In the name of healing

Around 10:40 a.m., hospital workers began infusing a solvent also used as a gasoline additive into Laura Michalski's abdomen.

•

Hours later, she died.

By KEITH C. EPSTEIN and BILL SLOAT
PLAIN DEALER REPORTERS

AN INVESTIGATIVE ANALYSIS

First of four articles

She was given a code name, "TE3."

To this day, the federal government won't say who she was or what it knows about how she died.

It hasn't even told her family.

Laura Michalski's husband, naturally, knew her as the center of his life.

They met one night in 1938 at a 15-cent jitterbug dance. He recalls "we floated on that floor as if it was ours. I thought right then: This girl I have to marry."

Laura and Alexander taught their five children to be proud Polish Catholics and oversaw their chores in the family's grocery a floor below their Philadelphia apartment.

Come Christmas and Easter, she would stuff kielbasa for the store and still manage to assemble a lavish holiday spread for her own large family.

"You could have invited the president," Alexander would say.

At suppertime, everyone was expected at the table. No excuses allowed.

She was strict, but spiritual, too. She knitted angels, crocheted angels, collected figurines of angels.

By the time Laura Michalski checked into Philadelphia's Hahnemann University Hospital, she was 64, the beloved grandmother of 19. Her kidney system was failing. There were gallstones, the pain intense.

"I can't find a comfortable place in this bed," she would say. "Sometimes, I wish to God the angel would come for me."

One morning, "they told me she was going to have this new treatment," said Alexander.

It was June 7, 1988. Around 10:40 a.m., the medical records show, hospital workers began infusing a solvent also used as a gasoline additive into Laura Michalski's abdomen. A pioneering radiologist, Dr. Steven K. Teplick, believed the solvent, methyl tertiary butyl ether, held promise as a method of dissolving gallstones. Physicians at the Mayo Clinic, and in Germany, had conducted similar experiments.

The idea was that MTBE would help patients avoid surgery. Researchers had to convince the federal Food and Drug Administration that it worked and was safe.

By midafternoon, records show that from 142 to 360 cubic centimeters of the solvent, nearly enough to fill a small coffee cup, had been infused.

Michalski's heart speeded to between 140 and 150 beats per minute. Her blood pressure fell. Her fingernails began turning blue. After she was rushed to intensive care, her heart weakened, then gave out.

At 6:50 p.m., a few hours after the infusion ended, Laura Michalski was pronounced dead.

"When all my kids got there, I was still crying," Alexander said. "This was my love, my friend. We're together 47 years. I'd hoped to God for 50. . . . Then, suddenly — after it seemed like there was going to be no problem — she's not there."

Listed on her death certificate as contributing causes: heart arrest, aspiration of body fluids and a disease of the gallbladder known as cholangitis.

The Plain Dealer identified Laura Michalski as TE3 by matching information from an FDA file to her death certificate. The documents matched on time, place and cause of death.

SEE CONSENT/14-A

DRUG TRIALS
Do People Know the Truth About Experiments?

DECEMBER 15, 1996

DAVID I. ANDERSEN / PLAIN DEALER PHOTOGRAPHER

Alexander Michalski, holding a portrait showing his late wife, Laura, is flanked by two of their children, Bernadette McCloskey and Dennis Michalski.

THE PLAIN DEALER • DRUG TRIALS • SUNDAY, DECEMBER 15, 1996

Risks may be obscured by eager doctors

CONSENT FROM 1-A

"We were never told it was [after] an experiment. We had no idea what was going on," or what the federal government eventually learned about the clinical trial, said Michalski's daughter, Bernadette McCloskey.

A year later, inspectors from the FDA happened to be conducting a routine audit when they found out about TE3 — as well as TE4, TE7, TE8, TE10, TE11, TE15, TE19, TE21 and TE25.

Both before and after Michalski's death, nine of 29 patients suffered "adverse effects ... in close proximity" to infusions.

The forms had stated "the drug will probably be effective." Consent forms "failed to adequately address the foreseeable risks and discomforts," the FDA found.

Teplick said he had obtained consent from every patient and did not believe that any harmful side effects were caused by MTBE.

The FDA halted further research "due to unreasonable and significant risk to human subjects."

It was hardly the first time the government had made such a discovery.

And after the fact.

On the frontiers of medical science, for the greater good of society, well-meaning doctors sometimes employ an ounce of salesmanship for a pound of cure.

Since 1977, the FDA has conducted 4,154 inspections of researchers testing new drugs on people. More than half the researchers, 53 percent, were cited by FDA inspectors for failing to clearly disclose the experimental nature of their work, a Plain Dealer analysis shows.

The risks, alternatives or uncertainties were obscured or incompletely explained.

In 46 clinical trials, drugs were tested on people without written evidence they had consented. The records are key safeguards required by law, signed receipts showing patients agreed to roll the dice with their health.

Altogether, at least 1,000 men, women and children were participants in the 46 pharmaceutical studies questioned by the FDA. The experiments, in 23 states, were sponsored by federal agencies and drug companies.

The analysis of the FDA files is strikingly similar to what a White House advisory committee discovered in 1995 when it examined patient-consent documents from more than 100 ongoing government research projects. The experiments, or clinical trials as they are more commonly known in scientific circles, are research studies designed to evaluate the safety and effectiveness of new treatments.

"Some consent forms currently in use are flawed in morally significant respects, not merely because they are difficult to read but because they are uninformative or even misleading," the Advisory Committee on Human Radiation Experiments concluded.

Asked about the FDA's inspection reports, Mary Pendergast, the FDA's associate commissioner, said she considered them "representative of biomedical clinical research as a whole."

Many experiments do occur with appropriate safeguards. The fact that nearly half of all inspected research is conducted without deficiencies in informed consent suggests that following proper procedures is hardly impossible.

Ruth Macklin, bioethics professor at Albert Einstein College of Medicine in New York, said even complex human research could be conducted in an ethically responsible manner. The challenge is to determine needed changes to ensure that clinical trials are "in accord with the highest standards," she added.

Each year, government and industry spend at least $20 billion financing research on hundreds of thousands of human beings, yet the government discloses surprisingly little about those people, the risks they face, the injuries they endure or the benefits to them.

"Most people don't understand they're in clinical research. They think it's therapy," said Case Western Reserve University bioethicist Thomas Murray, appointed this year to a new National Bioethics Advisory Commission.

How many experiments are there? How many people take part? At best, the experts can hazard little more than wild guesses.

Asked how many clinical trials take place, senior FDA official Paul Goebel Jr. replied with an ancient riddle. It has no answer. "How many angels can dance on the head of a pin?"

What the government lacks in hard data about humans, it more than makes up for with volumes of statistics about laboratory animals. Wonder how many guinea pigs were used in U.S. research? The Agriculture Department knows: 333,379. How many hamsters in Ohio? 2,782.

"There are more inspections for laboratory animals carried out by the Department of Agriculture than there are for human subjects carried out by the entire Department of Health and Human Services," observed Charles McCarthy, a consultant on the use of laboratory animals and until 1992 director of a federal office meant to safeguard people in government research.

His successor, Gary B. Ellis, a University Heights native, is the first to acknowledge the government is more aggressive about protecting laboratory animals than humans. "Research subjects are real people, our fellow Americans. But in 1996, we do not have the tools necessary to ensure that they — and all human subjects — are protected."

Only this month, the FDA for the first time required consent forms to be dated "in response to problems ... verifying that informed consent was obtained" before clinical trials started.

Just one of the clinical trials in the FDA files, obtained under the Freedom of Information Act, involved at least 500 adults and children at a Miami Beach hospital who were injected with a radioactive dye without their permission.

Researchers acknowledged to the FDA they didn't think consent was necessary.

The FDA's Pendergast said it was a "company-to-researcher miscommunication. We got strong assurances and 'mea culpas' from the researchers that they recognized the problem and that they wouldn't do it again."

The experiment took place at Mt. Sinai Medical Center between 1980 and 1982.

'They told me she was going to have this new treatment.'

ALEXANDER MICHALSKI, husband of woman who died

The investigational drug, known as pipida, was mixed with a radioactive tracer and injected.

Dr. William M. Smoak, who worked on the team studying pipida, said he knows of no one harmed by the drug.

Earlier tests "convinced us it was a safe material, and then we were just doing tests adding volume [numbers of patients], looking for more unusual side effects. What are you supposed to tell people about hazards if you don't know any for sure?" Smoak said.

"Juveniles as young as 15 years of age received injections and there was no informed consent," an FDA supervisor, Melvin Zymash, noted in an internal report.

As for the men, women and children who received the injections — the FDA abandoned efforts to identify them when it closed the case in 1983.

By then, the era that allowed the use of unwitting patients for the sake of science and the greater good was supposed to be history.

What happened in Tuskegee, Ala., is still the most widely talked about medical experiment of our time. The U.S. Public Health Service wanted to find out what happened to men with syphilis. So, starting in 1932, the government diagnosed more than 400 black men with the disease but didn't tell them.

It just observed them.

While distinguished scientists collected data, at least 28 men died.

When the world learned about Tuskegee in 1972, the outrage triggered new rules. Explicit informed consent was required. Ethics committees had to weigh predictable risks against anticipated benefits.

Today, every human subject is supposed to understand hazards, uncertainties and — even if chances of physical harm are remote — be able to say no.

As Yale University Professor Jay Katz, who served on the advisory committee that examined the Tuskegee experiment 22 years ago, puts it: "Research is a voyage into the unknown."

Last month, for the first time, the FDA relaxed the nation's informed consent rules. In an emergency, medical researchers can administer experimental drugs without a patient's permission. The patient must be insensible, relatives unavailable and the condition life-threatening.

It was a sea-change in policy and eroded the first principle of an ethics code enacted by The American Medical Association on Dec. 11, 1946: "The voluntary consent of the person on whom the experiment is to be performed must be obtained." The code of ethics was developed for prosecutors at the Nuremberg medical trial in Germany at the end of World War II. It evolved into a system of rules, laws and international standards governing informed consent.

Before a drug can be tested on people, it must be tested on animals. If the animal studies go well, the sponsor, usually a drug company or government agency, asks the FDA for permission to begin a clinical trial of the "investigational new drug."

The experiment, normally in three phases, each involving a larger number of people, is intended to answer: What happens to the body? What is the best dose? What side effects surface? How does the drug compare to those already approved?

Only one in five investigational drugs makes it to market.

Thus, test subjects are critical to medical advances.

That pressure to recruit, says CWRU's Murray, may tempt some researchers to camouflage risks and uncertainties.

Mary Poppins would have called it a spoonful of sugar.

In 1992, nearly 16,000 women across the United States and Canada were being asked to take part in a test of a synthetic hormone called tamoxifen. The National Cancer Institute wanted to learn if the drug could prevent breast cancer in healthy women.

A variety of consent forms were prepared. Some stated the pill had been approved by the FDA; it was, but only as a follow-up therapy for women already diagnosed with breast cancer.

Some consent forms said nothing about lab mice on tamoxifen developing liver cancer.

The FDA's Goebel found another problem: It wasn't clear in every consent form that the drug was being tested for safety.

"The toxicities are minimized and the positive benefits emphasized, resulting in undue influence being placed on women to enter the trial," an internal memo said. "Use of the word 'therapy' to describe this study is inappropriate, as it implies treatment of a disease rather than the conduct of well-controlled research."

Contemporary experiments on people for the pharmaceutical industry are more shrouded in secrecy than the radiation studies of the Cold War.

The existence of a clinical trial involving an investigational drug, and the identity of the sponsor, "is confidential, commercial information," said Pendergast.

The names of errant researchers, too, are closely held. They rarely face severe consequences.

Neglecting to fully inform test subjects. Failing to disclose deaths or injuries. Failing to get permission from ethics committees of their peers. Faking data. In each instance, written criticism and a letter usually satisfies the FDA.

Those who face the harshest penalty, having their names added to a list of 82 researchers barred from obtaining investigational new drugs, need have little fear of being found out by peers or patients.

Names of "Disqualified Investigators" — the FDA's "blacklist" — are distributed only among an inner circle of agency bureaucrats.

As Bernadette McCloskey studied the 47-page FDA file on the Philadelphia experiment, provided to her by The Plain Dealer for the first time last summer, she turned the pages slowly.

Whatever emotions she felt, she tried to keep to herself. Only for the briefest moment did her forehead wrinkle, chin quiver, eyes water.

She fought for composure, laboring to absorb this new picture of her mother's last hours.

"We had no idea," McCloskey said. "No one has ever told us anything. It's certainly upsetting to find out there's something we weren't told."

Six years after her mother was buried in Philadelphia's Holy Redeemer Cemetery, the agency "disqualified" Teplick from conducting clinical trials with investigational new drugs.

SEE CONSENT/15-A

Researchers face few penalties for their errors

CONSENT FROM 14-A

FDA Commissioner David A. Kessler signed the formal notice. "You have repeatedly and deliberately failed to comply with the regulatory requirements regarding investigational new drugs," Kessler wrote. Besides "failing to document informed consent," he noted, Teplick had not reported adverse effects "probably caused by" the investigational drug.

Teplick, now on the faculty of the University of South Alabama in Mobile, said he never saw Kessler's order, nor had the opportunity to challenge it. Every patient consented, he said, and MTBE caused no harmful effects.

McCloskey, the administratrix of her mother's estate, has hired a lawyer, who in September filed a malpractice lawsuit in the Court of Common Pleas in Philadelphia County against the hospital and the doctor. In a preliminary ruling Dec. 6, a judge dismissed the portion of the lawsuit dealing with informed consent, on grounds that under Pennsylvania law "a claim for lack of informed consent only applies to surgical procedures. The administration of a therapeutic drug is not a surgical procedure."

Alabama granted him a medical license in 1994 as a "distinguished professor," after peers from around the country wrote letters of praise. "Conscientious, honest and thoughtful physician," one Wisconsin professor wrote. "Well-respected."

"It's amazing that the FDA, with all the expertise at its fingertips, can't tell the state what it finds out about a researcher," said John M. Goldberg, a lawyer with the Illinois Department of Professional Regulation. He learned of FDA action against a doctor while Illinois prepared its license revocation case against her.

The Illinois doctor, Chavonee Aroonsakul, had been reprimanded by Kessler for "repeatedly and deliberately" failing to comply with the regulations. "You failed to obtain informed consent," Kessler stated when he placed her on the "blacklist" in 1991.

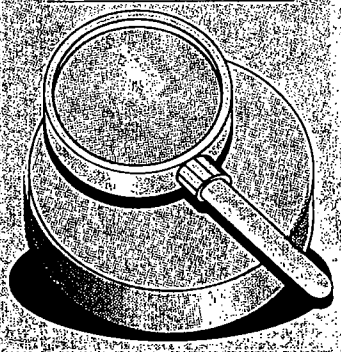
She said the charges were "false and unfounded" and that she always got consent from her patients. She says her only goal was to help people — administer her patented treatment for Alzheimer's disease — and that the government had conspired to stop her.

"The FDA didn't want to tell us anything," said Goldberg. "Who are they trying to protect? The doctor? Some drug company? The system is nuts."

MIKE LEVY / PLAIN DEALER PHOTOGRAPHER

Roger Bull Sr. is one of Dr. Chavonee Aroonsakul's patients.

RESEARCH SITES WITH THE MOST CONSENT PROBLEMS



Number of consent deficiencies: 19
University of Michigan Medical Center
State: Michigan
City: Ann Arbor

Consent deficiencies: 18
University of Miami School of Medicine
State: Florida
City: Miami

Consent deficiencies: 16
Duke University
State: North Carolina
City: Durham

Consent deficiencies: 16
Mayo Clinic
State: Minnesota
City: Rochester

Consent deficiencies: 16
Johns Hopkins University
State: Maryland
City: Baltimore

Consent deficiencies: 16
Tulane University School of Medicine
State: Louisiana
City: New Orleans

Consent deficiencies: 14
Columbia University
State: New York
City: New York City

Consent deficiencies: 13
Emory University Hospital
State: Georgia
City: Atlanta

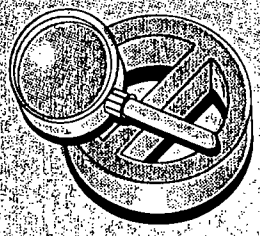
Consent deficiencies: 13
University of California
State: California
City: San Francisco

Consent deficiencies: 13
Baylor College of Medicine
State: Texas
City: Houston

Consent deficiencies: 13
University of Pennsylvania
State: Pennsylvania
City: Philadelphia

Deficiencies include inadequate consent or no record of consent. Based on Plain Dealer analysis of Food and Drug Administration inspections of researchers at identifiable sites, 1977 through 1995.

