PROTECTING HUMAN SUBJECTS

Office of Biological and Environmental Research • U.S. Department of Energy • Summer 2000

NIH's Fogarty Center addresses international research ethics

The Fogarty International Center (FIC) has launched a worldwide effort to discuss and find solutions to the ethical dilemmas raised by clinical research programs conducted in developing nations. An arm of the National Institutes of Health (NIH), FIC was established to serve as the NIH's organizational locus for international activities, a task that involves, among other things, fostering research partnerships between American scientists and foreign counterparts.

Focusing on clinical research in developing countries, FIC has begun to address some of the ethical dilemmas that relate to human subjects protection that may cause difficulties and frustrations for researchers, local governments, pharmaceutical companies, and for the research subjects and the communities in which they live.

Global forums

One of the ways in which FIC has chosen to address these concerns is to initiate a series of Global Forums for Bioethics in Research.

"We are doing this," says Karen Hofman, a Science Policy Analyst at FIC, "because there is a need for an open discussion between parties from all parts of the world, developed and developing, about ethical concerns that have been percolating for quite a while and are beginning to surface as serious concerns.

"In addition, researchers have frustrations about getting clearance for their work through Institutional Review

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Inside

Sandie Medina is back with the old gang again

Part Navajo and part Spanish, steeped in the language and the environment, educated in its schools, Sandie Medina understands well the culture and people of the Southwest.

Sandie grew up in Espanola, New Mexico, in a family whose roots are also firmly held in the culture of the Southwest and in the DOE community. Her brother is the wastewater plant supervisor at Los Alamos National Laboratory. Her father is a division group leader at the lab. And her mother just completed her 50th year working for DOE at Los Alamos.

A 240-mile commute, every workday for 26 years

Sandie Medina

When Sandie finished school, she took a job that for 26 years had her commuting 240 miles every work day from her home in Las Vegas to the Nevada Test Site's Area 12.

For those years from 1970 to 1996, Sandie was the entire fulltime staff for Area 12's

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"One of the key ethical issues is whether the rules that govern research should be the same no matter where you are."

Boards or from the Office for Protection from Research Risk."

The first of the Global Forums took place this past November. About 120 people from 34 countries participated. They included people from developing countries, pharmaceutical organizations, and communities where medical research is under way.

Partnerships

During the forum, participants addressed the issue of partnerships required between research sponsors and investigators involved in clinical trials in developing countries as well as the long-term needs for international multicentered training programs.

Since then, the FIC, together with other NIH partners, has developed a Request for Application that will fund curriculum development and training for developing country trainees in research bioethics. The first of these grants will be funded by the end of the current fiscal year.

The second Global Forum will be held in October 2000 in Bangkok, Thailand, the third in 2001 in The Gambia, and the fourth in 2002 in Latin America or the Caribbean. Together with the FIC, a consortium of sponsors includes other institutes at NIH, the World Health Organization, the U.K. Medical Research Council, the Pan American Health Organization, and the U.S. Centers for Disease Control.

Universal or local standards

"One of the key ethical issues is whether the rules that govern research should be the same no matter where you are, whether you are in the United States or in the developing world," says Hofman.

The earliest international guidelines for medical research include the Nuremberg Code of 1947 and the Helsinki Declaration of 1964 (revised in 1975).

Another set of guidelines, known as the Council for International Organizations on Medical Sciences, was formulated by the World Medical Association in collaboration with the World Health Organization.

"Developing country issues are addressed, but many people question whether they are sufficient," Hofman said. "The research situation differs from country to country and region to region. There are many questions and not enough answers."

standard of medical care available may be very minimal?

"Another big question," Hofman said, "is whether trials should be done in countries where a drug, a device or a vaccine being tested would be unaffordable once the clinical trial is over."

An example of the kind of issue that arises, Hofman explains, was an AIDS study recently conducted by U.S investigators and Ugandan collaborators in rural Uganda. Ethical questions were raised when treatment for HIV was not offered to those whose partners tested positive.

This arose in a setting where the local government demanded that the researchers not disclose HIV status to sexual partners without permission. Viewed from the U.S. perspective, this restriction could be seen as being of questionable ethics. But who is to decide for a sovereign nation?

Should trials be done in countries where a drug, a device, or a vaccine being tested would be unaffordable once the clinical trial is over?

In the U.S., a presidential panel, the National Bioethics Advisory Commission (NBAC), is attempting to address some of these questions.

"Some of these difficulties include how to deal with requirements for informed consent in transcultural settings or how to design clinical trials in settings in which the usual

"Disclosure of HIV status in many developing countries creates very different problems than they would here in the U.S.," Hofman says. "We have developed a level of tolerance, but in some places the stigma attached to the diagnosis is so great that people can be turned out of their home or even

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"The addition of these projects resulted in dramatic increases from last year in the number of projects, facilities, funds, and human subjects reported."

