to clear the Food and Drug Administration. FDA officials described it on Thursday as an important tool in helping doctors select the medications most likely to fight each patient's HIV.

The AIDS virus naturally grows resistant to medications through evolution. Experts estimate 60 percent of patients have a virus that is resistant to at least one drug.

Until now, most HIV patients have kept tabs on how well their treatment is working by undergoing tests to see how much of the AIDS virus is in the bloodstream. A spike can mean that HIV is growing resistant to one or more drugs, and it's time to try to a different medicine.

But to specifically check a patient's blood for genetic mutations that mean one of the 15 anti-AIDS drugs won't work has required additional laboratory testing not routinely available.

With Trugene, a doctor sends a patient's blood sample to one of 130 labs where Visible Genetics so far has trained personnel. A computer decodes the HIV genes in that blood, identifying all the genetic mutations present. Then a

software program matches those mutations to a list of more than 70 mutations currently linked to resistance in specific drugs.

The lab mails the doctor a report listing the likelihood that each AIDS drug would work according to the viral mutations currently coursing through that patient's blood, said Visible Genetics president Richard Daly.

The test is 98 percent accurate, said FDA medical reviewer Dr. Andrew Dayton. Better, as scientists discover additional mutations that cause drug resistance a rapidly changing field the new information can be added to the software promptly so that the test remains useful in real-world practice, he said.

The test takes three days to complete and will cost between \$300 and \$500 per patient, Daly said. "It's a major step forward in HIV treatment," said Dr. R. Scott Hitt, president of the American Academy of HIV Medicine. But "it is only one piece of the puzzle" in picking the best therapy, Hitt cautioned, urging patients to seek treatment from HIV specialists who can properly interpret test results.

FDA researchers set up the computer gene sequencer in an agency lab to understand the novel test fully and approved its sale late Wednesday after a year of review, record review time for such a complex new science, Daly said. Testing became available Thursday.

Clinical Research Websites of Interest

Association for Assessment and Accreditation of Laboratory Animal Care (www.aaalac.org): AAALAC is a private nonprofit organization that promotes the humane treatment of animals in science through a voluntary accreditation program. This site contains information on the AAALAC accreditation program, animal care & use resources, international resources, plus an online newsletter.

Title 45 Code of Federal Regulations (www.access.gpo.gov/cgi-bin/cfrassemble.cgi?title=199945): Regulations governing the proper conduct of clinical research and the makeup of institutional review boards (IRB) pertaining to federally funded research. Elements of informed consent documents are also discussed

The National Reference Center for Bioethics Literature (www.georgetown.edu/research/nrcbl): The NRCBL is a specialized collection of books, journals, newspaper articles, regulations, codes, government publications, and other relevant documents concerned with issues in biomedical and professional ethics. The library holdings represent the world's largest collection related to ethical issues in medicine and biomedical research.

Biowire (www.biowire.com): This site provides free, easy-to-use analytical tools and scientist-authored reviews of high-end, experiment-specific research products, such as enzymes, antibodies and reagent kits. It invites scientists to write a review on specific products and protocols, which are published on the website, allowing readers to benefit from the experience of other researchers.

LabVelocity (www.labvelocity.com): This is a free resource for biotechnology and life science with on-line listing of techniques and resources with links to many related sites.

Title 21 Code of Federal Regulations (www.access.gpo.gov/cgi-bin/cfrassemble.cgi?title=199921): Federal regulations governing the proper conduct of clinical research and the makeup of IRB. Elements of informed consent documents are also discussed.

BioMedNet (www.bmn.com): This site is for biological medical researchers and allows one to search for biomedical laboratory supplies, on-line journals, scientific news, and jobs.

Recently Approved Protocols at WRAMC (cont. from page 5)

Hematology-Oncology Service

01-16004: Expression of Human Papilloma Virus in Second Primary Malignancies Associated with Chronic Lymphocytic Leukemia
PI: CPT Joseph M. Flynn, MC 18 September 2001

Infectious Disease Service

01-19000E: Comparison of Screening Tests for Latent Syphilis
PI: LTC Glenn Wortmann, MC 6 July 2001

Nephrology Service

01-87000E: Physician to Physician Electronic Consultation: The WRAMC Ask a Doc Project
PI: LTC Kevin C. Abbott, MC 19 July 2001