COMMON PROBLEMS FOUND BY THE FDA



Inadequate or no consent records — 53%

Deviating from protocol (ground rules) — 32%

Inadequate and inaccurate records — 27%

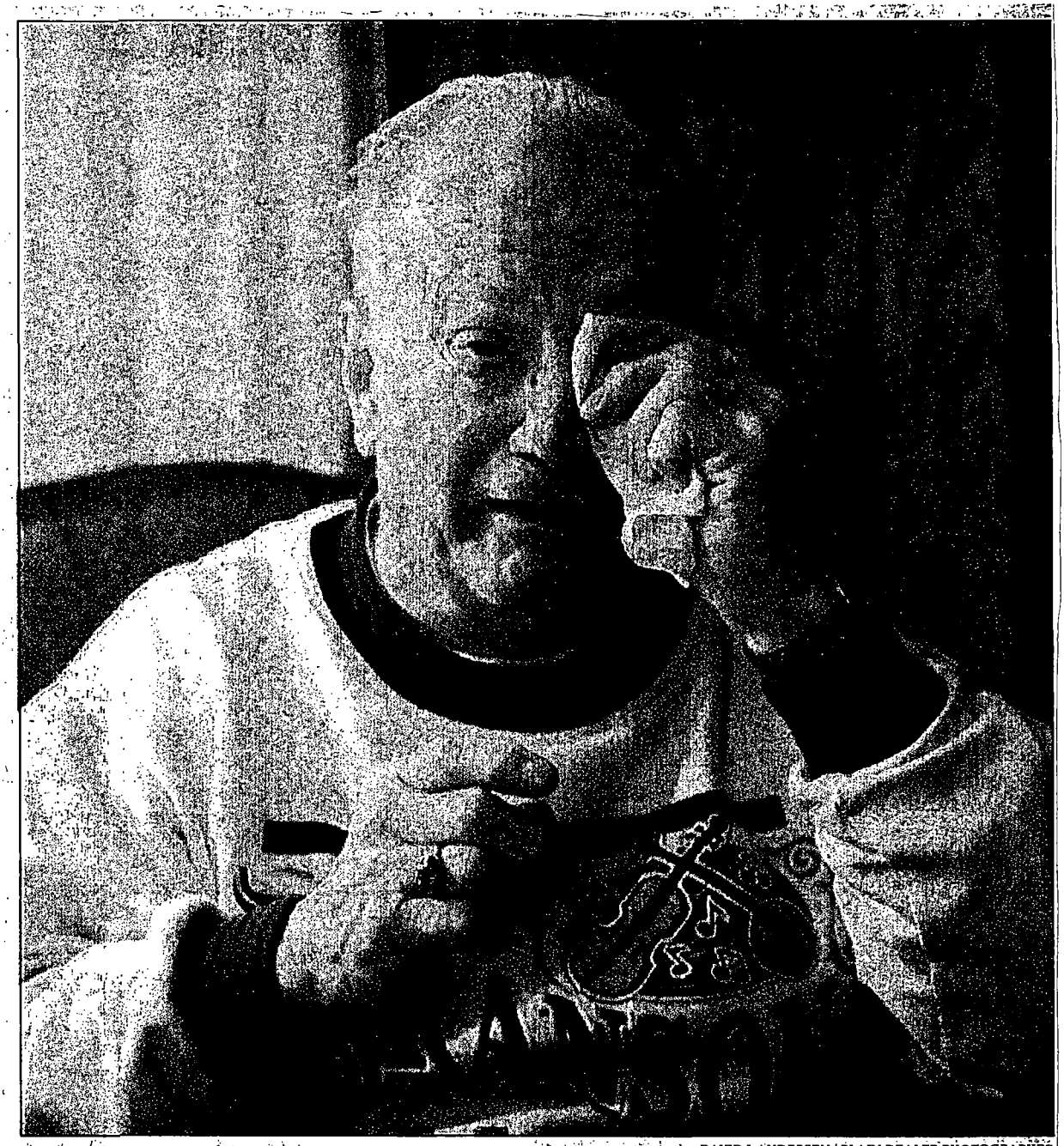
Inadequate drug accountability — 22%

Failure to inform ethics committee of changes — 9%

Using other medicines, unreported side effects, falsifying data. — 7%

Unavailable records, failure to document ethics committee approval. — 6%

Based on Plain Dealer analysis of Food and Drug Administration inspections, 1977 through 1995.



DAVID I. ANDERSEN / PLAIN DEALER PHOTOGRAPHER

Alexander Michalski says his late wife, Laura, was "my love, my friend."

Next of kin not told of drug

FDA cites policy for its silence on deaths

By BILL SLOAT
and KEITH C. EPSTEIN
PLAIN DEALER REPORTERS

The Maryland death certificate of Ralph W. Koontz says that he died of septic shock, pneumonia and lung cancer.

The National Cancer Institute and the federal Food and Drug Administration recognized another contributing factor: An experimental cancer drug.

"Drug-related early death," an FDA inspector noted in a report next to Koontz' code number, 59-54-36.

"The patient died a toxic death contributed to by the drug therapy," agreed the NCI researcher.

There was more.

Other cancer patients died in the Baltimore experiment. "Drug-related," the researcher noted about patients 52-54-04 and 54-90-52. And this: "Early death."

"They told us he died of pneumonia," said Rose Koontz, his widow. "Shouldn't [the FDA] tell people? They should have told me and my family what was going on, but they didn't."

The FDA's explanation for not telling families: policy.

It notifies the researcher. It notifies the sponsor. But it seldom notifies "third parties," — including people used in medical research or their families.

FDA Associate Commissioner Mary Pendergast said the agency might rethink its policies.

"Is there an automatic feedback loop that needs to be made to patients or their families? It's certainly worth thinking about," he said.

Koontz was a 50-year-old electrician who smoked more than a pack of cigarettes a day. He died in June 1977, four months after being diagnosed with lung cancer and two months after first receiving the test drug.

The Plain Dealer was able to identify Koontz by matching his Maryland death certificate to one in the FDA file. The family was contacted for this story.

There were 39 patients in the clinical trial. A nurse could find consent forms for only 24.

One of those who consented was Koontz, his widow said. "I told him they were using him as a guinea pig. He said if he could help someone else, he was willing to go through with it."

Alan Lisook, whose FDA division of scientific investigations compiled a thick file on the Baltimore experiment, said the agency keeps quiet under a legal opinion from its general counsel that goes back to the late 1970s.

The FDA is only allowed to notify those with a direct interest in the drug of inspection results.

Other agencies name names. The Nuclear Regulatory Commission discloses problems in nuclear power plants. The Federal Aviation Administration supplies identities of airlines in near-misses. The Environmental Protection Agency must publicize the worst air polluters.

Outside the research realm, the FDA rarely misses a chance to inform the public about a regulatory crackdown. Its 44-member public relations unit stands ready to spread almost all the news.

In one month, the FDA announced that frozen fish fillets stored in a Massachusetts warehouse had to be destroyed. Inspectors found them mislabeled: haddock was packaged as pollock.

Soviet-made night vision binoculars bound for American bird-watchers were snared by Customs agents at the FDA's request; it feared possible laser radiation.

In fact, there were five pages of such "Investigators' Reports" in the agency's April 1995 monthly news magazine.

But not a word about a North Carolina doctor, Paul W. Boyles, who was disqualified from receiving investigational new drugs. The FDA said he falsified ethics committee letters allowing him to try the drugs on people, some of whom "did not meet inclusionary criteria" — pre-existing conditions should have kept them out of the test.

Boyles responded to the FDA: "In this country, one is considered innocent until proven guilty, which they have not done."

Inspector Barbara M. Frazier thought that signatures on consent forms didn't match those on other records. One name was misspelled. Frazier suspected forgeries.

Her suspicions were never tested because FDA higher-ups said the agency couldn't afford a handwriting expert.

"The FDA can say whatever they want, but it's all untrue," Boyles said from his office at the Southern Correctional Institution in Troy, N.C., where he now is a prison physician. "I have certainly suffered the maximum harassment they can give you. You have the whole story right there."

Nothing in the FDA's files obtained by The Plain Dealer suggests Boyles' patients or their families were told of the FDA's findings.

"The sanctions are weak" in the United States, said Frank Wells, the recently retired medical director of the Association of the British Pharmaceutical Industry. "Just to disbar a person from doing research, what's that? A very minor sanction, a sanction that's rarely imposed. Such a system is really wanting."

But if doctors can dodge publicity or penalty, drug companies potentially face severe consequences if researchers fail to protect test subjects.

In September 1983, Louisiana researcher Henry W. Jolly was trying to demonstrate for a European pharmaceutical giant how safe and effective a new treatment for skin infections was.

The FDA said he tested it on prisoners in a Louisiana jail without written evidence 99 of 126 inmates had consented.

Officials responsible for the Orleans Parish prison system were "unaware of the performance of an investigational drug study at the prison," the FDA said in an internal report.

"I don't remember a damn thing about it. I didn't know they were doing anything," said Sheriff Charles G. Foti. "We never have allowed [doctors] to do any kind of experimentation on prisoners."

FDA official Frances C. Kelsey notified the company it would have to find data from other re-

searchers to support the company's claim that the drug was safe and worked — a potentially costly delay.

As for Jolly, he "will remain eligible to perform investigational new drug studies," the FDA decided, because two other experiments conducted by him were "relatively free of deficiencies."

His name would not appear on the blacklist.

Jolly, who lives in Baton Rouge, retired from medicine in 1992. A woman who answered the phone at Jolly's home said he was too ill to be interviewed.

When a drug company wanted to test the "therapeutic efficacy and side effects" of a schizophrenia drug on older people with psychiatric problems, it turned to the medical director of a Chester, Pa., nursing home, Dr. Richard J. Morris.

Some patients had delusions, couldn't care for themselves and didn't always know where they were.

Morris, who sometimes worked with University of Pennsylvania scientists, wanted to increase knowledge about the effects of drugs on older people.

Forty-seven of them were signed up — not that all of them did sign, or even could.

Patient 2 scribbled an X on the consent form.

Patient 7 scratched out a full name but had dense cataracts and impaired hearing.

The patients' "ability to exercise fully their power of choice is questionable," state health officials noted.

Permission to experiment on Patient 33 was given by a son — himself committed to a mental institution, an FDA inspector reported.

Thirteen patients died, eight receiving the drug and five within six weeks after being taken off of it. At no other study site had there been such a frequency of deaths, according to the FDA's Kelsey.

As for Morris, the FDA concluded he had "repeatedly or deliberately violated regulations pertaining to the proper conduct of a clinical study."

Some patients' ailments should have excluded them from the experiment, accurate case histories were not kept, and the deaths were not reported, according to an FDA inspection.

Kelsey offered to close the case "should you provide us with adequate assurances . . . as to research subject protection."

He accepted her terms. "I have learned my lessons," Morris replied. "I agree to abide by the FDA rules."

Kelsey was satisfied.

Morris avoided the blacklist.

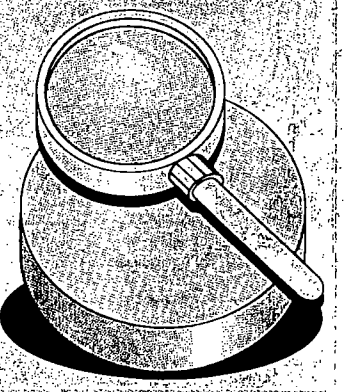
In 1985, former congressional aide Ben Gordon was helping the National Council of Senior Citizens assemble a report, "Abusing the Elderly: Drug Experimentation in Nursing Homes," when he learned of the Morris case — and others.

He found instances in which retirees who had refused experimental drugs were surreptitiously given the medications hidden in applesauce and ice cream, and in which consent forms were signed by people who were illiterate, did not speak English or were disoriented.

The report was all but forgotten.

What eventually stripped the Chester Extended Care Center of its license was not research or the question of informed consent but the sort of issues states usually focus on: urine bags being changed at the dining table, unauthorized physical restraint of patients, poor oral hygiene.

FDA INSPECTIONS AND PERCENTAGE OF TIME SANCTIONS ARE RECOMMENDED



No record of consent 2%
Number of deficiencies: 47

Inadequate patient consent form 3%
Deficiencies: 2,145

Ethics committee approval missing 6%
Deficiencies: 108

Deviating from protocol (ground rules) 8%
Deficiencies: 1,345

Inaccurate records 10%
Deficiencies: 1,141

Failure to report adverse reactions 13%
Deficiencies: 94

Selling an unlicensed drug 15%
Deficiencies: 13

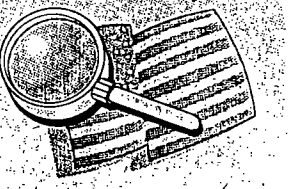
Records not available 17%
Deficiencies: 148

Administering a drug before approved for experimental use 70%

Submission of false information 94%
Deficiencies: 50

Based on Plain Dealer analysis of Food and Drug Administration inspections, 1977 through 1995.

WHAT PEOPLE MUST BE TOLD



CONSENT FORMS FOR FEDERAL RESEARCH MUST TELL PEOPLE:

1. That they are part of an experiment, why it is being conducted and how.
2. About any reasonably foreseeable risks and pain.
3. About any benefits that might reasonably be expected.
4. About alternative procedures and conventional prescriptions.
5. Whether any compensation or treatment will be available if injury occurs.
6. Whom to contact for further information or in an emergency.
7. That participation is voluntary and refusal to participate will involve no penalty.

JAMES OWENS / PLAIN DEALER

RESEARCHERS FAILED TO DOCUMENT CONSENT AT 46 SITES.