Updated human subjects database

The fiscal year 1999 update of the DOE Human Subjects Research Database has been posted on the web at **http://www.eml.doe.gov/hsrd/**. This successfully completes the sixth cycle of collecting, reviewing, and organizing information on all nonexempt human subjects research projects conducted with DOE funding, DOE personnel, or at DOE facilities.

The FY 99 database consists of 294 projects, of which 71% were conducted at DOE facilities and 29% at non-DOE facilities such as hospitals and universities.

There are 43 reporting research facilities; 12 are DOE laboratories and 31 are non-DOE facilities.

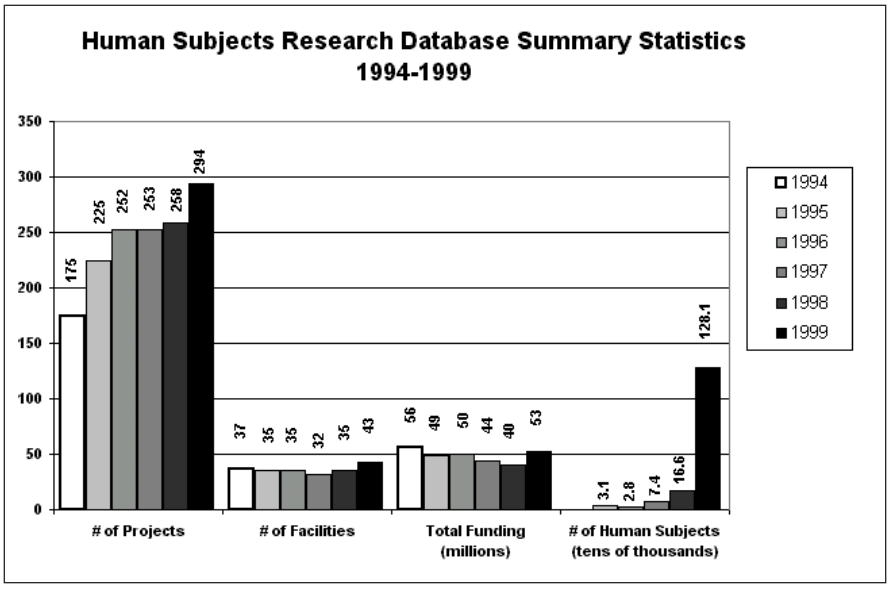
The funding from DOE that was directly associated with tasks or portions of projects involving the use of human subjects was about $41 million while funding from other federal and private sources at DOE facilities was $12.4 million.

A total of 1,281,042 human subjects were reported. About 97% are from registries, questionnaires, surveys, and epidemiological studies, primarily from available records.

In the FY 99 update, DOE-funded projects conducted by the National Institute for Occupational Safety and Health (NIOSH), and some additional Former Worker Projects (FWP), were added to the database for the first time.

The addition of these projects resulted in dramatic increases from last year in the number of projects, facilities, funds, and human subjects reported.

Illustrating these increases, the figure shown below presents the long-term trends for several significant database parameters.



The database includes 294 projects from 43 facilities involving 1.28 million human subjects

For database information, contact Richard Larsen, Human Subjects Research Database Project Manager.
Telephone: 212-620-3524.
Email: larsenr@eml.doe.gov.Δ

(Correction: In the last issue of *Protecting Human Subjects*, the web address for the database was incorrect. Thanks to readers who let us know about the error.)

Science and ethics by telephone

Human subjects group begins first of a series of phone conference sessions on beryllium disease

A novel and inexpensive way of delivering educational seminars by experts on beryllium disease was launched this spring by Dr. Susan Rose, manager of the DOE Human Subjects program.

These topics are important to DOE's effort to protect beryllium-exposed workers at DOE sites.

The first of many planned educational telephone conferences was held on March 3. They are designed to provide a greater understanding of the scientific and ethical issues such as identification and surveillance of Chronic Beryllium Disease (CBD).

Lee S. Newman, a physician at the National Jewish Medical and Research Center in Denver, Colorado, opened the series with an overview of the disease itself.

He outlined the course, diagnosis, and treatment of CBD, explaining that the disease affects the breathing capacity of the lungs in some people after they breathe in small beryllium particulates that get trapped inside the lungs. (See details of this talk on page 5.)

These one- to two-hour telephone conferences are held for the members of the DOE Human Subjects Working Group.

More calls are to follow every month or two. Lecturers will include doctors, workers, researchers, and ethicists who are working to unravel both what causes CBD in some people and the ethics of workplace testing. For more information about Chronic Beryllium Disease, visit these internet sites.