Pulmonary & Critical Care Service

01-17012E: Retrospective outcome analysis of abdominal plain film use for patients with gastrointestinal bleeding admitted to a medical intensive care unit
PI: CPT Allan H. Andrews, MC 27 June 2001

01-17013E: Serum lysozyme in sarcoidosis
PI: MAJ Andrew Shorr, MC 6 September 2001

Rheumatology Service

01-37001: Visconsupplementation in the Treatment of Chondromalacia Patellae
PI: Jonathan D. Roebuck, MC 16 August 2001

Department of Neurology

01-71002: Investigation of the Administration of Baclofen Injection for the Management of Spasticity Associated with Stroke, Medtronic Protocol #D98-072
PI: LTC Kevin Cannard, MC 10 September 2001

01-71003: Genes for X-linked Torsion Dystonia-Parkinsonism in the U.S. Veterans of Panay Filipinos
PI: COL Bahman Jabbari, MC 17 July 2001

Department of Nursing

01-75004: Job Satisfaction Among Army Nurses
PI: LTC Patricia A. Patrician, AN 17 September 2001

01-75005: Medication Error Reporting and the Work Environment in a Military Setting
PI: LTC Patricia A. Patrician, AN 7 September 2001

01-75006: Research Utilization of Registered Nurses in U.S. Army Hospitals
PI: LTC Laura R. Brosch, AN 19 September 2001

01-75007: Army Hospitals: Work Environment, Quality of Care and Intent to Leave
PI: LTC Patricia A. Patrician, AN 10 September 2001

01-75008: Examining the Weight Management and Exercise Behaviors Among Active Duty Nursing Personnel in Maintaining Compliance with the Army's Weight Control Standards
PI: LTC Patricia A. Patrician, AN 7 September 2001

01-75009: Patient Handling Study
PI: LTC Laura R. Brosch, AN 17 September 2001

Department of Obstetrics and Gynecology

01-44018E: A Review of Granulosa Cell Tumors Of The Ovary And Development Of Breast Or Endometrial Cancer
PI: LTC G. Scott Rose, MC 13 August 2001

Department of Pathology

01-48004: Extending the Expiration Date of Thawed Fresh Frozen Plasma and Plasma Frozen Within 24 Hours of Collection From 24 Hours to 48 Hours
PI: William L. Turcan 19 September 2001

Department of Pediatrics

01-64009E: The Availability of In-School Resources for Children with Diabetes While at School
PI: COL Patricia A. Powers, MC 5 September 2001

01-65001a: The Role of Caveolin-1 in Thyroid Carcinoma
PI: LTC Patricia A. Powers, MC 20 June 2001

01-66002: ANBL00B1: Neuroblastoma Biology Studies
PI: LTC Glenn E. Edwards, MC 20 July 2001

Department of Pharmacy

01-36001: Perceptions of Pain Control: Oncology Patients and Their Physicians
PI: MAJ Matthew R. Rutledge, MS 18 July 2001

Department of Psychology

01-73002E: Does Depression Affect Performance on the Portland Digit Recognition Test?
PI: Jill McConnell, Ph.D. 2 August 2001

Department of Radiology

01-47003: Field Trial of Mobile Digital Telemammography - Phase I (Installatin and Testing)
PI: COL Michael P. Brazaitis, MC 16 July 2001

(Continued on page 11)

Fiscal Year Cutoff Reminder

Investigators are reminded that protocols funded by DCI have **year-specific use-or-lose restrictions**. DCI operates under the same budget limitations as other Clinical Departments at WRAMC. We lose all funds not obligated by 30 September of each fiscal year. For example, protocols that are approved for FY2001 monies must be obligated by 30 September 2001. Funds not utilized in one fiscal year will not automatically roll over to the next fiscal year. The year(s) for which funds are approved are indicated in the approval letter from Research Review to the PI.

To insure obligation of supply funds, requests should be submitted to DCI 6 weeks in advance of 30 September (by mid-August). If the cost of supplies or equipment is \$2,500 or more, your request should be submitted to DCI no later than 3 months prior to end of the fiscal year (1 July). DCI will prepare and process a Purchase Request (DA3953) through the Department of Contracting.