1 California: 6√
2 Los Angeles
2 San Francisco
1 San Diego
1 Irvine

2 Florida: 5√
2 Miami
1 Miami Beach
1 North Miami Beach
1 Jacksonville

3 Louisiana: 4√
4 New Orleans

4 Minnesota: 4√
2 Minneapolis
2 Rochester

5 Georgia: 2√
1 Atlanta
1 Augusta

6 Massachusetts: 2√
1 Boston
1 West Roxbury

7 North Carolina: 2√
1 Durham
1 Fayetteville

8 New Jersey: 2√
2 New Brunswick

9 New York: 2√
1 Great Neck
1 New York City

10 Tennessee: 2√
1 Memphis
1 Chattanooga

11 Texas: 2√
1 Arlington
1 Houston

12 Wisconsin: 2√
1 Madison
1 Milwaukee

13 Arkansas: 1√
1 Little Rock

14 Washington: 1√
1 Seattle

15 Illinois: 1√
1 Chicago

16 Indiana: 1√
1 Indianapolis

17 Kansas: 1√
1 Wichita

18 Kentucky: 1√
1 Louisville

19 Mississippi: 1√
1 Jackson

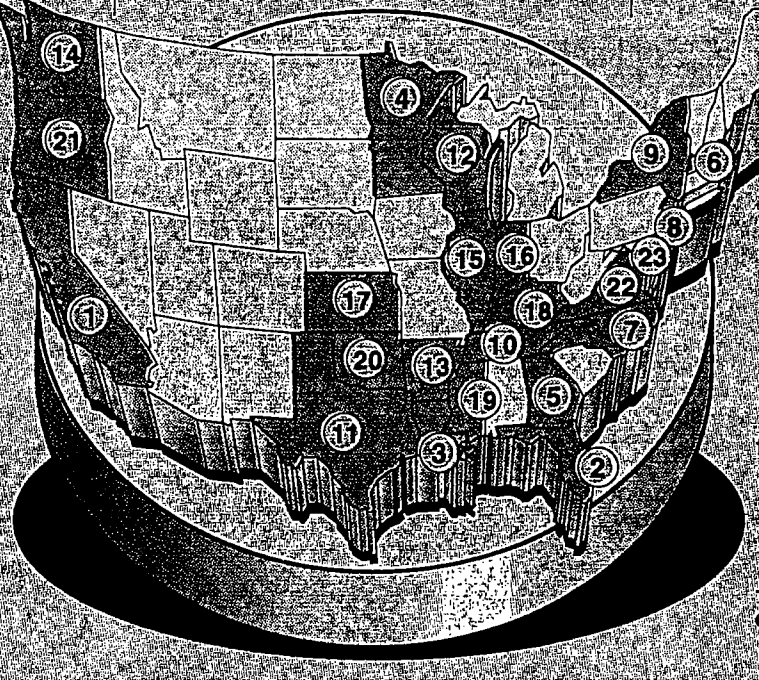
20 Oklahoma: 1√
1 Oklahoma City

21 Oregon: 1√
1 Portland

22 Virginia: 1√
1 Winchester

23 Washington D.C.: 1√
1 Washington

Key
√ Total consent violations in state



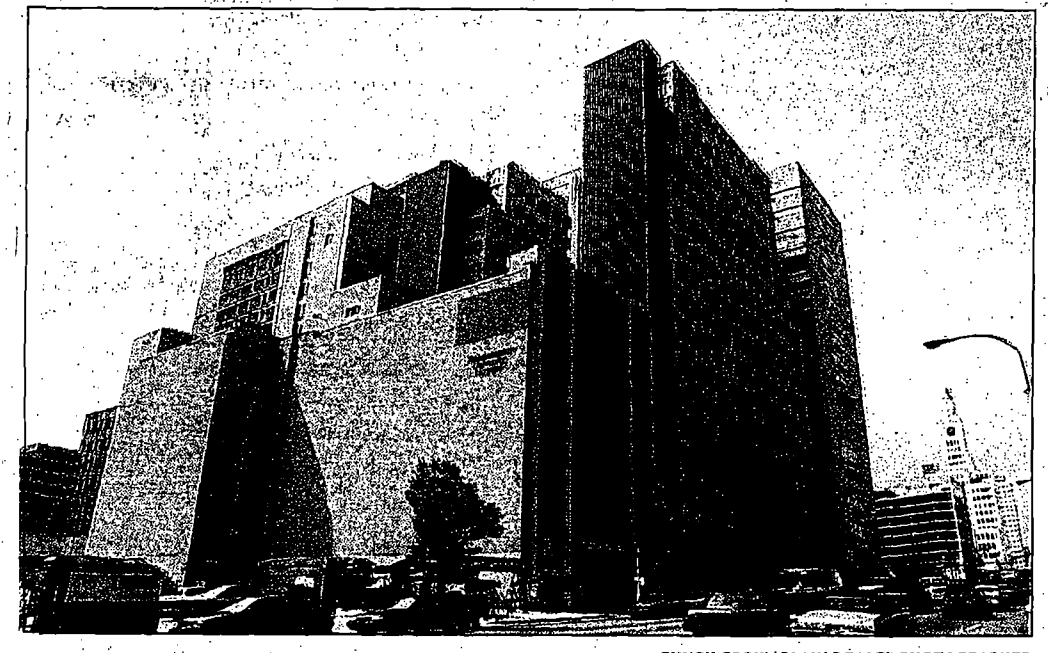
"Some consent forms currently in use are flawed in morally significant respects, not merely because they are difficult to read but because they are uninformative or even misleading."
—The Advisory Committee on Human Radiation Experiments.

"There are more inspections for laboratory animals carried out by the Department of Agriculture than there are for human subjects carried out by the entire Department of Health and Human Services."
—Charles McCarthy, former director of a federal office meant to safeguard people in government research.

SOURCE: From FDA records

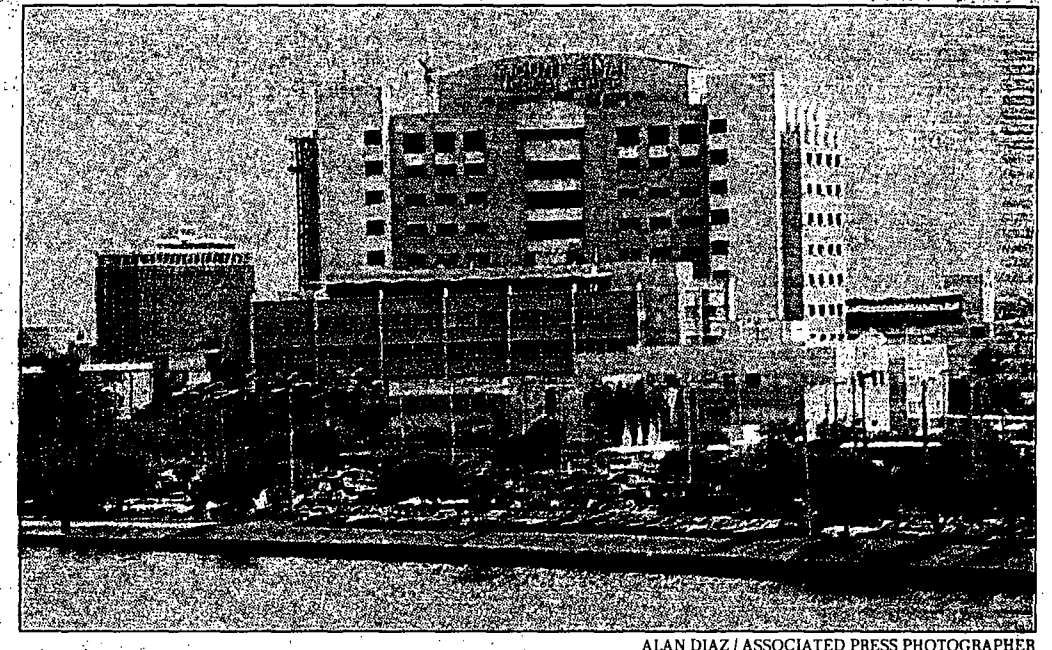
JAMES OWENS / PLAIN DEALER

THE PLAIN DEALER • DRUG TRIALS •
SUNDAY, DECEMBER 15, 1996



CHUCK CROW / PLAIN DEALER PHOTOGRAPHER

Hahnemann University Hospital in Philadelphia was the site of a pioneering radiologist's research using a solvent to dissolve gallstones.



ALAN DIAZ / ASSOCIATED PRESS PHOTOGRAPHER

FDA inspectors questioned why there was no written evidence people consented to be part of a clinical trial at the Mt. Sinai Medical Center in Miami Beach.

DRUG TRIALS

Do People Know the Truth About Experiments?

RAMON MENA OWENS / PLAIN DEALER PHOTOGRAPHER

Ella Mae White Tail says that when she signed up her daughter, Sacheen, for a hepatitis vaccination, she didn't know the vaccine's safety was being tested on children at the Standing Rock Sioux Reservation.

THE PLAIN DEALER • DRUG TRIALS •
MONDAY, DECEMBER 16, 1996

'Using our kids as guinea pigs'

An investigation of medical research records shows the U.S. government is still in the business of conducting and paying for tests on unsuspecting Americans

By BILL SLOAT
and KEITH C. EPSTEIN
PLAIN DEALER REPORTERS

AN INVESTIGATIVE ANALYSIS

Second of four articles

Not long after school started in the fall of 1991, Sacheen White Tail came home with a note from her teacher.

It was addressed to her parents, and no, the sixth-grader wasn't in any kind of trouble.

Her classwork was fine. She was still winning ribbons at swimming meets.

The note was an invitation almost too good to pass up. If her mother approved, Sacheen was eligible for a free hepatitis vaccination.

Two shots, a month apart, would "provide lifelong immunity."

Something called the "Hepatitis A Vaccine Prevention Program" was behind the offer, sent to hundreds of parents on the Standing Rock Sioux Reservation that spreads across the grasslands of the Dakotas.

Without hesitating, Ella-Mae White Tail returned the accompanying form. Her 11-year-old would get the shots at school.

"I was interested in protecting my daughter," she said.

Sacheen also wanted the gift researchers were offering. "It was an expensive mousse gel for my hair, good stuff," she said.

What Sacheen's mother didn't realize then was that the "Hepatitis A Vaccine Prevention Program" wasn't just a prevention program. It was a research project sponsored by the Centers for Disease Control and the Indian Health Service. The vaccine was being tested for a British pharmaceutical company.

"They were using our kids as guinea pigs," White Tail said. "In the beginning, I thought it was approved by the [Food and Drug Administration]. And then, I found out it wasn't."

Among other things, the government wanted to evaluate the vaccine's "safety," before allowing its use on all American children — a purpose that never appeared on the consent form distributed to the Sioux parents.

Neither did the word "experimental." Or "research."

"When you say 'experimental,' it scares off a lot of people," said Tim Yellow, the tribe's health director in Fort Yates, N.D. where a boulder marks the burial site of Sitting Bull.

Yellow had welcomed the researchers. His own daughter, Lisa, got the shot. Hepatitis A was endemic on the reservation. The contagious disease could be thwarted by better sewage and plumbing systems and more careful handwashing — and now, it seemed, also with the vaccine.

That the parents felt misled would be putting it mildly, said Yellow. His friendships grew strained. Traditional drummers at the Bear Soldier Hall appealed to the spirits to heal hard feelings and protect the children.

SEE TESTS/8-A

Unwary public still guinea pigs in drug research

THE PLAIN DEALER • DRUG TRIALS
MONDAY, DECEMBER 16, 1996

TESTS FROM 1-A

While the vaccine was eventually determined to be safe, Yellow said, the uproar has barely subsided on the reservation, where many raise buffalo and cattle a few miles south of Gen. George Custer's old 7th Cavalry headquarters.

What happened at Standing Rock is not an isolated incident.

Decades after notorious syphilis experiments on blacks at Tuskegee, Ala., and radiation studies on civilians during the Cold War, the government is still in the business of conducting and paying for medical tests on unwary Americans.

In fact, a computer analysis shows that in medical research, the pharmaceutical industry is not the most likely abuser of basic human rights.

It is the U.S. government.

Researchers working for the government have camouflaged the truth. They have omitted vital information about risks. They have failed to properly obtain permission before testing unapproved drugs with uncertain effects.

Even with prescription drugs, whose effects are largely known, doctors are expected to disclose the pros and cons and allow patients a free choice. For experimental drugs and vaccines, federal law and professional medical ethics compel doctors to disclose what they know — and don't know.

"Because the patient may not benefit. Because you may be doing harm; you don't know what the risks might be. Because this is not veterinary medicine, this is another human being," said Dr. Bernadine Healy, dean of the Ohio State University medical school and former director of the National Institutes of Health.

"In an experimental trial, you don't have the answers; that's why you're doing an experiment. So you have the heightened obligation to tell the patient — someone who trusts you with their most precious possession, their life and well-being — you don't know the answers."

Yet American test subjects have been kept in the dark or only partially informed in 63 percent of all medical research that The Plain Dealer could identify as government-sponsored from 1977 through 1995. The newspaper's analysis was based on internal FDA inspection records obtained under the federal Freedom of Information Act.

Consent forms were unclear; sometimes they were missing altogether. Such forms are like signed receipts, crucial evidence that patients were given all the information to which they were entitled.

Some forms described experimental drugs as "new therapies" or "treatments."

FDA records show that consent forms were adequate in 37 percent of clinical trials at federal research sites, such as veterans hospitals and the National Institutes of Health. Others, such as private research contractors who test drugs for the pharmaceutical industry, gave full disclosure in 50 percent of their experiments. University and hospital researchers were only slightly better than the government. They disclosed complete information to their subjects 42 percent of the time.

"If there's one principle firmly established," said Case Western Reserve University bioethicist Thomas Murray, "it's that you do not trim the truth or deceive people just because a research project is important. Some ethics questions are tough. That one's a slam-dunk. It's a short step from withholding information from subjects to what happened at Tuskegee."

The Plain Dealer's analysis parallels barely noted discoveries by a 1994 presidential advisory committee. That committee's central focus was the Cold War era, a 30-year period from the mid-1940s when federal agencies sponsored 4,000 radiation experiments involving tens of thousands of subjects, many of whom had no knowledge they were test cases.

Yet President Clinton's Advisory Committee on Human Radiation Experiments also uncovered more contemporary examples of research on unwitting Americans. "The most serious concerns focus on informed consent," the committee reported 700 pages deep within an imposing volume, thick as a Sears, Roebuck & Co. catalog.

On page 717, the committee said, "Human subject protections may be more effective in radiation research than elsewhere" — in other words, patients could be more at risk nowadays in nonradiation experiments than in the kind that triggered the committee's inquiry.

It was the radiation experiments that Clinton apologized for, agreeing to compensate some of the patients who had been exposed.

"Informed consent means your doctor tells you the risk of the treatment you are about to undergo. In too many cases, informed consent was withheld," the president declared. "The deception extended beyond the test subjects themselves to encompass their families and the American people as a whole."

Just last month, the government paid $4.8 million to 12 victims injected with uranium and plutonium without their consent. "When the government does wrong," Clinton said, "we have a moral responsibility to admit it."

Although the committee said its other discoveries involving nonradiation research were "findings that cannot be ignored," the written evidence — disclosing locations of experiments, researchers' names and the agencies involved — was boxed and shipped to a warehouse in Maryland, filed and forgotten. Some records were opened by National Archives lawyers at The Plain Dealer's request.

"Human subjects," as scientists refer to them, include the poor, the vulnerable, the medically dependent. They include former soldiers at hospitals of the Department of Veterans Affairs.

They include women with breast cancer at the National Cancer Institute. Alcoholics with hepatitis at the National Institutes of Health.

Unwary Americans used in tests

They include the Lakota people in the Dakotas, where parents like Ella-Mae White Tail effectively shut down the Centers for Disease Control's hepatitis A experiment in 1992.

Although the vaccine, Havrix, was approved by the FDA in 1995 (based on tests involving 40,000 people elsewhere) the Pine Ridge Sioux sued the government.

A federal court in January 1993 tossed out the lawsuit by the parents as moot — the clinical trial had already been halted — but not before expressing "grave doubts" about the government's conduct.

The court said the government failed to give parents "an adequate basis for informed consent."

And the court added that it expected the government to be "less cavalier . . . on Indian reservations or anywhere else."

Around then, far from the prairies, J. Thomas Puglisi had heard of a different Centers for Disease Control vaccine experiment on children, although in the barrios of inner-city Los Angeles, the CDC's preferred word was "project." As chief of the NIH's compliance oversight branch of the division of human subject protection, Puglisi monitors government-sponsored clinical trials. In this instance, the CDC was the sole sponsor.

To the mothers in Los Angeles, it all seemed routine, just another trip to the neighborhood health clinic. Their babies, 24 to 45 weeks old, were weighed and measured. Nurses collected blood samples, administered free shots, filled out charts.

Where was the infant born? the nurses would ask the mothers, many of them immigrants. Date of birth? Race? *Esta de Mexico? Esta de El Salvador? De donde esta?*

There were at least 302 Hispanic babies, 245 black babies, 58 white babies.

Mothers signed forms that mentioned something about a "project" in which "public health policy-makers" wanted to "determine the best measles vaccine strain" and "the best schedule for age of measles vaccination."

With the "E-Z vaccine," the form assured the mothers, "your child may be protected earlier against measles."

The mothers didn't see the Centers for Disease Control documents that spelled out a reason the agency started inoculating infants with E-Z during May 1990: to test the vaccine's "immunogenicity and safety."

An FDA document the mothers never saw stressed that the mothers should be warned that the outcome was uncertain.

Paul D. Parkman, an FDA official, had cautioned the CDC well before the experiment began, in October 1989, that because unpublished data suggested effects on babies' immune systems and "since the use of the E-Z measles vaccine is unlicensed in the United States and therefore experimental . . . it seems imperative that there be a strong warning on the consent form to the mothers . . . that their infants may not be protected."

Specific neighborhoods were targeted: East Los Angeles, West Los Angeles and Inglewood — communities that had experienced measles outbreaks.

To combat this resurgence, government scientists confidently turned to E-Z in a dose up to 100 times more potent and administered much earlier than Moraten, the only measles vaccine approved for American children.

"It certainly was a good potential weapon," recalls Stephen Hadler, director of the epidemiology and surveillance division of the national immunization program at the centers' Atlanta headquarters.

But in their enthusiasm, government scientists seized upon a vaccine that backfired.

In Africa, children were dying.

Months before the first California baby got a shot, immunologists were making frightful discoveries in the former French, British and Portuguese colonies near Cape Verde. Some inoculated children were dying within three years.

A French researcher saw it in Dakar, Senegal, in 1989. A Danish immunologist in January 1990 pleaded with the World Health Organization to look at his numbers from Guinea-Bissau and Senegal. It did, and so did the Centers for Disease Control.

Scientists suspected the vaccine somehow weakened the immune system, making children more susceptible to a variety of ailments. Diarrhea and pneumonia were leading causes of death in Africa.

Researchers doubted children in relatively healthy U.S. environments would be harmed, although with weaker immunity they might still become sick.