- DOE Worker Health-Related Studies
  www.sc.doe.gov/production/ober/humsubj/workrtop.html
- The DOE Chronic Beryllium Disease Prevention Program
  http://tis-nt.eh.doe.gov/be/
- The National Jewish Medical and Research Center–Beryllium
  http://www.NationalJewish.org/beryllium_medfact.html
- Oak Ridge National Laboratory Beryllium Disease Prevention
  http://128.219.152.164/oshp/be.html
- Center for Epidemiologic Research, Oak Ridge Institute for Science and Education, Beryllium Surveillance Program
  http://www.orau.gov/cer/BMSP_pro/be-home.htm
- Beryllium Disease Prevention Program, Lawrence Livermore National Laboratory
  http://www.llnl.gov/Be-prevention/
- The Hanford Beryllium Webpage
  http://www.hanford.gov/safety/beryllium/index.htm

. . . Fogarty and international ethics

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murdered if it becomes known that they have AIDS."

Standard treatment?

One of the biggest controversies erupted a couple of years ago when researchers were forced to stop clinical trials involving mother-to-infant HIV transmission in South Africa, Thailand, and Uganda.

In this situation, it was thought that the use of a placebo arm of the trial was not ethical when it was already the standard of care in this country to use a regimen of AZT that cost 20 to 50 times the per capita spending on all health needs in the developing countries.

"Many people objected to the trials," she said, "because they thought the research subjects in the placebo arm of the trials should have been given the treatment routinely used in the West. Others, many of them researchers from the developing world and their governments, strongly disagreed.."

The intention of the Fogarty International Center is to ensure that the developing world scientists, ethicists, and public officials participate in the debate as equals.Δ

"We do not know yet whether everybody who becomes sensitized will eventually develop the disease."

Lee Newman on beryllium disease

For many years, Lee Newman, a physician at the National Jewish Medical and Research Center, has studied the clinical course of beryllium disease, seeking the most effective treatments and trying to understand the ways exposures, genes, and immune response combine to cause illness in many exposed workers. In this discussion, Newman provides an overview of chronic beryllium disease.

Lee Newman

By Lee Newman

Beryllium disease predominantly affects the lungs, although it can and usually does affect the lymph nodes in the chest. It can occasionally affect the skin and on rare occasions can involve other organs, including the liver, although that's rare.

The disease is caused originally by exposure to beryllium, which can lead to sensitization (immune response) and then to full onset. Beryllium is the fourth lightest element, has a high melting point and high tensile strength, and is corrosion resistant—all of which make it an excellent material for high technology applications. Beryllium is present at very low levels in soil and air in most urban centers.

Some estimates suggest that as many as 800,000 people may have been exposed to beryllium in the United States. At least 20,000 workers were thought to have been exposed at DOE weapons facilities. Between 2 and 16 percent of exposed workers may have developed chronic beryllium disease (CBD).

Currently, 448 DOE workers and former workers have beryllium sensitivity, and 149 of them have been diagnosed with or show symptoms of CBD. The numbers are rising.

Manufacturing workers, especially machinists, in the ceramics, electronics, aerospace, dental prosthesis, and nuclear weapons industries have an increased risk of developing sensitization.

Patient's perspective

From the patient's perspective, CBD causes shortness of breath, a dry cough with gradual onset, fatigue, and chest pain. In rare instances, we'll see people with recurrent fevers, unexplained weight loss, and loss of appetite.

Many people identified through medical screening programs have no clinical signs at all. Beryllium exposure is demonstrated by an abnormal response to a blood test that shows the person has sensitized lymphocytes in their blood, which recognize beryllium as a foreign invader. The test is the beryllium lymphocyte proliferation test (BeLPT).

Lung pathology

To be diagnosed as having beryllium disease, usually one must have evidence of lung pathology. This requires one of several procedures to obtain pieces of lung tissue.

The gold standard diagnosis relies on demonstration of pathology that's consistent with the disease, meaning lung biopsy tissues, and a positive BeLPT. Breathing and exercise tests establish the severity of the condition.

The first thing that happens after exposure to beryllium is sensitization, which means the blood has an abnormal reaction to beryllium when the patient's lymphocytes are placed in a test tube culture in the presence of beryllium.

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"From the patient's perspective, CBD causes shortness of breath, a dry cough with gradual onset, fatigue, and chest pain."

. . . back with the old gang again

(Continued from page 1)

clerical and administrative support. She handled pay records, medical files, personnel forms, and almost every other detail of the employees' workday lives. She knew the men and women more intimately than almost anyone else at the test site.

These connections to the people and the region were a big part of the reason Sandie was named union project manager with the DOE Nevada Test Site Medical Surveillance Project. It is also the quality that makes Sandie so unique in her participation in the DOE's Human Subjects Working Group.

Working Group Chair Dr. Susan Rose says Sandie was invited to become involved with the group because of her background , her personal interaction with workers and her deep concern for them.

"When she attends meetings and educational programs," Dr. Rose said, "Sandie brings the perspective of the workers. She also helps get information back to workers about their rights and responsibilities."

Late in 1996, Sandie accepted the position with the Medical Surveillance Project, which is operated in association with the University of San Francisco, the Boston University School of Public Health, and the University of Nevada's Medical School Department of Family Medicine.

"I had enjoyed the job I had. I didn't even mind the long commute," she says, "because I liked the people I worked with. They were my friends. They were more than my friends; they were my family. They were the people I loved and cared about. I spent all my time with them.