It is important for the investigator to closely assess the fiscal year(s) in which he/she expects to utilize intramural funds. For example, if the PI receives the approval letter in July 2001, he/she will have 2 months remaining in FY01 to use those funds. The investigator should consider requesting funds in the following fiscal year (October 2002). If the study must be implemented in the current fiscal year, it is recommended that the investigator request

only those funds he/she reasonably expects to use by 30 September and to allocate the majority of dollars in the following fiscal year when the greater amount of research supplies are expected to be consumed. If greater than \$7,500 per fiscal year, maximum \$15,000 for 2 years, is needed to complete the study, the PI may want to consider extramural funding (CRDA or grant). Remember, however, that it is DCI policy not to grant intramural funding when extramural funds have been secured (i.e. the PI should not count on combining DCI intramural funds with extramural funds).

Investigators whose funds have expired and are still in need of financial support should submit an addendum to the CIC. A detailed explanation will be required on why the timelines indicated in the approved protocol were not followed and what progress has been made with funds already spent. As customary, addendums should be submitted through the Research Review Service.

All intramural funds are subject to availability. We often are able to fund all requests, however, in FY01 the demand was greater than allocation. TDY requests are processed on a first come-first served basis, subject to availability of funds. The later in the fiscal year the request is made, the greater the chances that travel funds are depleted.

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.

Taylor KF, Bojescul JA, Howard RS, Mizel MS, McHale KA. **Measurement of isolated subtalar range of motion: a cadaver study.** *Foot Ankle Int* 2001 May;22(5):426-32.

Turiansky GW, Levin SW. **Bluish patches on the ears and axillae with dark urine: ochronosis and alkaptonuria.** *Int J Dermatol.* 2001 May;40(5):333-5.

Mckiernan SP, DiFazio MP. **Index of suspicion. Case 3. Diagnosis: Infantile pseudotumor cerebri.** *Pediatr Rev* 2001 Jun;22(6):211-5.

Netzer NC, Kristo D, Steinle H, Lehmann M, Strohl KP. **REM sleep and catecholamine excretion: a study in elite athletes.** *Eur J Appl Physiol* 2001 Jun;84(6):521-6.

Burch HB, Solomon BL, Cooper DS, Ferguson P, Walpert N, Howard R. **The effect of antithyroid drug**

pretreatment on acute changes in thyroid hormone levels after (131)iodine ablation for graves' disease. *J Clin Endocrinol Metab.* 2001 Jul;86(7):3016-21.

Owens BD, Murphy KP, Kuklo TR. **Arthroscopic release for lateral epicondylitis.** *Arthroscopy* 2001 Jul;17(6):582-7.

Shorr AF, Torrington KG, Hnatiuk OW. **Endobronchial biopsy for sarcoidosis : a prospective study.** *Chest.* 2001 Jul;120(1):109-14.

Barekman CL, Aguilera NS, Abbondanzo SL. **Low-grade B-cell lymphoma with coexpression of both CD5 and CD10. A report of 3 cases.** *Arch Pathol Lab Med.* 2001 Jul;125(7):951-3.

(Norton SA. **On first looking into Pernkopf's atlas (part 2).** *Arch Dermatol.* 2001 Jul;137(7):867-8.

Aronson NE, Cheney C, Rholl V, Burris D, Hadro N. **Biliary Giardiasis in a Patient With Human Immunodeficiency Virus.** *J Clin Gastroenterol.* 2001 Aug;33(2):167-170.

(Continued on page 10)

The Necessary Risks of Medical Research

By David A. Shaywitz & Dennis A. Ausiello

A recent article reprinted from *The New York Times*, 29 July 2001

BOSTON-Fatal Disease Cured by New Therapy" it's the headline of researchers' dreams.

As modern biological science generates an ever-rising flood of promising discoveries, from the potential of embryonic stem cells to the nature of the human genome, the idea of one day being able to cure cancer, Parkinson's disease and other terrible illnesses no longer seems so fanciful. In fact, there is often an exhilarating sense these days that a cure for something or for everything is near.

It is not surprising, therefore, that following the recent deaths of Jesse Gelsinger and Ellen Roche in government-sponsored clinical trials at two major American universities, some have questioned why, in the era of transgenic mice and computer modeling of molecules, we still experiment on people. As one patient recently asked, "Why don't they just give us the good stuff?"

The answer is that it is terribly difficult to figure out what the good stuff is. And while the lab can identify promising new therapies, proof that they work can only come from clinical research, in which real people are carefully administered medicine and the results are meticulously documented. More often than not, even the most obvious and intuitive of treatments provide wholly unexpected results.