By April 1990, the news out of Africa was even grimmer. As part of a data-monitoring safety team, the Centers for Disease Control knew that the "excess mortality" had become statistically significant.

But one month later, in May 1990, its Los Angeles test went forward.

SEE TESTS/9-A

TESTS FROM 8-A

In early November, the government quietly participated in a decision, with the European researchers, to stop giving high-dose E-Z to African infants.

Among those present: the CDC's leading scientist overseeing the U.S. trial.

That same CDC scientist informed the FDA of the African deaths on March 6, 1991.

An FDA official's notes said the CDC scientist reported "a large number of children who got hi-dose EZ died" in Africa. The notes indicate that about 52 out of 300 children died, compared with 32 out of 300 who got a placebo or another vaccine.

In Los Angeles, the experiment continued.

The evidence out of Africa, explains Hadler, was just "not compelling."

Wasn't compelling until Neal Halsey came along.

A Johns Hopkins University researcher under contract to the State Department's Agency for International Development, Halsey had during the 1980s inoculated babies with E-Z in a Haitian shantytown. Doubting the findings in Africa, he went back to the shantytown, expecting to show the Haitian babies were better off.

"We actually set out to demonstrate there wasn't an effect," he said. "We found there was." High doses of E-Z were associated with increased mortality.

Halsey dialed the CDC. The Los Angeles test was stopped.

By then, it was October 1991, and the mothers of 1,192 children had allowed their children to randomly receive two vaccines, one of which was E-Z. Four hundred and eighty-five babies had received the highest dose. Another 217 had been inoculated with a less-intense form of E-Z.

"So far, there's no evidence of any untoward effects," say Hadler. "In the U.S., there's n evidence this vaccine causes problem in healthy children."

CDC internal data obtained b The Plain Dealer do show som changes in the immune syster of some vaccinated children, bu the significance remains unde study.

Then there was Ricardo Muno the son of a 21-year-old Mexica immigrant, Rafaela Lopez Bara jas.

Ricardo, nearly 23 months ol died on July 14, 1992, of "clostr dium dificile enteritis" an "probable viral gastroenteritis according to the coronor's report

The CDC has not publicly iden tified the boy. It acknowledge died 15 months after receiving standard dose of E-Z. CDC docu ments show the death occurre when the child was 23 months ol in July 1992. A document state "causes of death per death certi icate" were: "clostridum dificil enteritis" and "probable vira gastroenteritis."

A search of California record showed no other death of a bo that age from those causes in Jul 1992.

"It came all of a sudden," sai Maria Socorro, Ricardo's c madre, or godmother. She live with the boy and his mother in cramped, yellow stucco walkup i the largely Hispanic enclave Bell Gardens, Calif.

"The little boy was nice, an healthy, sweet fat cheeks. He wa a happy child. And then, all of sudden . . . two days of vomiting diarrhea and coughing, and thi illness took him."

On the evening of the secon day, he was found unconsciou vomit like coffee grounds aroun his head. "Natural causes," cor cluded the coroner.

The CDC, in public descrip tions of the death, acknowledge only that a child vaccinated wit a less intense dose of E-Z died o acute dehydration and shock fo lowing several days of diarrhea

cteria were found in his stool. also said the death was unre-ed to the vaccine.

A month after The Plain Dealer terviewed CDC officials about e vaccine research, the agency sued a press release that for the st time publicly disclosed the easles study.

Once more, the agency stated tegorically that "no problem is pected" among the children in os Angeles.

"Disingenuous," was how Brian ard reacted to the government's atements, after The Plain ealer provided him with a copy Ricardo's autopsy report and e immunologic data on the Los ngeles children from the CDC's ternal files. Ward, in Montreal McGill University's Center for ropical Diseases, is a leading xpert in infectious diseases.

He theorizes that E-Z might rev p the immune system against ertain ailments, while weak-ning it against others.

Ricardo's death seems "com-atible with the deaths that oc-urred" in Africa and Haiti, Ward aid.

Yet neither is there proof the accine was to blame for Ricar-o's death; E-Z may have had othing to do with it.

"Based on what I've seen, you an't prove it either way. It's an pen, legitimate question," said Vard.

And while the CDC points to re-earch in other developed coun-ries as evidence of safety, Ward autions that too few children vere involved to draw a firm con-lusion.

Despite its pronouncements of ertainty, the government is still ollecting blood samples to learn vhether the vaccine harmed or nly insignificantly altered the hildren's immune systems. Re-ults are due in July.

"We fully acknowledge that it vas a mistake" not to tell the fam-lies the vaccine was experimen-al, said Dixie E. Snider Jr., asso-iate director of the Centers for Disease Control. "The major problem is that the consent form did not specifically identify the E-Z vaccine as being an unlicensed vaccine. Some people would call that experimental."

Last summer, the goverment fi-nally notified the parents in Los Angeles that the E-Z shots were experimental, thanking them for helping "benefit medical science by increasing our knowledge."

In Atlanta, the CDC research staff was ordered to undergo training in "human subject pro-tection."

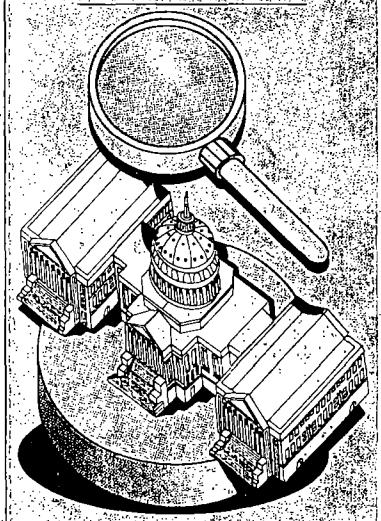
RAMON MENA OWENS / PLAIN DEALER PHOTOGRAPH

When you say 'experimental,' it scares off a lot of people," says Tim Yellow, tribal health director for the Standing Rock Sioux.

JACK KUSTRON / ASSOCIATED PRESS PHOTOGRAPHER

Dr. Bernadine Healy, dean of the Ohio State University medical school and former director of the National Institutes of Health, says researchers have a "heightened obligation" to patients in clinical trials.

FEDERAL RESEARCH SITES WITH THE MOST CONSENT PROBLEMS



Number of consent deficiencies: 8
National Institutes of Health
State: Maryland
City: Bethesda

Consent deficiencies: 8
Veterans Administration Medical Center
State: Florida
City: Miami

Consent deficiencies: 8
Veterans Administration Medical Center
State: Minnesota
City: Minneapolis

Consent deficiencies: 6
Veterans Administration Medical Center
State: California
City: Los Angeles

Consent deficiencies: 5
Veterans Administration Medical Center
State: Georgia
City: Augusta

Consent deficiencies: 5
Veterans Administration Medical Center
State: California
City: Long Beach

Consent deficiencies: 5
Veterans Administration Medical Center
State: New Mexico
City: Albuquerque

Consent deficiencies: 4
Middletown Veterans Administration Hospital
State: Wisconsin
City: Madison

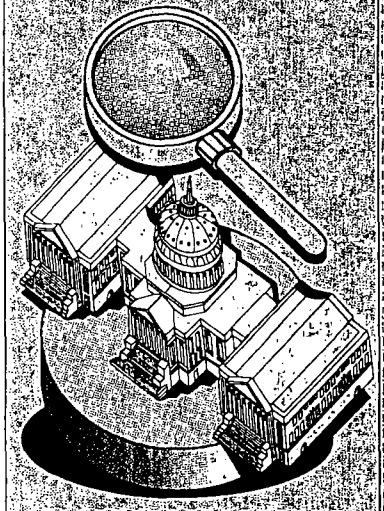
Consent deficiencies: 4
Carl T. Hayden Veterans Administration Medical Center
State: Arizona
City: Phoenix

Consent deficiencies: 4
Audie Murphy Veterans Memorial Hospital
State: Texas
City: San Antonio

Deficiencies include inadequate consent or no record of consent. Based on Plain Dealer analysis of Food and Drug Administration inspections of researchers at identifiable sites, 1977 through 1995.

JAMES OWENS / PLAIN DEALER

POSITIONS DEDICATED TO MONITORING GOVERNMENT-SPONSORED HUMAN RESEARCH



Department of Health and Human Services ▷ 57 positions

Food and Drug Administration ▷ 33 positions

Department of Defense ▷ 80 positions

Department of Energy ▷ 7 to 10 full-time positions, with program director devoting 85 percent of time to human subject protection

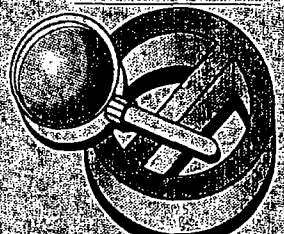
Veterans Administration ▷ 51 full-time field staff

NASA ▷ Equivalent of half-time position

CIA ▷ One senior staff physician (four hours per month)

This estimate includes full-time equivalents, the combined efforts of employees who spend part of their time monitoring human research.

PROBLEMS FOUND BY THE FDA WITHIN GOVERNMENT RESEARCH FACILITIES



Inadequate or no consent records — 63%

Deviating from protocol (ground rules) — 31%

Inadequate and inaccurate records — 25%

Inadequate drug accountability — 21%

Based on Plain Dealer analysis of Food and Drug Administration inspections, 1977 through 1995.

U.S. records show consent forms often incomplete

By KEITH C. EPSTEIN and BILL SLOAT
PLAIN DEALER REPORTERS

The government's use of Americans in medical research without written evidence of their informed consent goes far beyond chilling accounts of Cold War radiation experiments.

Such research has been sponsored by agencies with sterling reputations for benefiting society: the National Cancer Institute, the National Institutes of Health, the Department of Veterans Affairs.

Members of the White House Advisory Committee on Human Radiation Experiments, convened in 1993 to investigate Cold War-era abuses, happened upon some startling if unheralded discoveries about contemporary government research.

In the course of its work, the committee analyzed 100 federally financed experiments under way in the 1990s. The committee agreed that almost half of the consent forms were flawed.

"I was stunned by what we found. I thought maybe things had improved, but they hadn't," recalled Jay Katz, a Yale University professor who served on the 14-member presidential committee. In the 1970s, he worked on a similar inquiry after the Tuskegee experiment was disclosed.

University of Pennsylvania physician Eli Glatstein, another committee member, said it looked as if federal scientists rounded up test subjects "the way some people sell used cars."

Files of the FDA and National Institutes of Health depict years of ethical breakdowns, well into the 1990s. Those 2,060 pages of reports and medical data gathered during 216 inspections of government-sponsored researchers were obtained under the federal Freedom of Information Act. They parallel findings of the White House committee, whose records are stored in a vault at the National Archives and were opened at The Plain Dealer's request.

In one study, consent forms stated a cancer drug "may shrink your tumor or cause it to temporarily disappear, and/or prolong your life and/or improve the quality of your life."

The committee determined researchers wanted to learn the drug's toxic effects.

Doctors trying another new drug failed to make it clear that the substance was suspected of causing irreversible brain damage. That crucial piece of information," the committee found, "was not highlighted as a specific risk."

Veterans in a Defense Department study of bladder cancer weren't told that two of 27 people had died on the experimental drug, and that the consent form "wildly overstates reversibility of side effects," the White House committee wrote.

A better, proven drug was not offered to them, the committee reviewer said.

Men, women and children in a National Institutes of Health cancer study were offered alternatives, but "in a coercive manner," according to the committee. Doctors downplayed benefits of proven drugs to their patients and suggested the unknowable — that the test drug would help them.

In a 1993 clinical trial, an Energy Department researcher paid people $100 to take cocaine intravenously.

Some were addicts recruited from the Northport, N.Y., Veterans Affairs Hospital detox center.

Brookhaven National Laboratory wanted to find out if the brain of a cocaine addict responds differently to cocaine from the brain of a nonaddict.

"Ethically unacceptable" was how the reviewer for the presidential committee saw it. The experiment had "no medical benefit." The consent forms were "wholly inadequate — terrible, in fact."

The doses were small, but the committee remained concerned about "undue inducement. ... These are probably cocaine addicts, probably not employed, in a long detox," the reviewer noted. Also questionable was exposing healthy nonaddicts to "greater than minimal risk."

Nora D. Volkow, the Energy Department scientist in charge of the cocaine study, called the criticism "a totally and absolutely irresponsible, automatic, knee-jerk reaction."

The test subjects were not harmed, said Volkow, director of nuclear medicine at the laboratory.

After the White House committee challenged the study, Brookhaven resubmitted the project to three ethics boards, which said the project could proceed.

"We use trace doses. The cocaine is in the microgram range," said Volkow. "Sure, all of our patients are in detoxification, but there is no reason we cannot investigate addicts. How else would you learn how it affects them? This is research."

FDA inspectors have also raised questions about research at veterans hospitals. In five experiments since 1977, inspectors were unable to find signed consent forms. In 108 studies at 54 hospitals, veterans were given deficient consent forms.

The research questioned by FDA inspectors included the following.

In Long Beach, Calif., in 1990: Researchers signed up test subjects who were either drunk, sedated or psychotic.

In Los Angeles in 1988: The FDA caught a researcher experimenting on two veterans without getting any consent. The physician said he had made a mistake, though he had been caught making the same mistake five years earlier.

In Portland, Ore., in 1980: No written documentation was found that a doctor had obtained consent from alcoholics injected with a test drug. A number of patients died several months after the study.

The physician maintained the deaths resulted from "the patients' inherent medical disabilities."

In Salt Lake City in 1985: "Severe deficiencies in ... informed consent" were found, including a failure to explain "procedures which are experimental." There were no written records that two patients had given consent.

In Madison, Wis., in 1983: The hospital lacked written evidence of consent from at least 28 of 51 veterans given an experimental antibiotic for urinary tract infections. The urologist said it had been "an oversight."

When the National Research Council took a close look at experimentation in veterans hospitals in the 1970s, it found 28 percent of patients interviewed at four hospitals "were not aware they were taking part in a research study."

Only one VA researcher, in 1983, has been denied access to investigational new drugs.

Study after study, some financed by the VA, focused on another problem: Patients needed a college education to understand most consent forms. The University of Colorado in 1989 said patients needed the reading comprehension level of a college sophomore. Fewer than one-third of VA patients are college educated.

Congress first gave the FDA authority to police studies of experimental drugs, including government-financed studies, in the 1960s. It happened after a alert FDA medical officer Frances O. Kelsey, almost singlehandedly brought to light the uncontrolled testing on pregnant women of a sedative, thalidomide that caused severe birth defects.

Since then, Kelsey has overseen more than 4,000 FDA inspections.

"I've seen a tremendous improvement since 1962, but we can hardly breathe a sigh of relief and say we don't have to worry about this anymore," she said.

More than most people, Paul Melstrom knows why.

When Melstrom, 56, signed up at the National Institutes of Health to try a test drug in 1991, he thought it might rid his body of hepatitis. The drug, fialuridine, says Melstrom, "was a failed cancer chemotherapy drug. They tried it as a lip balm ... for cold sores. Then AIDS makes it dawn on civilization, and they try for that. Then hepatitis."

Doctors thought the drug was safe. There had been tests on woodchucks that weren't harmed.

"I took a swig of this stuff – you had to measure it out of a bottle — and I was told there was absolutely nothing to worry about, there were absolutely no side effects from this drug," Melstrom recalled.

"It tasted marvelous, much like [the orange liqueur] Grand Marnier."

Three months later, his legs started cramping. The pain limited his ability to walk. The drug, he said, had permanently

damaged his nerves.

In July 1993, the government sent him a letter explaining that the drug was toxic in humans. Five people in the experiment were dead and two others needed liver transplants. The research project had to be halted.

Fiactibine, a closely related drug, had already caused trouble.

A year before Melstrom began swigging, fiactibine had been tested by a veterans hospital researcher in San Diego.

Two people died.

The FDA came down hard in 1994, when inspectors concluded that the consent form adopted by the San Diego VA hospital failed to clearly explain to patients that the two related drugs carried "risks of nervous system toxicity."