"We did things together on the weekend. We ate lunch together. We worked together. I knew their families and played with their children."

And now she helps them in a way she would never have imagined in the old days.

Explaining the benefits

The surveillance project screens for radiation, silicosis, asbestosis, thyroid disease, and hearing loss. Her job as union project manager is to track down the men and women who worked at the site between 1951 and 1992.

Once she finds them, she has to explain the benefits and importance of their participation in the screenings.

They are the friends with whom Sandie spent 26 years and so she has both the personal contacts that enable her to locate them and the understanding that enables her to talk with them about their concerns and needs.

The people she looks for worked in underground testing areas and atmospheric testing. They spent their days in drill holes or shafts, exposed to a variety of workplace conditions. She tracks down former workers and then schedules them for medical screenings as part of the Former Workers Study. She handles the paperwork.

She explains the project. "It's good to see the old gang again, to see my friends from back in the early days. We considered ourselves a family."

The relationship she developed during those early years with the test-site workers is one of the main reasons Sandie was hired as the union project manager, the same reason she contributes so much to the working group.

"It's because I know these guys," she says. "It made things work easier, smoother. I know how to talk to them. They know me and I know them. I started at Area 12 right out of college, so I was raised with these people.

I was only the third woman allowed in the test site. Everyone was very aware of me."

The surveillance project examines close to 200 people in each screening. Seven screenings have been done-nearly 1400 people. "The response is overwhelming. Our next screening, in June, is already booked up."

Sometimes the people she finds are people she hasn't seen in many years; other times they are fellow workers with whom she has had a continued friend-

> "Now she knows them in a way she would never have imagined in the old days."

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"Not-for-cause" educational reviews occur every three years at major DOE laboratories and operations offices

California reviews continue in July

In July, DOE's Human Subjects performance reviews will continue with site reviews at the University of California at Los Angeles, Lawrence Livermore National Laboratory, Lawrence Berkeley National Laboratory, and the Oakland, California, Operations Office.

These intense, yet educational reviews occur every three years at each major DOE laboratory (and DOE Operations Office) that performs research involving human subjects.

They are primarily "not-for-cause" reviews. They often include educational seminars that encourage site-wide attendance and help frame the bioethics dialogue.

Review teams may include scientists, ethicists, human research subjects, and Institutional Review Board (IRB) staff picked specifically for each site's research agenda.

The California review team includes Patti Tobler (teacher/mother of study subject), Dr. Michael Duffy (Texas A&M University), Dr. Susan Koletar (Ohio State University), Larry Turner (Emory University School of Medicine), Dr. Richard Reba (University of Chicago), Mr. Matthew Van Patton (Spartansburg Regional Medical Center), Dr. David Price (University of California, San Francisco), Charles Pietri (HiTech Consultants, Inc.), and Marianne Elliott (University of Illinois at Chicago).

California sites are among the most active in the system and conduct a range of diverse and unusual projects. The field offices are reviewed as well to see if they stay in contact with their site's human subjects projects.Δ

The agenda for performance reviews includes

- an overview of the lab or field office by the manager
- how human subjects research fits into the lab's mission
- how it manages "common rule" implementation
- an examination of the work performed
- an assessment of human subjects educational site-wide outreach
- an evaluation of how problem correction is handled
- individual interviews with IRB chair, community member, and several principal investigators

Each site is asked to provide

- two years of IRB minutes
- copies of multiple or single project assurances
- the IRB membership
- list of adverse events or noncompliance reports or investigations
- active project protocols for the previous year

Possible discussion questions/topics

- educational activities
- community outreach
- IRB checklists
- project renewals
- IRB membership
- appropriate review
- informed consent
- adverse events
- vulnerable subjects
- collaborative agreements
- subject accrual/recruitment
- compensation for subjects
- subject bill of rights
- tissue banks/sample storage
- noncompliance reporting

Education in human research

Educational programs to increase the understanding of those involved in research with human subjects are being developed by the Department of Energy's (DOE's) laboratories, facilities, and operations offices.

The programs are designed to provide guidance on the most appropriate ways to protect these subjects in research activities conducted by or for DOE institutions, supported by DOE funds, or performed by DOE employees.

All institutions were requested to submit educational program plans for evaluation by the DOE Human Subjects Program.

A peer review of these plans for programs at DOE institutions was conducted in 1999 by DOE's Human Subjects Program in the Office of Science to evaluate the extent of their education and their level of performance.

Developing guidelines

Another purpose of this review was to use such plans to develop guidelines for structuring DOE human subjects educational programs.

Sites responded with many different approaches to provide education to a variety of people, including principal investigators, administrators, Institutional Review Board (IRB) members, human subjects, and others.

However, although the plans were useful, there did not appear to be a compelling focus that either identified all potential participants or provided them with adequate education or plan.

The results of this evaluation were shared with all the laboratories and DOE Operations Offices so that they could remedy any deficiencies and enhance their human subjects educational programs.