A classic example is the group of drugs called beta-blockers, medicines known to decrease the strength of heart muscle contraction. For years, they were not given to patients with weak hearts, until clinical trials demonstrated they actually helped patients live longer.

Or consider the use of bone marrow transplants to treat patients with advanced breast cancer. In part because other treatments were often only minimally effective, transplant seemed like a promising alternative. So promising, in fact, that it was difficult to set up clinical trials, as no one wanted to be randomly assigned to the non-transplant group. It took a decade until several studies concluded transplant was no better than conventional therapy.

Equally revealing are the raw statistics of new drug discovery: for every 5,000 compounds evaluated for treatment, only five will make it to clinical trials, of which just one will make it to market. How can the best scientists with the best labs money can buy be wrong 4,999 out of 5,000 times?

Ever since the discovery of DNA's structure in 1953, it has seemed only a matter of a few years before biology became a predictable process for understanding diseases at the most fundamental level, and then designing cures for them.

It was in this hope that special programs were established at the National Institutes for Health and other research

institutions to encourage doctors to pursue this new science. As a result, many of the country's most prominent doctors including J. Michael Bishop, chancellor of the University of California at San Francisco, and Harold Varmus, president of Memorial Sloan-Kettering Cancer Center made their reputations through elegant laboratory investigation. Dr. Bishop and Dr. Varmus received the Nobel Prize for their discoveries.

Recently, however, doctors have begun to ask why the cures that molecular biology promised have not appeared, and to wonder if the laboratory is the best place to pursue them. Patients continue to suffer from cancer and heart disease, despite national crusades against both. And treatments for molecular diseases like sickle cell anemia and cystic fibrosis have evolved little, even though the genetic defects have been exquisitely defined.

The problem is that most biological systems remain too complex for science to predict how they will react to theoretically valuable treatments. And for that reason, the work that has actually changed how doctors treat the sick has come mostly from those researchers who focus on patients, not genes. For example, landmark population-based studies like the British Doctors' Study, the Framingham Heart Study and the Nurses' Health Study revealed the risks of smoking, hypertension and high cholesterol, and encouraged treating these problems aggressively.

Overall, it is becoming increasingly apparent that what really makes a difference for patients is not a doctor's detailed knowledge of the biology, but rather, his or her familiarity with the existing clinical literature, and particularly with current clinical trials. The best evidence of this is that the doctors other doctors turn to for care are usually not medical scientists, but scholarly clinicians fluent with the best data. Some have even had a role in generating it.

This is not to say that laboratory science has been neglected. Laboratory scientists are playing increasingly important roles in clinical research for example, by suggesting disease genes for which patients might be screened. This year alone, such approaches have led to discovery of genes responsible for some forms of liver disease, lung disease, and diabetes in infants.

In addition, while drug discovery in the past relied heavily on trial and error, the medicines of the future will result from a careful study of the underlying biology.

(Continued on page 12)

Applying Research Ethics

Federal regulations give us the three basic protections of human subjects involved in research: Review by an Institutional Review Board, informed consent and institutional assurances. Institutional assurances are a mechanism to apply the federal regulations to all human subject research. When institutions sign assurances, they pledge to apply the Health and Human Services regulations to all research in the institution regardless of the source of funding.

So how do we decide whether or not research is ethical? From the principle of respect for persons we need to conduct initial and continuing informed consent. We need to evaluate whether the research allows subjects to withdraw from the research and maintains the welfare of each subject. From the principle of beneficence we need to evaluate the social and scientific value of the research, the scientific validity of the research, and determine whether the research has a favorable risk benefit ratio. From the principle of justice we need to evaluate whether there is fair subject selection.

We also need to evaluate the inclusion and exclusion criteria and the methods of recruitment. The glue that holds this evaluation together is the independent review by the IRB. The IRB will ask the following questions relevant to the ethical principles described in the *Belmont Report*:

RESPECT FOR PERSONS

-Does the consent process maximize autonomy for the

human subject?

-Does the protocol maximize autonomy?

-What additional protections have been put in place for vulnerable populations?

-Does this study maximally protect subject privacy?

BENEFICENCE

-Is the research design adequate? Can it be improved?

-What are the risks? Have they been minimized?

-What are the benefits? Have they been maximized?

JUSTICE

-Does recruitment for the study target the population that will benefit from the research?

-Does the recruitment unfairly target a population?

-Are the inclusion/exclusion criteria fair?