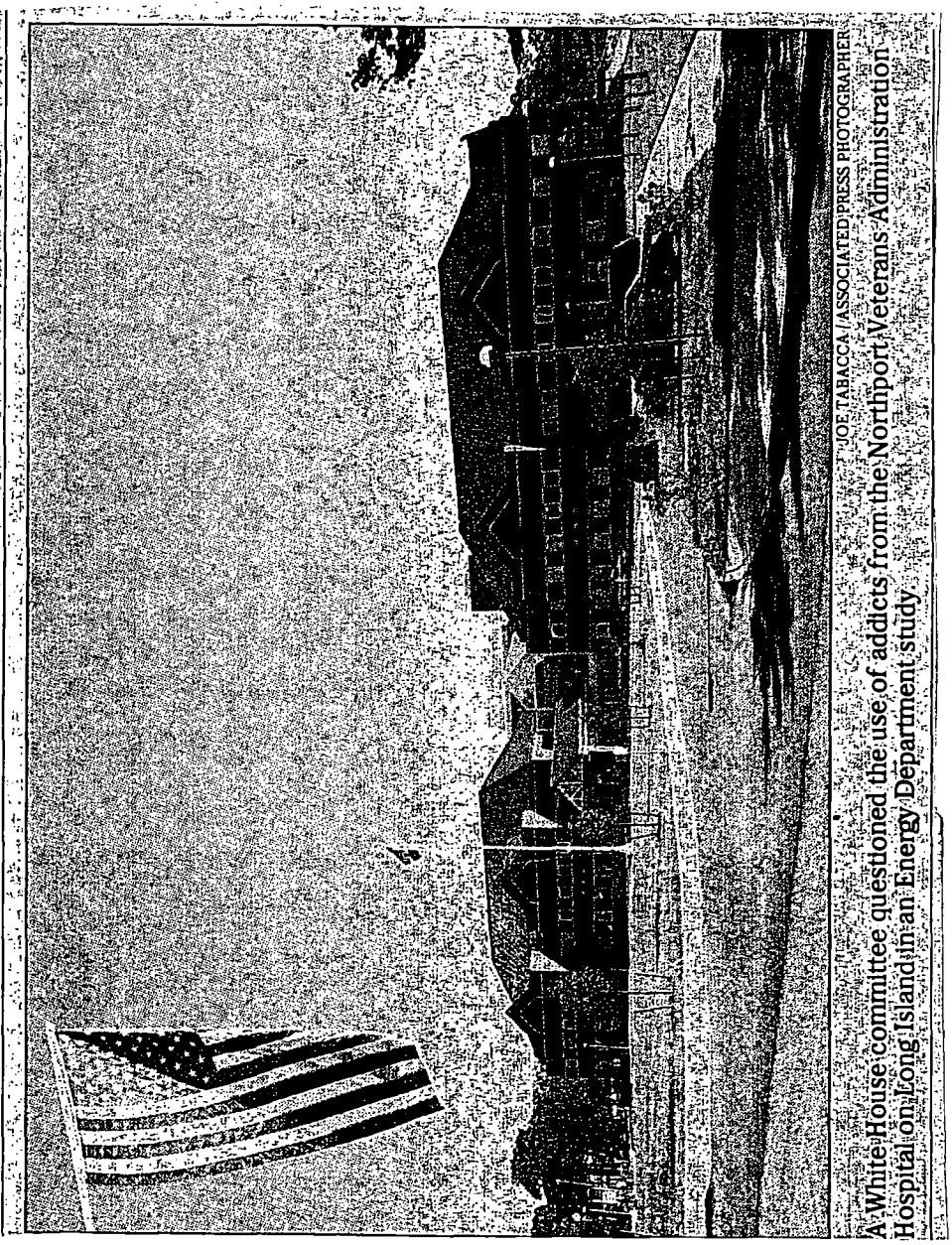
The FDA also found that the researcher, Douglas Richman, had failed to report the injuries and deaths to proper authorities.

Richman declined comment, except for referring to a 1995 National Academy of Sciences report as a "quite balanced" account of the affair. The report concluded federal researchers were "blind-sided" by the drug's toxic effects.

Roger L. Williams, director of the FDA's office of pharmaceutical science, said the deaths in Richman's study "might have predicted and prevented" the later deaths. "Without a doubt the information [about the earlier studies] should have ended up in the consent form."

Melstrom agrees: "I didn't find out anybody was dead until after I'd taken it. There was no mention of somebody dying in San Diego. It wasn't mentioned in the consent form. Nobody said anything. That would have alerted me that this was something I wouldn't want."

THE PLAIN DEALER • DRUG TRIALS • MONDAY, DECEMBER 16, 1996



JOE TABACCA / ASSOCIATED PRESS PHOTOGRAPHER

A White House committee questioned the use of addicts from the Northport Veterans Administration Hospital on Long Island in an Energy Department study.

LANDMARK EVENTS IN HUMAN SUBJECT PROTECTION

From 1977 through 1995, federal Food and Drug Administration inspectors find 2,201 consent problems, records show.

THE EVENT

Unsuspecting patients given thalidomide, causing severe birth defects.

National Institutes of Health finds few protections for people in research.

Injection of live cancer cells into older patients at Jewish Chronic Disease Hospital revealed.

Human radiation experiments at University of Cincinnati made public.

Disclosure that treatment was withheld from black men with syphilis in Tuskegee, Ala.

YEAR '61 '62 '63 '64 '65 '66 '67 '68 '69 '70 '71 '72 '73 '74 '75 '76 '77 '78 '79 '80

FEDERAL ACTION

First federal law requiring consent of research subjects.

Surgeon General issues guidelines for protecting federal research subjects.

Congress enacts first human subject protections. Research without consent is banned.

National commission established by Congress to make recommendations on bioethical issues.

First regulations for research involving fetuses, pregnant women and prisoners.

Previously classified Cold War era human radiation experiments revealed.

President's Advisory Committee on Human Radiation Experiments questions human protection system.

'81 '82 '83 '84 '85 '86 '87 '88 '89 '90 '91 '92 '93 '94 '95 '96

Health and Human Services adopts regulations for research involving chlidren.

Fifteen federal agencies adopt consent regulations known as the Common Rule.

National Bioethics Advisory Commission begins review of existing rules.

JAMES OWENS / PLAIN DEALER

DRUG TRIALS

Do People Know the Truth About Experiments?

Foreign tests don't meet U.S. criteria

Hype, hope and heartbreak a chronic condition

By KEITH C. EPSTEIN and BILL SLOAT
PLAIN DEALER REPORTERS

Trouble started on Oct. 12, 1994, when two inspectors from the Food and Drug Administration entered Dr. Geoffrey Dusheiko's cramped office on the 10th floor of London's Royal Free Hospital and flashed their badges like FBI men.

They got straight to the point. Did ribavirin really work?

The government had been asking the same question for two decades.

The first time, the drug's maker hailed it as a treatment for viruses like influenza.

The FDA said it wasn't.

In the 1980s, activists smuggled it from Mexico when scientists touted it as a therapy for AIDS. The FDA said it wasn't.

Now, it was back — a drug in search of a disease.

The hope this time: Ribavirin could combat a deadly strain of hepatitis virus that infects almost 2 million Americans.

For the desperately ill, there finally seemed a glimmer of hope. On Wall Street, investors were tantalized; sales of the capsules might exceed $500 million a year. In Ohio, the teachers' pension fund sank almost $14 million into the drugmaker's stock.

Without much ado, Dusheiko defused the optimism. After four years of European tests, he privately told the FDA inspectors in his office that ribavirin had shown no sustained benefit. Despite improvements in liver function tests, Dusheiko's research had demonstrated "little antiviral activity."

PHOTO BY MICHAEL CRABTREE

Dr. Geoffrey Fairhurst was denounced by his peers in England who said he had involved his patients in pharmaceutical trials without their knowledge. Story, 10-A.

AN INVESTIGATIVE ANALYSIS

Third of four articles

The manufacturer, ICN Pharmaceuticals Inc., had submitted Dusheiko's findings as evidence that ribavirin was safe and effective. The FDA inspectors concluded he had incomplete biopsy reports, had failed to record all adverse effects and had used an inadequate consent form.

Once again, the FDA rejected ribavirin, though for four months only a handful of insiders knew. When word spread, the stock plunged — 42 percent within two weeks. Some shareholders accused insiders of selling stock before bad news deflated the price. Soon, the FBI — the real FBI — started asking questions.

SEE FOREIGN/10-A

THE PLAIN DEALER • DRUG TRIALS • TUESDAY, DECEMBER 17, 1996

Foreign testing standards don't meet FDA's criteria

FOREIGN FROM 1-A

Possible insider trading. Thrilling projections. Criticism from an American agency. Questions about consent. The FBI. It all left the researcher in London, who thought he had played by the rules in England, feeling bewildered.

"We did not know that the results would be submitted to the FDA," Dusheiko said. His lawyer said the study "did not violate any legal standards in England. ... FDA standards were not applicable."

The cycle of hype, hope and heartbreak surrounding clinical trials has become a chronic condition in the increasingly global pharmaceutical industry, which now initially tests nearly two-thirds of all products for Americans overseas, 64 percent more than in 1975.

Previously undisclosed foreign records and more than 2,000 pages of internal FDA documents contain accounts of fraud, concealed side effects, improvised experiments and human rights abuses. Consent forms were incomplete or inadequate in 65 of 137 FDA inspections of foreign drug trials. In the most inspected nation, Canada, consent forms were inadequate in 21 of 36 inspections.

"Fraud and unethical conduct and sometimes mistreatment of human subjects is present everywhere," observed Jean-Marc Husson of the French pharmaceutical firm Roussel-Uclaf, who estimates one in 10 European drug trials is fraudulent. "We need to have a better global system to detect and deal with fraud."

But the industry's most crippling ailment is this: More than half the foreign research submitted by pharmaceutical companies to the FDA during the last decade lacked vital documentation such as X-rays, blood tests, biopsies, lab reports and patient charts.

Verifiable scientific data was missing from 53 percent of the international research known to have been submitted to the FDA, contrasted with only 27 percent of research submitted from the United States, a Plain Dealer computer analysis shows.

Asked about The Plain Dealer's analysis, FDA Associate Commissioner Mary Pendergast said the reason for the disparity is that overseas trials of investigational new drugs can begin without FDA permission.

Thus, she said, "there's no expectation up front" that human research will meet U.S. regulations.

Any company with the $116,500 deposit for a New Drug Application can make an exciting claim and submit summaries of research findings. Only the details contained in humdrum, everyday medical records can separate the miracle cure from the snake oil.

Examples of missing, manufactured, altered or omitted data have been found by FDA inspectors on five continents.

Hopes for a new low-dose birth control pill for American women were dashed when doctors in Mexico City were unable to produce any records from tests on 1,000 patients. The records had been thrown away, the doctors said, because they wanted to avoid Mexican taxes on income from a U.S. drugmaker.

In Edmonton, Alberta, a few years later, the FDA found records. But they differed from summaries the British drugmaker submitted in 1986. Women on a breast cancer drug were said to have had a "partial response" when they had no response. A woman reported to have "no change" in her condition had actually gotten worse. And in a patient with a tumorous mass, doctors noted "no measurable disease."

In Glasgow, Scotland, in 1990, cardiologists testing for an American pharmaceutical company did not disclose to some patients the risks of a heart drug and could supply no written evidence they had obtained consent from 10 other patients, an FDA inspector found. Researchers also lacked lab data and failed to mark dates of echocardiograms, and some side effects went unreported, according to the inspector.

"Nobody's immune to this problem or its potential consequences. Missing records and faulty records always raise red flags,"

THE SERIES

SUNDAY: At least 1,000 Americans in 23 states have been used in medical research without required evidence of their informed consent.

YESTERDAY: Decades after notorious syphilis experiments on blacks at Tuskegee and radiation studies on civilians during the Cold War, the government is still conducting medical tests on unsuspecting Americans.

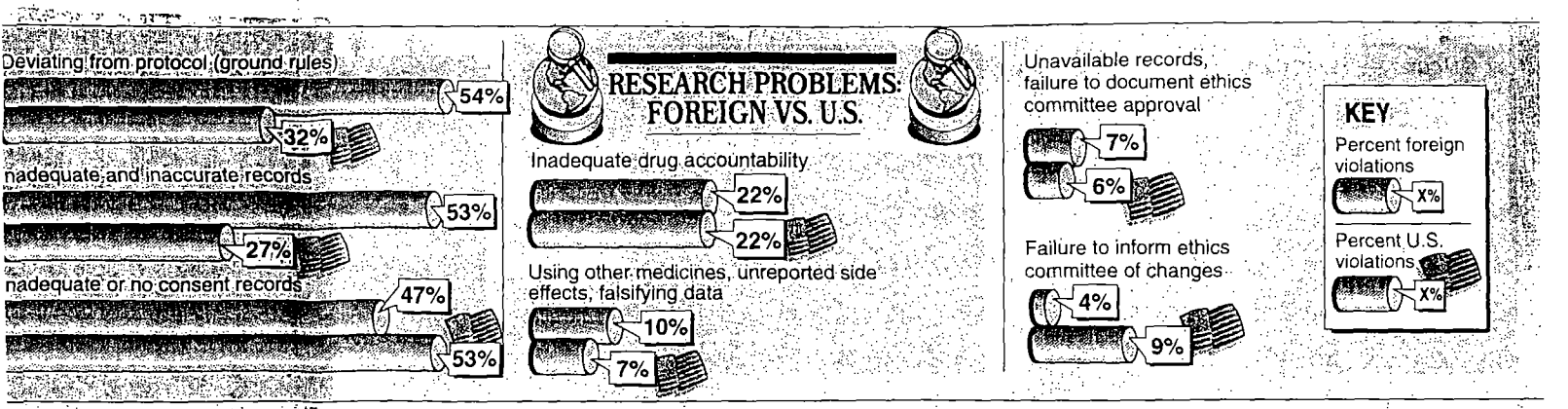
TODAY: More than half the foreign research submitted to the Food and Drug Administration over the last decade was unreliable. Verifiable scientific records from other countries were missing in 54 percent of requests for new drug approvals in the United States.

TOMORROW: Local ethics committees, the front line in protecting test subjects, frequently fail to ensure that people know they are being used in medical research.

If you have comments about the series, call 999-5260, fax 999-6366 or e-mail the reporters at:

tgaumer@plaind.com

Include your name and a daytime telephone number.



d on a Plain Dealer analysis of Food and Drug Administration inspections worldwide, 1977 through 1995.
lving drugs seeking FDA approval for use in the United States.

JAMES OWENS / PLAIN DEALER

said Arthur Horowitz, who prepares researchers for FDA investigations by inspecting them first himself.

Horowitz has a list of excuses he has heard. The alibis sound like "my dog ate it," the schoolboy's classic excuse for missed homework: They were destroyed in a fire/flood/hurricane/earthquake. They were dropped in a sewer. They were lost in a boating accident. My office was burglarized. They were lost in the mail. My father-in-law threw them out.

For Hans-Joachim Giesecke, a busy German internist in the industrial city of Mainz, the difficulty arose over quinapril capsules. During 1985 and 1986, Giesecke tested them on his elderly patients with congestive heart failure.

Like Dusheiko, he had no idea his results would be offered as evidence that the product should be approved for Americans. And how could he? Back then, even the Parke-Davis Group of pharmaceutical giant Warner-Lambert Co. had no plans to seek U.S. approval. At most, Parke-Davis anticipated the drug might be successful in Europe.

"The U.S. marketing department wasn't interested," recalled Hans Gunther Stelzer, who oversees Parke-Davis research in Europe. "Our goal was Europe, that was all."

Within a few years, Parke-Davis sensed it had missed the mark — or was about to. Worldwide sales of the newest class of drugs for congestive heart failure, known as angiotensin-converting enzyme (ACE) inhibitors, by 1992 soared to $5 billion, nearly $2 billion in the United States.

Parke-Davis again compiled the paperwork given to German authorities, who had approved the drug.

By 1993, summaries of the research, by Giesecke and two other German physicians, were at FDA headquarters. All three declined to be interviewed.

It fell to Stelzer to double-check the data. As manager of clinical quality assurance, he often treks across Europe conferring with researchers and examining their records. When the FDA asks to inspect, Stelzer's job is to try to get there first.

When he got to Giesecke's office at 1 Erthalstrasse to check the patient records, the doctor "invited me into his basement and said he was sorry but he couldn't find them anymore."

Then, on May 24, 1993, a pair of FDA inspectors showed up at Giesecke's doorstep. With Stelzer looking on, the doctor began giving them records.

"I was sitting there, and I was very surprised when [Giesecke] suddenly showed them some records that hadn't been there before," recalled Stelzer. "I was very nervous indeed."

The ink appeared to be fresh, an FDA inspector noted. A study card for patient No. 11 bore erroneous dates, Feb. 4 to May 30, 1996, still three years in the future.

How could this be? the inspectors asked.

"I don't know," they quoted Giesecke as answering. "It was a very big mistake."