Task group

As a consequence of this effort, a task group of Human Subjects Working Group members is being formed to assist in the development of strengthened guidelines for DOE human subjects educational programs.

Asked what they would do to enhance their educational efforts, IRB administrators explained where they would focus. All mentioned IRB funding as the most critical issue.

Terence Reser, of Sandia National Laboratory, said "The two biggest obstacles I face are time and money. My role as IRB administrator accounts for only one third of my job, so I simply do not have time to develop a comprehensive training plan.

"Another problem is overload. researchers everywhere are constantly bombarded with new information, so they have to prioritize what they pay attention to. Our principal investigators who regularly do research involving human subjects know the drill and review our web site for changes and updates.

However, those who only rarely deal with human subjects don't want to invest more time than necessary to learn about what regs they have to follow. They want the IRB to filter information and summarize everything for them.

"Traditionally, we've focused our efforts on one-on-one training because it gets the right information to the minimal number of folks who need it. This fits our time and budget constraints. We also have a web site that contains lots of very useful information. In the future, we'll be focusing our efforts on some type of interactive, online tutorial."

Sherry Davis-Cross, Pacific Northwest Laboratories, said she wants to extend human subjects training to everyone involved, including the lab director, the IRB researchers, and their staff, as well as contract- staff associated with the projects and the local DOE staff.

Shirley Fry, of Oak Ridge Associated Universities, said for her, too, funding continues to

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"... we'll be focusing our efforts on some type of interactive, online tutorial."

"Beginning with applications submitted for the January 2001 council round, IRB approval is not required prior to NIH peer review of an application."

Research applications

Changes in IRB approval process

A significant change in the timing of IRB approval for human subjects research applications has been announced by the National Institutes of Health (NIH).

Beginning with applications submitted for the June/July 2000 receipt dates, IRB approval will **not** be required prior to NIH peer review of most applications.

NIH has released the following statement on the new policy:

"It has been NIH grants policy that applications submitted to NIH, which include research involving human participants, are required to have IRB approval at the time of submission or within 60 days after application receipt date."

Fewer than half funded

Since fewer than half of all applications submitted to NIH are funded, this change will significantly reduce burdens on applicants and IRBs.

As part of the peer review process, the peer review group carefully considers whether the application includes the necessary safeguards to protect the rights and welfare of research participants.

This change in policy is intended to provide flexibility at the institutional level. The institution may still determine that certain lines of research (e.g., scientifically or ethically controversial research) or mechanisms of research (e.g., multicenter clinical trials) should receive IRB review prior to submission of the application.

As before, no grant award can be made without IRB approval.

Therefore, following NIH peer review and notification of priority score/percentile, institutions can then proceed with IRB review for those applications that appear to be in a fundable range.

The term *fundable range* does not signify a certainty of funding. Guidance is currently being developed that will assist applicants in determining their status related to a particular institute or center's fundable range.

Reducing work loads

This change in NIH policy is intended to enable institutions to reduce the work load burdens that many IRBs are facing. It also should allow them time to more adequately review more complex protocols.

This change is consistent with the requirements of 45 CFR 46 (The Common Rule).

At this time, this flexibility is being provided only to IRBs.

Due to Public Health Service policy language, applications including research with animals will continue to require review by the Institutional Animal Care and Use Committee at the time of submission or within 60 days thereafter.Δ

From Ethel Jacob, DOE Environmental Measurements Laboratory

"... carefully considers whether the application includes the necessary safeguards to protect the rights and welfare of research participants."

. . . Newman on beryllium disease

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Progression to disease
We do not know whether everybody who becomes sensitized will eventually develop the disease.

We do have fairly strong figures indicating that those who are sensitized progress into disease at a rate of 10 percent a year. This means that after a determination of sensitivity, a person will, a year from then, have a one in ten chance of having the disease if they didn't already have it when first tested. Between 50 and 100% of those with an abnormal blood BeLPT already have CBD when first screened.

It is almost never a fast-progressing disease. About two years is a usual time for patients from the first diagnosis to the development of clinical symptoms or to the appearance of one or more abnormalities on clinical tests, such as crackles heard in the lungs or abnormal oxygen levels found in blood.

For some patients, it takes five to seven years before they reach the point where they are ill enough for us to begin talking about treatment.

This means people need careful medical monitoring once they are diagnosed as being sensitized because a high percentage of them will go on to develop the disease. And those with early disease symptoms need to be in regular medical follow-up because they are at high risk of developing symptoms that require treatment.

Treatment
The typical treatment for the disease is prednisone, a naturally occurring corticosteroid. It is an anti-inflammatory used to quiet the immune system. Prednisone is commonly used for various immune system disorders, such as rheumatoid arthritis and asthma, but it has potentially serious side effects.

Sometimes, when using prednisone at a very early stage of the disease, its side effects might outweigh the benefits, so we usually wait.