The principles of ethical research are discussed in the required research course entitled, "WRAMC DCI Research Course" and the optional DCI workshop entitled, "Research in Clinical Medicine: Basic Concepts Approach." For more information on these courses, please contact DCI at (202)782-6389.

*This article was taken in part from UNIT 1. HISTORY and ETHICAL PRINCIPLES of the Collaborative IRB Training Initiative (CITI) Human Subjects Research Education Module (www.ci4.miami.edu/courses/irbtraining) by Elizabeth Bankert, MA (Director, Dartmouth IRB; Dartmouth College) and Jeff Cooper, MD (Associate Medical Director and IRB Chair; Albany Medical Center).

Recent WRAMC publications (cont. from page 8)

Netzer N, Eliasson AH, Netzer C, Kristo DA. **Overnight pulse oximetry for sleep-disordered breathing in adults : a review.** *Chest.* 2001 Aug;120(2):625-33.

Warden DL, Bleiberg J, Cameron KL, Ecklund J, Walter J, Sparling MB, Reeves D, Reynolds KY, Arciero R. **Persistent prolongation of simple reaction time in sports concussion.** *Neurology.* 2001 Aug 14;57(3):524-6.

Ales N, Flynn J, Byrd JC. **Novel Presentation of Acute Myelogenous Leukemia as Symptomatic Galactorrhea.** *Ann Intern Med.* 2001 Aug 21;135(4):303-304.

Walden BE, Grant KW, Cord MT. **Effects of amplification and speechreading on consonant recognition by persons with impaired hearing.** *Ear Hear.* 2001 Aug;22(4):333-41.

Abbott KC, Agodoa LY. **Etiology of bacterial septicemia in chronic dialysis patients in the United States.** *Clin Nephrol.* 2001 Aug;56(2):124-31.

Jones A. **An examination of the MMPI-2 Wiener-Harmon Subtle subscales for D and Hy: implications for parent scale and neurotic triad interpretation.** *J Pers Assess.* 2001 Aug;77(1):105-21.

Moses F. **Sunflower seed rectal bezoar in an adult.** *Gastrointest Endosc.* 2001 Sep;54(3):420-1.

Shorr AF, Torrington KG, Hnatiuk OW. **Endobronchial involvement and airway hyperreactivity in patients with sarcoidosis.** *Chest* 2001 Sep;120(3):881-886.

Abbott KC, Oglesby RJ, Hypolite IO, Kirk AD, Ko CW, Welch PG, Agodoa LY, Duncan WE. **Hospitalizations for fractures after renal transplantation in the united states.** *Ann Epidemiol.* 2001 Oct;11(7):450-7.

Kristo DA, Eliasson AH, Poropatich RK, Netzer CM, Bradley JP, Loube DI, Netzer NC. **Telemedicine in the sleep laboratory: feasibility and economic advantages of polysomnograms transferred online.** *Telemed J E Health.* 2001 Fall;7(3):219-24.

Guide to Completing the Informed Consent Document (cont. from page 4)

(b) DATE is completed by the consenting adult or parent/legal guardian. Every page (from page 2 on) must be dated.

(c) SIGNATURE OF LEGAL GUARDIAN (If volunteer is a minor) is signed by the parent or legal guardian who consents to include their legal minor in the research; this block may be initialed on subsequent pages.

(d) PERMANENT ADDRESS OF VOLUNTEER is printed on page 2 by the consenting adult or parent/legal guardian; this block may be left blank on subsequent pages.

(e) TYPED NAME OF WITNESS is typed or printed on page 2 by someone who has witnessed the volunteer or parent/legal guardian sign the consent form. The purpose

of the witness is to confirm the authenticity of the signature, not to confirm the volunteer's or the parent's/legal guardian's understanding of the research. The witness may be a member of the study team other than the principal investigator, a member the clinic staff, or a family member or friend of the research participant. The witness name must be printed on page 2, but on subsequent pages this item may be left blank.

(f) SIGNATURE OF WITNESS and DATE are completed by the witness on page 2; this block may be left blank on subsequent pages.