Perhaps, he speculated, somebody spilled coffee on the original in 1986 or 1987 and the nurse made a new card with incorrect dates.

"I think he was embarrassed and, because the FDA was coming, he wanted to show he kept good records," Stelzer speculates. "But it all looked so new."

At the two other test sites, there wasn't enough reliable data for FDA approval; the company substituted results from Britain.

The British results were verified and finally, in October 1993, the FDA approved quinapril for U.S. marketing — a delay caused not by excessive bureaucratic red tape, but by the drug company's submission of questioned research.

Stelzer said the experience prompted changes at Parke-Davis. "Even though many German clinicians don't keep their records, and neither do many doctors in private practice throughout Europe, now we insist on it."

Quinapril has proven successful. Sales last year shot up 37 percent.

Raymond J. Lipicky, director of the FDA's Division of Cardio-Renal Products, which reviewed Parke-Davis' application, sees quinapril as "a perfect example of the problem of lack of source documents" in foreign research.

"We make decisions based on numbers and doing statistical tests on those numbers. If the results are not accurate ... all of our conclusions are wrong. If our conclusions are wrong, it means we've decided something is effective when it isn't, or safe when it isn't."

As for ribavirin, it continues to be used in the United States as a spray to treat infants hospitalized with severe respiratory tract infections caused by the respiratory synctal virus. Twenty-one developing countries have approved it for hepatitis.

ICN has granted Schering-Plough Corp. a license to try the promising combination of ribavirin with interferon A.

A special committee of ICN's board of directors has exonerated the company's top executive of insider trading. The lawsuits continue.

Meanwhile, scientists are on the trail of yet another potential breakthrough. They've started experimenting with a Syrian folk cure for hepatitis — a liquid extract from a plant called the salt cucumber.

THE PLAIN DEALER • DRUG TRIALS
TUESDAY, DECEMBER 17, 1996

Research standards overseas vary greatly

Europeans worry about fraud, sloppy drug experiments

By BILL SLOAT
and KEITH C. EPSTEIN
PLAIN DEALER REPORTERS

With human lives and huge investments at stake, the global pharmaceutical industry has a sense of anxiety over its growing reliance on research from outside the United States, where standards tend to be less strict and widely divergent.

"It's our little secret. ... It's frightening. I could tell you so many stories. We all can," said German pharmacologist Joachim Schwarz, whose North Carolina contract research company, Quintiles, runs experiments for drug companies on four continents.

Stephen Lock, former editor of the British Medical Journal and now a research associate at the Wellcome Institute in London, crisscrosses Europe these days, pleading for a renewed devotion to solid science.

He took his message to Cologne, Germany, in March, where mostly European pharmaceutical managers had congregated to learn the latest techniques for stanching the flow of bogus research. Such industry-sponsored training sessions on fraud and misconduct in clinical trials are becoming commonplace.

"Few people outside science realize it, but we've reached the point where we must be suspect of any data being submitted. Once, facts were sacred. Now we've got to query the facts," Lock told the gathering.

Iain E. Gillespie, former dean of the University of Manchester Medical School in England, was more blunt. The consequences of sloppy recordkeeping can be as harmful as fraud, he said. "Some people believe there are different degrees of sinfulness," Gillespie told the gathering. "I subscribe to a more Calvinist view — all sins are serious."

Within sight of the towering spires of northern Europe's largest cathedral, the cocktail chatter of the industry insiders turned to confessions of scientific sin.

"We just had a case," said Klaus-Peter Barth, who had overseen European tests of an anti-allergy medication. "All the patients were invented, every one. It hurts. ... Now we have to do [the study] again."

Peter Brock, medical director for Lederle-Wyeth U.K., offered another account. Without revealing too much, Brock said fraud by two researchers had stalled approvals of six drugs.

"It's all serious, because it can have a major impact on safety."

Nils Axelsen, of the Danish State Serum Institute, related a story about a U.S. drug company that offered a professor a completed paper ready for publication; all he had to do was sign his name.

Robert Donnelly of Janssen-Cilag Ltd. told of an English doctor who altered study dates and birth dates, "using real patients as phantom subjects." The drug test was designed for older patients who could not climb stairs; one patient turned out to be 16 years old.

What was common knowledge in Cologne is commonly denied in Congress, where the Food and Drug Administration is under attack for taking too long to approve drugs that are developed overseas. Republicans such as Rep. Joe Barton of Texas complain that the FDA is overzealous, and they urge even greater acceptance of drugs developed overseas. Barton has said he doubts there is more fraud and incompetence in Europe than in the United States.

That is not how Frank Wells sees it. In Europe, "nearly every one of us has some experience with fraud," said Wells, recently retired medical director of the Association of the British Pharmaceutical Industry.

In England, he was the keeper of the "gray list," a euphemism for the names of suspect researchers — those who broke or bent the rules but against whom no actions were taken. The medical profession polices itself, and in England, blacklists, like the U.S. version maintained discreetly by the FDA, are forbidden.

"It's all inside Frank Wells' head," said Lederle-Wyeth's Brock. "Now with him retiring, I'm rather concerned that when the gray list is passed on through folklore, our oral tradition, it will be lost."

In Germany, drug manufacturers turn to "The Man with the Golden Memory."

Since 1988 this anonymous individual at the *Fachgesellschaft der Arzte in der Pharmazeutischen Industrie*, the association of pharmaceutical industry physicians, has tracked unreliable and dishonest researchers.

Identities of doctors, firms and products are not public. But the inner circle can find out what it needs to know.

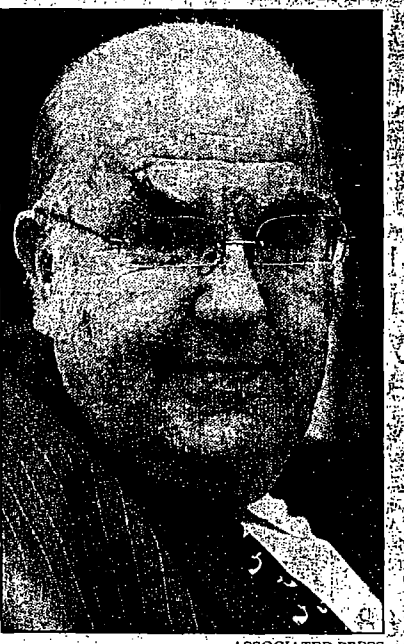
In England, Wells could refer cases to the General Medical Council, a professional association of physicians which conducts discreet inquiries and revokes medical licenses. Since 1991, the council has disciplined 17 doctors for "serious professional misconduct" in drug research; eight were forbidden to practice medicine.

There is no comparable national system of disciplining medical researchers in the United States. Trade secrecy laws prevent any disclosures about drugs before they are approved; the FDA cannot even confirm that a new-drug application has been filed.

In England, a doctor who is accused of research misconduct can be summoned to a court-martial-like proceeding before a panel of eight physicians.

Last March, they summoned Geoffrey Fairhurst to a room at the General Medical Council's headquarters in London, where oil portraits of famous doctors stare from high walls. Fairhurst was a prominent family doctor in a town outside Liverpool.

The council also summoned his patients and pharmaceutical company employees. From her



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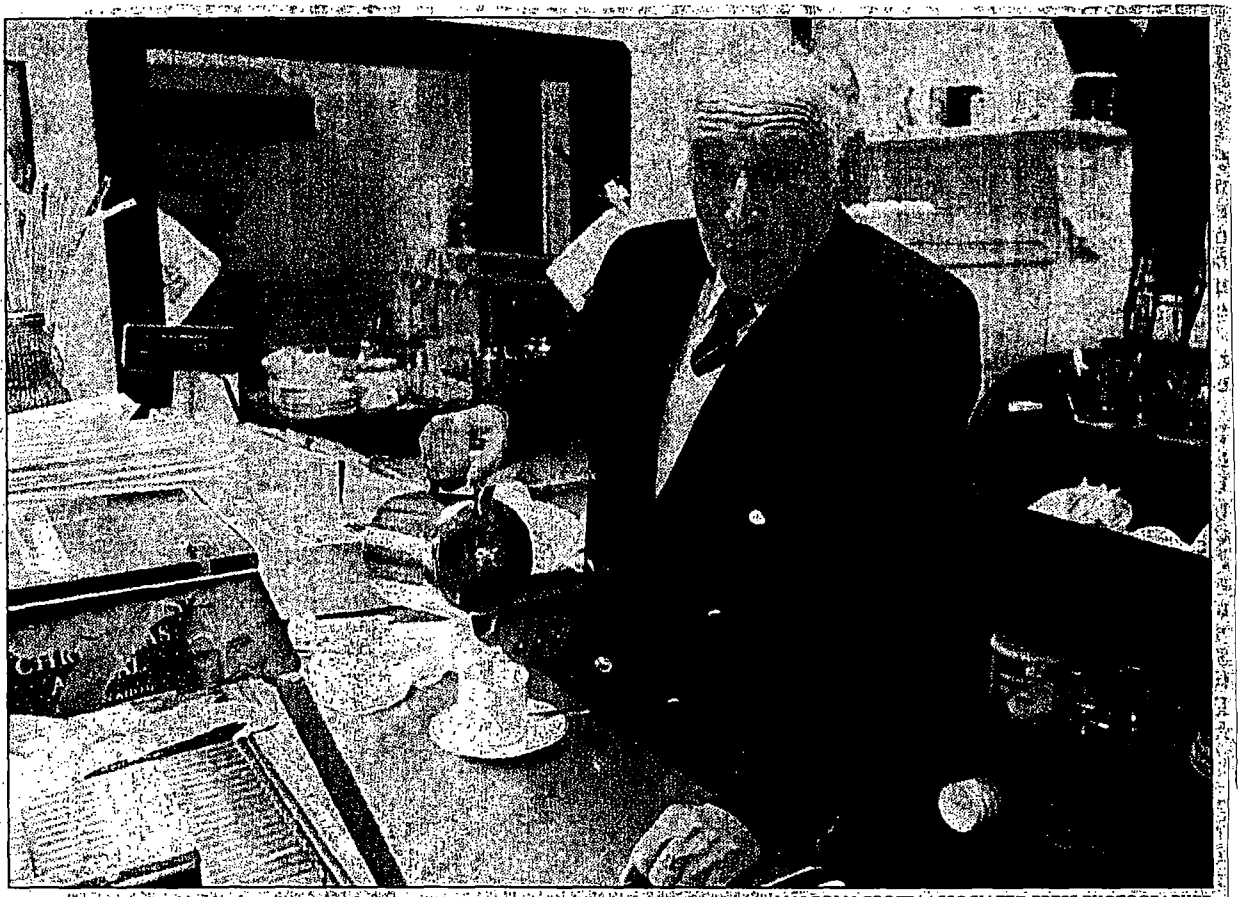
Frank Wells, the recently retired medical director of the Association of the British Pharmaceutical Industry, says: "Nearly every one of us has some experience with fraud."

THE PLAIN DEALER • DRUG TRIALS
TUESDAY, DECEMBER 17, 1996



MALCOLM CROFT / ASSOCIATED PRESS PHOTOGRAPHER

Cafe owner Harry Noble of Rainhill, Merseyside, one of Dr. Geoffrey Fairhurst's patients, says the doctor didn't tell him he was part of a drug research study.

wheelchair, Constance Mary Jerram related how she had seen Fairhurst for 12 years. He had treated the 73-year-old widow's arthritis and bronchitis and monitored her blood pressure.

"He called me by my first name," she told the panel from her wheelchair. "I was happy to go to him. I trusted him."

Then, one day last year, she recalled, another physician made a house call — and it wasn't to check her health. The doctor asked Jerram to examine a piece of paper from Fairhurst's files.

She studied the signature on the paper.

"Constance Jerram," she read.

It wasn't her writing.

She was shown another piece of paper.

Again, not her writing. "No, no," she said, "I never signed this."

Jerram had been placed in an experiment sponsored by Glaxo Pharmaceuticals, UK. The company was trying to assess the safety of a new blood-pressure drug.

"No, I've never consented," Jerram told the council judging Fairhurst. "Dr. Fairhurst never asked me to be in any trial or test."

It turned out that between 1988 and 1993, the doctor conducted three clinical trials for Glaxo, Merck, Sharp & Dohme and Leo Laboratories Ltd. There was no evidence the companies, which arranged to pay Fairhurst up to $900 per patient, were aware of any lack of consent.

"He put me on these heart tablets," recalls 75-year-old Harry Noble. "I thought he knew it was good for me. But it was experimental. The drug hadn't even come to market." When Noble found out, "I just couldn't believe it. He'd been my doctor for 30 years. I trusted him. He was like a friend, really."

Fairhurst's nurse said the doctor didn't tell his patients they were in research for fear they would refuse to participate. He said, "It's the kiss of death to recruitment," the nurse told the panel in London.

She also testified to back-dating echocardiograms for the doctor.

A handwriting expert suggested patients' signatures had been forged on consent forms.

Fairhurst's lawyer argued the doctor had been treated unfairly and was the victim of a partner's ambitions to take over his practice and research opportunities.

The testimony about Fairhurst's activities appalled the board, which found him "guilty of serious professional misconduct" and drummed him out of the medical profession.

"Trust lies at the heart of the medical profession," the chairman, Sir Donald Irwin, admonished. "You have repeatedly behaved dishonestly and have betrayed the trust placed in you by your patients ... by involving them in pharmaceutical trials without their knowledge.

"You have undermined the reputation of the medical profession and damaged the confidence of the public in the integrity of scientific research. Your behavior has not only been dishonorable but has also placed the welfare of patients at risk."

"I feel as if I'd been violated," says Jerram. "All doctors should ask permission first of the patient. When you stop to think about it, that's only right and proper. It's not very complicated. It's just common sense and common decency."

DRUG TRIALS

Do People Know the Truth About Experiments?

Overseers operate in the dark

Ethics panels only manage cursory reviews of research

By BILL SLOAT
and KEITH C. EPSTEIN
PLAIN DEALER REPORTERS

Twice each month, the University of Rochester summoned them: Four scientists, three doctors, a nurse, a priest, and a mother whose daughter died of cancer.

They convened around a long table in a conference room on the third floor of the Department of Medicine.

The door was always closed.

While obligated to preserve the proprietary secrets of companies developing new drugs, the Research Subjects Review Board was there to fulfill a single, vital mission: Protecting human test subjects.

On the frontiers of medicine, such committees are the front line.

"Actually the only line, like the thin blue line, all there is out there for protecting people against the risks of research," said Charles R. MacKay, an official at the National Institutes of Health.

Each time somebody wanted to conduct a new experiment, the Rochester committee was expected to pore over stacks of technical documents. It had to decide: Was the consent form clear? Did patients really volunteer? Did they understand the risks? Did they even realize it was research? Had alternative treatments been offered?

Not only that. The ethics committee was supposed to keep tabs on ongoing research, which meant still more volumes of paperwork.

Agendas were always full. Rochester's medical school — known well beyond New York state for retinal cell transplants, treatments for Parkinson's disease and potential AIDS vaccines — is a research center typical of large universities. It invests more than $90 million each year on medical research, most in grants from the National Institutes of Health.

During any given year, scientists at Rochester are conducting about 1,700 studies on people.

Rochester's ethics committee seldom meets for more than two hours, said its chairman, Dr. John Baum, a retired rheumatologist.

Average time for reviewing each experiment: two minutes.

SEE OVERSEERS/22-A

ASSOCIATED PRESS

Nicole Wan, a University of Rochester sophomore enrolled in a research project sponsored by the National Institutes of Health, died after getting an overdose of lidocaine.

AN INVESTIGATIVE ANALYSIS

Last of four articles

Ethics overseers operate in dark

OVERSEERS FROM 1-A

At such a clip, members were sometimes "unfamiliar with studies" up for approval, a Food and Drug Administration investigator reported last year. In April 1994, the committee adopted a list of new experiments "with no discussion on the individual studies themselves," the investigator noted.

The committee, the FDA concluded six months ago, was functioning in a way that "may not adequately protect the rights and welfare of human subjects of research."

The research reviewed by Baum's committee included a National Institutes of Health study of how smoking and air pollution can affect the human body.

Test subjects, paid up to $150 for volunteering, received lidocaine during a lung exam. The anesthetic is usually used for people with bronchial ailments.

For Nicole Wan, a healthy 19-year-old University of Rochester sophomore from Queens who loved children, enjoyed Mozart and wanted to be a teacher, it proved fatal.

Within two days of an overdose of lidocaine in April, she died of a heart attack.