Other treatments are being tried. One is methotrexate, which allows us to reduce the level of prednisone.

Exposure
People who get the disease are those who have inhaled beryllium into their lungs. Most CBD occurs in those who worked directly with beryllium, such as machinists. We are also seeing disease in front-office workers, secretaries, security guards, and others who have had only a passing opportunity for exposure.

We have seen sensitivity in people with as little as nine weeks of exposure, and we have seen the full disease develop in as little as three months. We have also seen it take as long as 30 years to develop into the full disease. So, once exposed, you are at lifetime risk of sensitization and becoming diseased.

It is important to note that those who have had little exposure, like office workers, are far less likely to become sensitized. It occurs in less than one percent of those people.

Those at higher risk are people who are dust disturbers, such as those in janitorial services, or who are otherwise generating particles of beryllium dust. This includes work that involves polishing, sanding, grinding, machining—all of which generate particles that are the perfect size to get into the deep lung, around 1–5 microns.

Genetic markers
At least one and probably three or four genes have been associated with the risk of beryllium disease. They are genetic susceptibility markers. The most well known is HLADPB1 glu–69. It isn't that beryllium causes the gene to mutate. It is that some people are born with this gene, which makes them more susceptible to the disease, but only, of course, after exposure.

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"Those who have had little exposure are far less likely to become sensitized. "

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. . . Newman

"there are patients with beryllium disease who have never had a positive blood test reaction. We can't tell you why. It could be the labs' testing methods, the person's blood on a given day, . . . "

There are people who do not have the glu–69 gene who get the disease anyway. This may be because either there are other genes we don't know about yet that increase susceptibility or the amount of exposure they had was sufficient that it didn't matter what their genetic makeup was.

The most risk-important factor is exposure. Genetic research is under way to find the genes that control the disease severity. This may benefit those exposed and may identify those who would be at highest risk if exposed.

Blood LPT test

The blood LPT test has been used since around 1970 to measure different kinds of reactions by the immune system—to beryllium and other exposures.

In comparison to other tests, it is much more sensitive, meaning it picks up more disease, and picks it up earlier than do tests such as chest X-ray and spirometry.

We don't do a medical evaluation for beryllium disease unless there have been two positive blood tests, partly because there are differences among labs in terms of their sensitivity.

Laboratories don't have much trouble agreeing on the people who are negative, but among the positives, the level of agreement between labs ranges from 25 percent up to about 70 percent. So, while the test is the best available method of detection, a confirmatory second test improves accuracy of diagnosis.

There are patients with beryllium disease who have never had a positive blood test reaction. We know this because in those people, biopsied lung cells react to beryllium. We can't tell you why. It could be the labs' testing methods, the person's blood on a given day, what else is going on biologically in the individual. There are lots of possibilities.

Ethical issues

Based on what we know today, the prudent approach to controlling the spread of CBD is to minimize beryllium exposures in the workplace and provide medical screening with the blood BeLPT as a "safety net" to identify as early as possible the people with sensitization and CBD.

There are other ethical issues. For example, is there a role for genetic testing either before or after placing someone in a place that might exposure them to beryllium? Would genetic testing prevent disease?

Even if genetic testing prevents disease, what are the implications for the worker's right to employment and to personal choice? What are the future economic and social consequences? What constitutes "informed consent" for genetic testing in the workplace? For beryllium exposure in the workplace?

Should efforts focus on minimizing exposure, or on the detection of genetic risk in individuals? Is DOE and DOD use of beryllium "worth" the risk to workers?Δ

"There are people who do not have the glu-69 gene who get the disease anyway. This may be because either there are other genes we don't know about yet that increase susceptibility or the amount of exposure they had was sufficient that it didn't matter what their genetic make up was."

News notes

Human subjects Protection

New DOE Human Subjects policy/order issued

DOE Policy 443.1/DOE Order 443.1 (replaces DOE Order 1300.3) became effective May 15, 2000. This covers human subjects policy for DOE-funded research and non-DOE funded research at DOE-owned, -leased, or -controlled facilities. For details, see the winter 1999/2000 issue of the Protecting Human Subjects newsletter, or visit the human subjects web site at http://www.science.doe.gov/ober/humsubj/regulation.html

Human Subjects Handbook revision

The Office of Biological and Environmental Research (OBER) is updating the DOE Human Subjects Research Handbook. Many of you are very familiar with the handbook and OBER wants your input. What would you like to see discussed in the Handbook? A new topic, or an update to one of the existing chapters?

OBER is especially interested in suggestions and materials regarding Human Subjects Research model consent forms and internet-based educational resources, but suggestions and comments of any sort are always welcome and encouraged. Send comments and materials to Ethel Jacob, Environmental Measurements Laboratory, 201 Varick St., N.Y., NY 10014,
email: jacob@eml.doe.gov
Susan.L.Rose@science.doe.gov

"Understanding clinical trials"

The April 2000 issue of Scientific American includes an article by Justin Zivin analyzing the three-part clinical trial process required to judge the efficacy and safety of potential treatments. Zivin is a professor in the department of neurosciences at the University of California, San Diego.