Recently Approved Protocols at WRAMC (cont. from page 7)

01-45002: Preoperative Evaluation of Breast Carcinoma Utilizing Tc99m-Depreotide
PI: CPT Jaime Montilla-Soler, MC 7 August 2001

01-45003: An Open-Label, Multicenter, Phase 3 Trial Evaluating Ventricular Function as Assessed by Left-Ventricular Ejection Fraction and Wall Motion using echnetium-99m Tetrofosmin Gated SPECT Imaging
PI: MAJ Robert S. Bridwell, MC 10 September 2001

Department of Surgery

Army Audiology & Speech Center

01-2570a: Spread of Masking by Harmonic Complexes in Normal-Hearing and Hearing-Impaired Listeners
PI: Marjorie R. Leek, Ph.D, DAC 5 July 2001

Orthopaedic Surgery Service

01-24013E: Development of a Cosmesis Evaluation Tool (Questionnaire) for Idiopathic Scoliosis
PI: LTC(P) David Polly, MC 28 June 2001

01-24014E: Functional Assessment of Adjustment Disorder in Combat Stress Control
PI: Anne Pas Colburn, EdD, DAC 19 July 2001

01-24015E: Congenital Hemivertebrae and Occult Intraspinous Anomalies: The Role of Routine Magnetic Resonance Imaging
PI: MAJ Kenneth F. Taylor, MC 13 August 2001

01-24006: Adolescent Idiopathic Scoliosis Single Overhang Curve
PI: LTC David W. Polly, MC 24 September 2001

01-24007: A Multi-Center Study to Evaluate the Safety and Efficacy of DePuy AcroMed Titanium Surgical Mesh and MOSS-Miami Spinal System Pedicle Screws
PI: LTC David W. Polly, MC 26 July 2001

01-24008: Functional and Clinical Outcome Following Arthroscopically Assisted Anterior and Posterior Cruciate Ligament Reconstruction in a High-Demand Patient Population
PI: MAJ Kenneth F. Taylor, MC 4 September 2001

Urology Service

01-28001: SWOG: S0000 -Selenium and Vitamin E Cancer Prevention Trial (SELECT), Phase III Study
PI: LTC Judd W. Moul, MC 26 July 2001

01-28003: AMS002.2: Evaluation of the Safety and Tolerability of Transurethral Dehydrated Alcohol Injection for the Treatment of Benign Prostatic Hyperplasia
PI: COL David G. McLeod, MC 23 July 2001

01-2857-98b: Study of CPDR Multicenter Database to Develop Nomograms on % of Positive Biopsy Cores, Gleason Sum, and Pre-Biopsy PSA to Predict Pathologic Stage in Radical Prostatectomy Patients
PI: LTC Judd W. Moul, MC 24 August 2001

Landstuhl Regional Medical Center

01-80002E: Nerve Fiber Layer Analysis Teleconsultation
PI: LTC Todd D. Hess, MC 6 September 2001

USA DENCOS-Fort Sam Houston

01-90000E: Dental Mobilization of the 29th Infantry Division, Virginia National Guard
PI: MAJ Jeffrey Chaffin, DC 5 September 2001



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 your **My Course** tab. To take a course, simply click on the course link. To receive credit for a course you must go through the entire course and then take the test at the end. As you complete each course, the course link will be removed from the **My Course** link and added to the **My Transcript** link.

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 10 & 24 October, 14 & 28 November and 5 & 12 December in Joel Auditorium.

The following DCI personnel have birthdays in the months of October, November & December:

Eleanor Bicknell (07 October)
SSG Lance Thomas (30 October)
Barbara Solomon (05 November)
Janet Jamison (12 November)
Wilfred Shelton (19 November)
Wendy Teleha (21 November)
Audrey Franklin (23 November)
Yvonne Lukes (31 December)



New York Times Article (From Page 9)

Already, the anti-cancer drug STI-571 and the protease inhibitor class of anti-H.I.V. medicines were developed with a specific drug target in mind.

Still, predicting how a new drug will work in the human body remains well beyond the reach of science. The clinical trial, not scientific theory, remains an absolute necessity.

The stakes are high. Clinical research is directly responsible for many advances in modern medicine, as well as for ensuring that patients do not waste time, money and hope on ineffective therapies. At the same time, as science generates ever more promising research leads, clinical investigators will feel pressed to work faster, with fewer safeguards.

When medical research causes the death of a human

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being, the wish to stop using people as test subjects is perfectly understandable. Such deaths should remind researchers of their absolute responsibility to explain experimental treatments to patients clearly and fully, and to do everything possible to minimize risks. But risk, in the end, defines why the research is being done. And even the most careful scientists and the most obsessive oversight cannot eliminate it entirely.

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