She had more than double the usual safe blood level of the anesthetic, dosages of which should have been limited by the ethics committee, New York's Health Department determined in September.

Baum's committee, it concluded, failed to "minimize the risks to volunteers."

"Research involving human subjects at the University of Rochester was being carried out with insufficient safeguards to adequately minimize risks and protect individuals," New York health Commissioner Barbara A. DeBuono said after a state investigation.

Baum's committee continues its work.

He wants to do better, but with only one assistant, two secretaries, a $100,000 budget — and 10 "very busy" professionals who receive no pay for their services — he admits the committee has limitations.

"To do what we should do, go out every so often and say to the researcher, 'Let me look at your records, your consent forms, are you informing the patients?' — I'd like to do that, but we don't have the time or the staffing," Baum said. "This is not work that is perceived as making a contribution to research."

Baum's plaint is heard often among medical researchers.

"These committees are overwhelmed by the work they have to do," said Princeton University President Harold T. Shapiro, chairman of a new federal commission created to study how people are protected in medical research. The National Bioethics Advisory Commission was appointed last summer after disclosures of Cold War-era radiation experiments on unwitting Americans.

Mackay, now coordinating for NIH the first in-depth attempt to figure out whether ethics committees are doing their jobs, shares Shapiro's concerns.

"If a committee is reviewing 1,000 clinical trials a year, one has to ask: How thorough are some of those reviews?"

The size of the workload also troubled the General Accounting Office, the investigative arm of Congress. It reported last March that "in some cases the sheer number of studies necessitate that IRBs spend only one or two minutes of review per study."

The lack of aggressive oversight "may permit human subject protection violations to go undetected," the GAO said.

Shapiro said that very issue was at the top of his agenda.

"My major concern is that [the ethics committees] do not always understand the weight of the responsibility on their shoulders," he said.

When it all began in earnest — in the aftermath of the notorious experiment in Tuskegee, Ala., in which the federal Public Health Service withheld treatment and diagnosis from 412 black men with syphilis — "institutional review boards," or IRBs, were widely regarded as an ingenious innovation.

It was "the best protection" for people used in research, a national commission was convinced in 1978.

IRBs were supposed to wrest the monopoly on decision-making from the scientific establishment, placing it in the hands of a group that could balance the best interests of medicine, human beings and the community.

There would be at least five members, including a nonscientist. One member was not to be affiliated with the research institution. They were supposed to represent the racial and cultural spectrum of American society.

Paul W. Goebel Jr., head of the FDA's Human Subject Protection Team, regards the committees as nothing less than the "cornerstone of the whole process" for making sure what happened at Tuskegee never happens again.

Evidence shows the cornerstone is cracking, at least partly due to the burden of an explosive growth in medical research.

'To do what we should do, go out every so often and say to the researcher, 'Let me look at your records, your consent forms, are you informing the patients?' — I'd like to do that, but we don't have the time or the staffing. This is not work that is perceived as making a contribution to research.'

DR. JOHN BAUM,
chairman of the University of Rochester's Research Subjects Review Board

The number of research sites has more than tripled in the last six years, from 6,000 to 18,500.

Nobody knows for sure how many thics committees there are, hough the number is estimated o be 4,000 to 6,000.

They operate at universities, ospitals, private research firms. he Army has them. NASA has hem. The National Institutes of Iealth has 14 of them.

There are even corporate ethics ommittees-for-hire.

None must register or be accredited by the government.

And when the FDA does conuct an inspection — there have een fewer than 1,000 this decade — records are frequently in a hambles.

Forty percent of the ethics ommittees could not produce vidence they had met, held disussions and voted. Research had een approved by committees hat had not even kept accurate sts of their members.

For 188 committees, the FDA iscovered more serious shortomings. Consent forms, injury eports and research proposals /ere missing from their files. here was no convincing proof hat these committees had fulilled their safety-monitoring iission.

Arthur Horowitz, a consultant who helps drug companies pre pare for FDA audits, recognize he problem. "All too frequently," ie said, "I've seen the wrong in ormed consent document in the ands of the IRB — or the wrong raft of the consent form in the ands of the patient. It's not the ame version submitted to the DA."

Pharmaceutical companies "as ume the IRBs know what they're loing. This is sadly not always the ase."

Not that ethics committees ar if much risk of punishment. Fo ailures the FDA identified at the University of Rochester, neithe he ethics committee nor the in titution faced penalties. They go a warning letter, the FDA's stan lard practice, and, from the fed eral Office for Protection from Research Risks, a list of recom nended improvements.

PHOTOCOPY PRESERVATION

"We are one of the least confrontational compliance operations within FDA," said Goebel, head of the FDA's Human Subject Protection Team. "We spend most of our time writing letters. But if we need it, we have the authority to disqualify them."

It is, for the FDA, the ultimate sanction: Seriously deficient ethics committees can be prohibited from approving any more research.

The FDA has put ethics committees out of business only once or twice.

Of course, by the time the FDA figured out what was going on, the Ethical Board of Review Inc., had already stopped meeting.

Last year in Austin, Texas, FDA investigator Maira Brading found the privately operated committee, among a growing number of ethics panels for hire, had not met for 13 months.

But drug companies and researchers were still getting correspondence from the Ethical Board of Review Inc. showing it continued to oversee their research.

Two years earlier, the FDA had cited the Ethical Board of Review Inc. for allowing medical research that had not been reviewed by a physician.

Gail Findlay, the majority owner, agreed to shut down the business last April. In a "consent agreement" with the FDA, she acknowledged "falsely representing the Ethical Board of Review Inc. as a properly constituted and currently functioning IRB."

By signing, she also agreed with the FDA's criticism of the committee's "failure to adequately protect the rights and welfare of human subjects involved in research."

Not that any of them knew anything about the IRB that failed to protect their rights and welfare.

The FDA doesn't tell.

Findlay did not respond to a message seeking comment.

Paul J. Godley, Ethical Board of Review Inc.'s chairman and minority owner, said he disagreed with the FDA's finding.

Godley, a hospital executive in Temple, Texas, said the committee was a serious operation that had proper "concern for patients and subjects" while in business, and that the committee got in trouble after his partner, a doctor named Steven Findlay, died of cancer in 1992.

Even if a committee is diligent and halts a medical experiment on sound ethical grounds, the study can be resurrected elsewhere. If a drug company or researcher doesn't like what one ethics committee says about its clinical trial, it can simply find another committee.

It is a practice known in the pharmaceutical industry as "IRB-shopping."

When the ethics committee at Bowman Gray School of Medicine in Winston-Salem, N.C., stopped a human test of experimental urinary catheters a few years ago because it found significant risk, the sponsoring drug company withdrew its big research grant, said Robert J. Sheretz, the physician who planned to conduct the study.

"Wishing to press on," the company said in its letter of cancellation, "we are forced to invite participation from another investigator."

The medical school stuck to its guns, Sheretz said.

So did the drug company, which took its experiment elsewhere.

Ezekiel J. Emanuel, a researcher at the Dana-Farber Cancer Institute in Boston, considers the system "just too haphazard." When he sought approval for the same experiment at 40 different sites, he got almost 40 different answers. Some committees approved; others rejected.

The system is so haphazard the government can't even find ever ethics committee to tell it, wha rules to follow.

At a recent FDA-sponsore conference for hundreds of pec ple who run ethics committees a hospitals, universities and for pr vate consultants, fewer than one third of the audience knew abou a change in the regulations — even though the government ha sent more than 3,500 letters t university presidents and com mittee chairmen.

"We still don't know if we'v sent that to every IRB in the na tion," said Gary Ellis, the Univer sity Heights-reared director o the Office for the Protection o Research Risks.

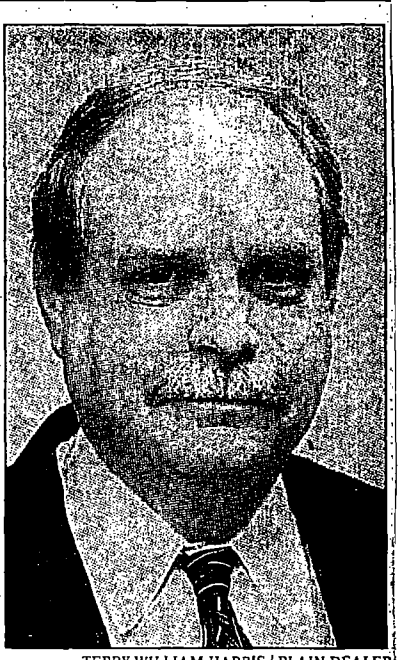
He explained: The governmer doesn't know where to find them.

Some argue the current syster is badly in need of repair. Ja Katz, the Yale University profes sor who helped write reform after Tuskegee, says protection for people in research should n longer be left solely to "low visibility" decision-making o IRBs with regulations that are po rous and invite abuse."

Ellis has poignant black-and white photos of the Tuskegee vic tims he shows to scientists as reminder of the cost of misstep in our work. I hope our succes sors will never be able to shov slides like these again."

Tucked away in the federa budget each year, 65 years afte the first blood samples were col lected from farm hands in the cot tonfields of Alabama, is an endur ing testament to th consequences of unfettered med ical research: $2.8 million in pay ments to 23 wives, 18 childrei and the 12 men who survived.

"These are real people, our fel low citizens," Ellis said. "Th government can never really re pay that debt."



TERRY WILLIAM HARRIS / PLAIN DEALER

"Consultant Arthur Horowitz says drug companies assume ethics committees know what they are doing but 'this is sadly not always the case.'"

The case of the missing ethics committee

Sometimes, the Food and Drug Administration has a hard time finding an ethics committee, even with an address supplied by a drug company.

For 18 months, FDA investigators crisscrossed the country looking for Medical Research Consultants Inc.

A small for-hire operation, it was overseeing 23 experiments for a variety of clients, from a small dental group in Maryland to a big drug company on the West Coast.

In December 1993, an inspector visited 6 Winding Creek Lane, Chapel Hill, N.C., the address that appeared on a pharmaceutical company's New Drug Application filed with the FDA almost two years earlier.

No sign of Medical Research Consultants Inc.

An inspector tried 68 Spyglass Circle, Groton, Conn., where the company's president, David Edelman, once lived.

No luck there.

Next stop: A town house at 20 Bedford Ave., Madison, N.J., where Edelman lived.

Another dead end. Residents said he was in California.

What was a regulatory agency to do? It turned to another pharmaceutical manufacturer for help.

The suggestion: Try San Diego.

Well, that was close. It was Edelman's hometown.

As for the ethics committee, it was still in North Carolina. So another FDA inspector went to 2605 New Hope Rd. in Chapel Hill.

Another private home. The resident said Karen Bley, an associate director of Planned Parenthood, used to live there.

That solved one puzzle: Bley was indeed the ethics committee's chairwoman and had been running its meetings at restaurants such as Sal's, a casual Italian place with a mural of the Leaning Tower of Pisa on the wall.

"We'd go to a few different places, just so there was a big table, a place to the side where we could hear each other talk," said Bley.

The FDA asked to see her files.

Nearly a year after it finally found Medical Research Consultants Inc., in May 1996, the FDA sent Edelman a warning letter.

"We have no assurance that your procedures are adequately protecting the rights and welfare of human subjects of research," it said.

The FDA cited "the problems inherent in an organization having its IRB [Institutional Review Board] administrator/secretary in California and its IRB membership in North Carolina."

Edelman, a consultant to pharmaceutical companies, said the FDA chastised him out of pique.

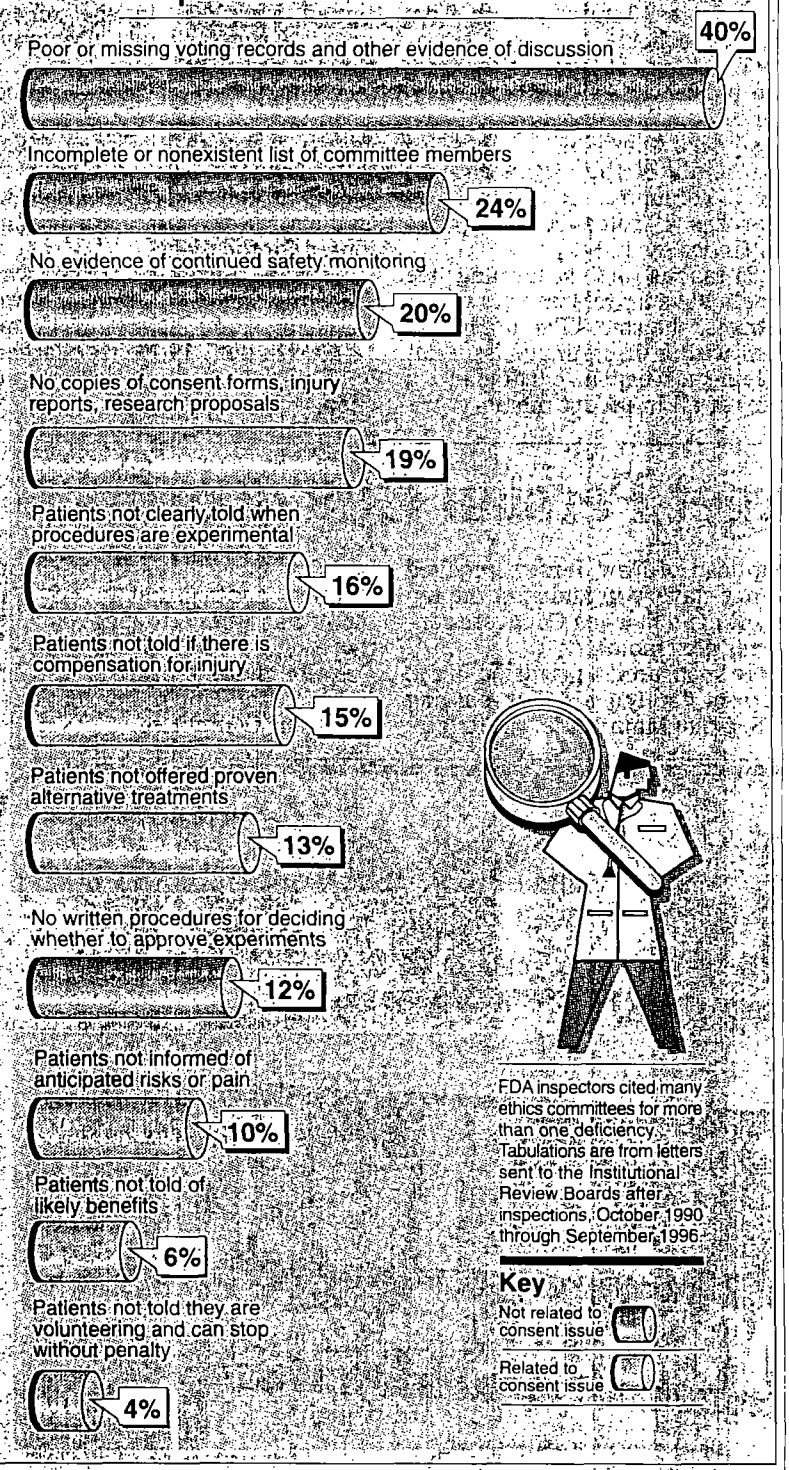
"There's nothing in the regulations that says that I have to be physically where the IRB is," Edelman said. It wasn't difficult to stay in touch, he said, with fax machines, pagers and telephones.

"There's never been a problem in the chairperson reaching me, or anybody we've ever reviewed studies for. Besides, if we placed people at extreme risk, why would it take more than 10 months for them to write us? If they thought we should be shut down, why wouldn't they do that right away?"

FAILURES ON THE FRONT LINE

When it comes to protecting people used in experiments, local ethics committees are the front line. The committees are supposed to make researchers minimize hazards, describe risks, offer alternative treatments, obtain written consent and let test subjects know they are volunteering for an experiment.

Most common violations in 942 inspections of ethics committees



JAMES OWENS / PLAIN DEALER

Payments to Make Amends For Secret Tests of Radiation

A1

By PHILIP J. HILTS

The Federal Government has agreed to pay $4.8 million as compensation for injecting 12 people with radioactive plutonium or uranium in secret cold war experiments.

Energy Secretary Hazel R. O'Leary, who announced the settlement yesterday in Manhattan, said it was part of a continuing effort to make amends for the many unethical experiments carried out by Government doctors, scientists and military officials from 1944 to 1974.

Before the end of the year, President Clinton will announce further action to compensate the subjects or their survivors and to make sure such experiments are not repeated, Secretary O'Leary said in a telephone interview.