Sign up for Human Subjects mailing list

If you want to be on the Human Subjects mailing list for announcements and reports (including the new guidelines for workers' studies that will be out soon), please send your name and mailing address to:

Human Subjects Research Program
Office of Biological and Environmental Research
SC-72
19901 Germantown Road
Germantown, MD 20874-1290
Fax: (301) 903-8251

Email: humansubjects@science.doe.gov

Peer group reviews DOE consent forms

Human subjects in research studies may participate willingly after having been adequately informed about the research to be performed.

Such voluntary participation means subjects have enough information and understanding to give true informed consent.

All DOE institutions performing research with human subjects provide an informed consent form to prospective participants in these studies.

To evaluate the adequacy of these forms, a review from a sampling of such forms from each laboratory was performed in 1999 by a peer review group convened by the DOE Life Sciences Division, Office of Science.

Another objective of the review was to examine ways of improving the effectiveness of these informed consents in protecting human research subjects.

Because the results of the review indicated a wide diversity in form and presentation, a task group composed of members of the Human Subjects Working Group is being formed to examine ways of preparing appropriate guidelines for informed consent. The group's job will be to help improve consent procedures at sites across the department. The recommendations will be shared with the human subjects protection community.Δ

—By Charles Pietri, Hitech Consultants

Web sites

for human subjects protection and related resources

DOE Human Subjects Research Database: The fiscal year 1999 database consists of 294 projects, of which 71% were conducted at DOE facilities and 29% at non-DOE facilities (such as hospitals and universities). There are 43 reporting research facilities; 12 are DOE laboratories, and 31 are non-DOE facilities.
http://*www.eml.doe.gov/hsrd/*

Office of Research Integrity: ORI is responsible for protecting the integrity of Public Health Services (PHS) extramural and intramural research programs. The site includes ORI forms, workshops, conferences, whistleblower issues, PHS administrative actions, legal decisions, appeals board information, and departmental appeals.
http://*ori.dhhs.gov/*

Clinical Trials: The U.S. National Institutes of Health, through its national Library of Medicine, developed this site to provide patients, family members, and members of the public current information about clinical studies. More than 4000 ongoing drug trials are listed.
http://*clinicaltrials.gov/*

National Institutes of Health (NIH) Bioethics Resources: This site contains a broad collage of annotated web links. The resources and organizations provide background information and various positions on issues in bioethics.
http://*www.nih.gov/sigs/bioethics*

NIH/Fogarty International Center Bioethics Education and Career Development Award: This is an invitation for applications from nonprofit, private or public, domestic or international, educational and research institutions to develop or expand on current graduate curricula in international bioethics related to performing research in low and middle-income nations.
http://*grants.nih.gov/grants/guide/rfa-files/RFA-TW-00-008.html*

Human Genetic Cell Repository, sponsored by the National Institute of General Medical Sciences (NIGMS). *http://locus.umdnj.edu/nigms/*

Report of the Workshop on Population-Based Samples for the NIGMS Human Genetic Cell Repository:
http://*www.nih.gov/nigms/news/reports/cellrepos.html*

Occupational Energy Research Program: An overview that includes information about studies conducted by the National Institute for Occupational Safety and Health (NIOSH), including NIOSH-supported contracts, grants, and cooperative agreements, and DOE worker surveillance projects with NIOSH involvement.
http://*www.cdc.gov/niosh/oeindex.html*

The National Bioethics Advisory Commission's final report "Research Involving Human Biological Materials: Ethical Issues and Policy Guidance," August 1999.
It is under reports at
http://*bioethics.gov/*

University of Houston Health Law News: Quarterly publication of the University of Houston, Health Law & Policy Institute. For subscriptions, email: healthlaw@uh.edu.
http://*www.law.uh.edu/healthlawnews/homepage.html*

Each issue of Health Law News has a special section on a health law subject.
Medical Privacy was covered in the March 1999, Vol. XII, No. 3 issue of the newsletter
http://*www.law.uh.edu/healthlawnews/03-1999.html*

DOE addresses the beryllium issue on many fronts

New beryllium rule finalized

The Department of Energy (DOE) is implementing the "strongest worker protection program in the world to prevent lung disease associated with exposure to beryllium," in the words of Secretary of Energy Bill Richardson.

The final rule on DOE's Chronic Beryllium Disease Prevention Program (CBDPP) was published December 8, 1999 (10 CFR Part 850). The rule is intended to provide better management of a health risk that is much greater than it was thought to be in the past

The new prevention program requires DOE facilities to minimize beryllium exposures with stricter workplace controls. The rule reduces the level of airborne beryllium dust that triggers protective action from 2 to 0.2 micrograms per cubic meter of air.

In addition, contractors operating DOE facilities must offer medical surveillance to all "beryllium-associated" workers for early detection and treatment of CBD.

This group includes current workers who may be exposed through beryllium work and those with known or possible exposures in the past at any DOE site. The program uses the beryllium lymphocyte proliferation test (BeLPT) to identify sensitized people.

Voluntary paticipation

Employee participation in medical surveillance is voluntary. Appendix A to the rule is a medical consent form that must be used when workers are tested for beryllium sensitization under the program.

Other sections of the rule require employers to offer medical removal from beryllium work—with protection of job status—to employees found to be sensitized or symptomatic.

Of importance to medical research on CBD is the requirement for DOE's Office of Environment, Safety and Health to maintain a registry of beryllium-associated workers. The records will include both exposure and medical surveillance data for each individual.

Protecting confidentiality

To protect confidentiality, each record will be labeled with a "unique identifier." Only the site occupational medical director will have the key linking the identifier with the individual employee.

DOE screening programs have identified 146 current and former workers with CBD and many others who are beryllium sensitized.

By the end of 1999, DOE had screened 13,700 workers and former workers with the BeLPT. An estimated 20,000 people may have been exposed to beryllium in DOE facilities.

This final rule can be found through the "Human Subjects Regulations, Orders, and Policy Statements" web page at http://www.science.doe.gov/ober/humsubj/regulation.html.

You may also want to read the GAO Occupational Safety and Health Report, "Government Responses to Beryllium Uses and Risks, GAO/OCG-00-6, May 2000.Δ

—By Lisa Carroll, Oak Ridge Institute for Science and Education

"To protect confidentiality, each record will be labeled with a 'unique identifier.' Only the site occupational medical director will have the key linking the identifier with the individual employee."

Protecting Human Subjects

This bulletin is designed to facilitate communication among those involved in human subjects research and to inform persons interested in human subjects research activities.

DOE Human Subjects Research Program Manager
Dr. Susan L. Rose

This newsletter is prepared at Oak Ridge National Laboratory, managed by UT-Battelle, LLC, for the U.S. Dept. of Energy under contract DE-AC05-00OR22725.

Managing Editor
Dr. Gloria Caton
catongm@ornl.gov

Editor, Designer
Tim Elledge
x3x@bio.ornl.gov

This newsletter is available at no cost to anyone interested or involved in human subjects research at DOE. Please send name and complete address (printed or typed) to the address below. Please indicate whether information is to (1) add new subscriber, (2) change name/address, or (3) remove name from mailing list. Enclose a business card, if possible.

Send suggestions and subscription information to —

Dr. Susan L. Rose
Office of Biological & Environmental Research, SC-72
U.S. Department of Energy
19901 Germantown Rd.
Germantown, MD 20874
Fax (301) 903-8521

Meetings

July 24–27, 2000
DOE 2000 Occupational Medicine Conference
U.S. Grant Hotel, San Diego, California.
Contact: Linda Sharp, Oak Ridge Associated universities, MS 50, P.O. Box 117, Oak Ridge, TN 37831-0117. Fax (865) 576-7903.
http*://tis.eh.doe.gov/med/occmedconf/register.html*

August 14–16, 2000
Ethical Research in the New Millenium: What the Belmont Report Didn't Anticipate. The focus of the workshop is Native Americans involved in research.
Portland, Oregon
Contact: Darlene Marie Ross (see above).

October 28–31, 2000
PRIM&R/ARENA
San Diego, California
Training for Institutional Review Board (IRB) newcomers: October 28, Hyatt Islandia.
Annual PRIM&R IRB meeting: October 29–30, Paradise Point Resort.
Annual ARENA IRB meeting: October 31, Paradise Point Resort.
Contact: info@primr.org.
http://www.aamc.org/research/primr

November 18–20, 2000
Research on Research Integrity
Washington, D.C.
Sponsors: Office of Research Integrity, American Association for the Advancement of Science, Association of American Medical Colleges, National Institutes of Health, National Science Foundation.
Contact: Nicholas Steneck, Ph.D., Office of Research Integrity, 5515 Security lane, Suite 700, Rockville, MD 20852.
E-mail: nsteneck@osophs.dhhs.gov.
http://ori.dhhs.gov/page1.htm

. . . education *(Continued from page 8)*

be a serious issue. She also said it would be helpful if the impending requirements for training and certification of IRB administrators included incentives.

Bree Klotter, Lawrence Livermore National Laboratory, said she intends to write an article for the Lab's newspaper titled, "Are You a Human Subject?" The focus of the article would be a description of various worker research studies. It would also provide employees with information about their rights as research subjects.

"I would guess," she said, "that we may see some protocols surface as a result of the outreach effort, simply because employees would know to ask, "Did this study receive IRB approval?"

. . . the old gang *(Continued from page 6)*

ship. "It's really fun when it's somebody I haven't seen in many years. I get to find out what they've been doing all this time.

"It's hard to see the guys who find out they're not OK. But what I feel really good about is that through both the surveillance project and the working group, we're looking for ways to help them, and to help all the workers who will come after them."Δ

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