Yesterday's announcement followed 18 months of investigation and hearings by the President's Advisory Committee on Human Radiation Experiments, which concluded last year that many of the Government-sponsored radiation experiments were unethical and that participants or their survivors should be compensated.

The financial settlement announced yesterday will end several court cases involving injections of radioactive material into 12 people in experiments in Rochester, N.Y., and elsewhere from 1945 to 1947. Most of the people were being treated for existing illnesses at hospitals when they were asked to participate in research, which Federal officials now admit had nothing to do with their disorders.

Lawyers for families in the 12 cases settled yesterday said that all the subjects suffered some ill effect, including cancer and immune disorders, that might have resulted from the experiments, though there was no medical proof. Government officials said they could not be sure that any of the illnesses were caused

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by the experiments. Of the 12, the only one still alive is Mary Jean Connell, 74, of Avon, N.Y. Mrs. Connell and the families of the 11 others will each receive an average of $400,000, with the money to be distributed by agreement among the family members.

Mrs. Connell said yesterday: "I feel wonderful about this. I feel very relieved."

She was 23 at the time of the experiment, and went into the hospital at the University of Rochester for problems with her metabolism. She was asked whether she wanted to participate in an experiment. She said that she declined, but was injected with radioactive uranium without her knowledge.

Now, she said: "I just want to get it all over with, so I can forget it. I hate to keep going over and over it, reliving it day after day."

Secretary O'Leary, in a meeting of the American Public Health Association yesterday in Manhattan, said, "This settlement in no way fully compensates families for what they have suffered and for what they haven't known about their suffering."

She said Government officials should make a commitment "that never again will the Government of the United States perform tests on our citizens and do so in secrecy."

What the Government needs, she said, "is a high level of humility" and a "moral compass as we go about our daily business."

Secretary O'Leary began the extensive inquiry into the radiation experiments after reports about them were made public in a Congressional hearing 1992 and later in articles in The Albuquerque Tribune.

The experiments in question yesterday were only a few among thousands of different kinds of experiments that were part of a long campaign to find out how the use of atomic weapons might affect soldiers and civilians in a nuclear war. The President's committee found more than 4,000 experiments were conducted on as many as 20,000 individuals.

E. Cooper Brown, a lawyer who is a leader of the Task Force on Human Radiation Experiments in Washington, a coalition of families of the subjects and advocates seeking redress for the experiments, said: "A lot of credit is due to Secretary O'Leary and the Clinton Administration for being responsible and carrying through on these issue in a way that the government has never done before. A lot has been accomplished."

But he added, "Having said that, we still want to make sure that all of the other victims are not forgotten."

The experiments ranged from marching soldiers through nuclear explosion sites, without informing them of possible risks, to directly injecting people with radioactive substances, again without their knowledge.

The cases of those injected directly with radioactive plutonium or uranium were counted as among the most egregious by the President's Committee. Government ? records show that 18 people were subjects of those experiments.

Before yesterday's settlement, the Federal Government had reached agreement with the family of only one other subject, also for about $400,000. Of the families of the remaining five subjects, four are still negotiating with Government lawyers. The family of the fifth has yet to be located, said Dr. Steven Galson, the Energy Department's chief medical officer.

Numerous claims from other experiments have also been filed against agencies and officials of the Government and the private institutions where the experiments were carried out, other department officials said. They are in negotiations and some may produce settlements soon.

One proposed settlement with the subjects of radiation experiments carried out at the University of Cincinnati would give subjects or their families $50,000 to $70,000 each.

Ray Heslin, a lawyer involved in the settlement announced yesterday, said that he was pleased that the families could be compensated, but said that the Government "still refuses to release names of other victims of the experiments, or to notify their families," adding, "That is outrageous."

One issue is that the Government has so far decided not to mount a campaign to get the names of all those in the experiments and to notify them that they were subjects of radiation experiments. The effort would be expensive and time-consuming, since government records in most cases do not list the names or addresses of the subjects of the experiments.

Instead, the National Archives has placed all the hundreds of thousands of pages of records produced by the President's committee in files accessible to the public.

Secretary O'Leary said she learned of the experiments for the first time three years ago and determined to open up Government files to find out what happened. The department was quickly flooded with 34,000 calls asking about the experiments.

She said that with three years of effort and its attending publicity: "I can't believe there are many people who have not been contacted. Our effort now is to focus on the people who come to the table with claims, while still being alert to the possibility that some families may come forward later."

She said it would be necessary for subjects to come forward with claims.

Additional information on some experiments has come to light since the President's committee reviewed the experiments, particularly on experiments in which radioactive rods were inserted in the noses of people to damage and shrink adenoids experimentally for purposes like preventing infection.

Dr. Stewart Farber, director of the Radium Experiments Assessment Project in Boston, a nonprofit research group looking into the experiments, estimates that about 7,500 military men and more than 200 civilian children were given high doses of radium in the initial experiments in the 1940's and 1950's. More may have been put in experiments later.

Among the other experiments in which claims may be made, were ones in which patients hospitalized at the University of Cincinnati and three other universities were exposed to radiation over their entire bodies, mainly to see the effects of the radiation rather than treat the illnesses; one at Vanderbilt University in which 820 pregnant women were given small doses of radioactive iron; and the case of the miners who dug out the uranium for the military who were never told of the hazard and never given protective gear.

Dr. Ruth Faden, the chairwoman of the President's committee, said of yesterday's settlements, "I hope this represents a beginning, and that many more steps will be taken by the Government, both to compensate subjects and make sure these abuses don't occur again."

The New York Times
WEDNESDAY, NOVEMBER 20, 1996

AIRLINES IN ACCORD ON DISASTER PLANS

7 U.S Carriers to Provide Lists of Those in Crashes Abroad

A1

By BARRY MEIER

The State Department and seven major United States airlines have reached an agreement intended to provide for the speedier notification of victims' families in the event of air disasters abroad.

The agreement, a memorandum of understanding signed on Monday, finally puts into effect a provision of a 1990 Federal law that called on the nation's airlines to provide the State Department a list of passenger names within three hours of such a crash.

Under the agreement, the State Department and industry officials are to share other information as well in the aftermath of a crash and to take part in joint crisis management training.

The long-delayed accord follows pressure from groups representing crash victims' families, which have often waited many hours, and sometimes days, to learn the fate of those aboard doomed jetliners.

"This will finally expedite the sharing of manifest information," said Hans Ephraimson-Abt, chairman of a group that represents families of the 61 American citizens who were among 269 people killed when Korean Air Lines Flight 007 was shot down by a Soviet fighter plane 13 years ago after the airliner had strayed closed to a Soviet military installation.

The agreement is only a first step — and, if a newly proposed Federal

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rule is adopted, should prove a relatively modest one — in a continuing Government effort to provide speedier information to the families of crash victims.

Where the memorandum of understanding signed on Monday requires the carrier to provide Federal officials only an unverified passenger list bearing each traveler's name, the new rule, proposed by the Department of Transportation, would require the carrier to provide those officials not only a "complete and accurate compilation" of each traveler's name but also the passport number and the name of a relative to contact. This information would have to be provided within an hour after the accident or, if that was not technically feasible, within three hours.

James Casey, deputy general counsel of the Air Transport Association of America, a trade group, said that the organization had voiced some criticism of the proposed Transportation Department rule but was generally supportive of it.

"We filed comments within the past two weeks that we would comply with the rule," said Mr. Casey.

As for the agreement reached on Monday, the carriers that have signed it so far are American Airlines, Continental Airlines, Delta Air Lines, Northwest Airlines, United Airlines, Trans World Airlines and USAir. Mr. Casey, the trade group official, said foreign carriers could also sign the agreement should they choose.

The accord was struck only four months after Trans World Airlines had come under particularly heavy criticism from Mayor Rudolph W. Guiliani of New York and others for having taken up to 12 hours to verify passenger identities and notify victims' families in the aftermath of the crash of Flight 800 off Long Island.

Phyllis Young, a spokeswoman for the State Department, said it was not immediately clear how the agreement would have affected the notification of vicitims' families after that crash had the accord then been in effect. While that was an international flight, the plane went down in domestic waters, and the State Department handles only those accidents involving American travelers aboard.

The notification of victims' families in domestic airline accidents is proceeding on a separate track. Under a law recently passed by Congress, the National Transportation Safety Board was given prime responsibility for coordinating a system to speed up those notifications.

In the wake of the bombing of T.W.A. Flight 103 over Lockerbie, Scotland, Congress passed the Aviation Security Improvement Act of 1990 requiring United States carriers to provide the State Department complete passenger lists on international flights that crashed outside the country. The law also required airlines to match up every bag on an international flight with a passenger before a plane could take off.

But while the bag match requirement went into effect, the passenger list mandate did not, in part because of opposition by airlines.

Momentum to get the process started again began in March not long after a hearing to address the notification issue at the Transportation Department. Mr. Ephraimson-Abt said he and M. Victoria Cummock, who lost her husband in the Flight 103 disaster, met with Transportation Secretary Federico F. Peña. Meetings were also held with State Department and industry officials, but Mr. Ephhraimson-Abt, for one, credited Mr. Peña with pushing the parties forward.

The New York Times
WEDNESDAY, NOVEMBER 20, 1996

THE WHITE HOUSE

Office of the Press Secretary

For Immediate Release October 3, 1995

REMARKS BY THE PRESIDENT
IN ACCEPTANCE OF HUMAN RADIATION FINAL REPORT

Old Executive Office Building

11:07 P.M. EDT

THE PRESIDENT: Let me begin with a simple thank you to everyone who participated in this extraordinary project and to everyone who supported them.

I am especially glad to see here today Senator Glenn, who's been so active in working on medical ethics issue, Congressman Markey, who's worked on this issue for a very long time, Congressman Frost, Secretary Shalala, Deputy Secretary of Veterans Affairs Herschel Gober, and of course, the Attorney General who basically tries to get us all to do the right thing all the time. (Laughter.)

I want to thank Secretary O'Leary for her extraordinary devotion to this cause. And you heard in her remarks basically the way that she views this. It's a part of her ongoing commitment to finish the end of the Cold War. And perhaps no Energy Secretary has ever done as much as she has to be an advocate, whether it is for continued reforms within the Energy Department or her outspoken endorsement of the strongest possible commitment on the part of the United States to a Comprehensive Test Ban Treaty, which I believe we will achieve next year in no small measure thanks to the support of the Secretary of Energy.

ethicists
D. M.D

And, of course, I want to thank Dr. Ruth Faden for her extraordinary commitment of about a year and a half of her life to this unusual but important task.

And all of you who served on the committee -- I remember the first time we put this committee together. I looked -- I said, that's a pretty distinguished outfit. I wish I could give them five or six jobs to do. (Laughter.) I'll expect you back next Monday and then we'll -- (laughter). I do thank you so much for the work you have done.

Let me tell you that, just as this is an important part of the efforts that Secretary O'Leary outlined, I saw this committee as an indispensable part of our effort to restore the confidence of the American people in the integrity of their government. All of these political reform issues to me are integrated. When I became the President, I realized we had great new economic challenges, we

had profound social problems, that a lot of these things had to be done by an energized American citizenry, but that our national government had a role to play in moving our country through this period of transition. And in order to do it, we needed to increase the capacity of the government to do it through political reform, but we also needed, as much as anything else, to increase the confidence of the American people that, at the very least, they could trust the United States government to tell the truth and to do the right things.

So you have to understand that, for me, one reason this is so important is that I see it as part of our ongoing effort to give this government back to the American people -- Senator Glenn's long effort to get Congress to apply to itself the same laws it i poses on the private sector; the restrictions that I imposed on members of my administration in high positions for lobbying for foreign governments; and when the lobby bill failed in the Congress, I just imposed it by executive order on members of the Executive Branch. All these efforts at political reform, it seems to me, are important.

But none of these efforts can succeed unless people believe that they can rely on their government to tell them the truth and to do the right thing. We have declassified thousands of government documents, files from second world war, the Cold War, President Kennedy's assassination. These actions are not only consistent with our national security, they are essential to advance our values.

So, to me, that's what this is all about. And to all those who represent the families who have been involved in these incidents, let me say to you, I hope you feel that your government has kept its commitment to the American people to tell the truth and to do the right thing.

We discovered soon after I entered office that with the specter of an atomic war looming like Armageddon far nearer than it does today, the United States government actually did carry out on our citizens experiments involving radiation. That's when I ordered the creation of this committee. Dr. Faden and the others did a superb job. They enlisted many of our nation's most significant and important medical and scientific ethicists. They had to determine first whether experiments conducted or sponsored by our government between 1944 and 1974 met the ethical and scientific standards of that time and of our time. And then they had to see to it that our research today lives up to nothing less than our highest values and our most deeply-held beliefs.

From the beginning, it was obvious to me that this energetic committee was prepared to do its part. We declassified thousands of pages of documents. We gave committee members the keys to the government's doors, file cabinets and safes. For the last year and a half, the only thing that stood between them and the truth were all the late nights and hard work they had to put in.

This report I received today is a monumental document -- (laughter) -- in more ways than one. But it is a very, very important piece of America's history, and it will shape America's future in ways that will make us a more honorable, more successful and more ethical country.

What this committee learned I would like to review today with a little more detail than Dr. Faden said, because I think it must be engraved on our national memory. Thousands of government-sponsored experiments did take place at hospitals, universities and military bases around our nation. The goal was to understand the effects of radiation exposure on the human body.

While most of the tests were ethical by any standards, some were unethical, not only by today's standards, but by the standards of the time in which they were conducted. They failed both the test of our national values and the test of humanity.

In one experience, scientists -- experiment -- scientists injected plutonium into 18 patients without their knowledge. In another, doctors exposed indigent cancer patients to excessive doses of radiation, a treatment from which it is virtually impossible that they could ever benefit.

The report also demonstrates that these and other experiments were carried out on precisely those citizens who count most on the government for its help -- the destitute and the gravely ill. But the dispossessed were not alone. Members of the military -- precisely those on whom we and our government count most -- they were also test subjects.

Informed consent means your doctor tells you the risk of the treatment you are about to undergo. In too many cases, informed consent was withheld. Americans were kept in the dark about the effects of what was being done to them. The deception extended beyond the test subjects themselves to encompass their families and the American people as a whole, for these experiments were kept secret. And they were shrouded not for a compelling reason of national security, but for the simple fear of embarrassment, and that was wrong.

Those who led the government when these decisions were made are no longer here to take responsibility for what they did. They are not here to apologize to the survivors, the family members or the communities who's lives were darkened by the shadow of the atom and these choices.

So today, on behalf of another generation of American leaders and another generation of American citizens, the United States of America offers a sincere apology to those of our citizens who were subjected to these experiments, to their families, and to their communities.

When the government does wrong, we have a moral responsibility to admit it. The duty we owe to one another to tell the truth and to protect our fellow citizens from excesses like these is one we can never walk away from. Our government failed in that duty, and it offers an apology to the survivors and their families and to all the American people who must -- who must be able to rely upon the Untied States to keep its word, to tell the truth, and to do the right thing.

We know there are moments when words alone are not enough. That's why I am instructing my Cabinet to use and build on these recommendations, to devise promptly a system of relief, including compensation, that meets the standards of justice and conscience.

When called for, we will work with Congress to serve the best needs of those who were harmed. Make no mistake, as the committee report says, there are circumstances where compensation is appropriate as a matter of ethics and principle. I am committed to seeing to it that the United States of America lives up to its responsibility.

Our greatness is measured not only in how we so frequently do right, but also how we act when we know we've done the wrong thing; how we confront our mistakes, make our apologies, and take action.

That's why this morning, I signed an executive order instructing every arm and agency of our government that conducts, supports or regulates research involving human beings to review immediately their procedures, in light of the recommendations of this report, and the best knowledge and standards available today, and to report back to me by Christmas.

I have also created a Bioethics Advisory Commission to supervise the process, to watch over all such research, and to see to it that never again do we stray from the basic values of protecting our people and being straight with them.

The report I received today will not be left on a shelf to gather dust. Every one of its pages offers a lesson, and every lesson will be learned from these good people who put a year and a half of their lives into the effort to set America straight.

Medical and scientific progress depends upon learning about people's responses to new medicines, to new cutting-edge treatments. Without this kind of research, our children would still be dying from polio and other killers. Without responsible radiation research, we wouldn't be making the progress we are in the war on cancer. We have to continue to research, but there is a right way and a wrong way to do it.

There are local citizens' review boards, there are regulations that establish proper informed consent and ensure that

experiments are conducted ethically. But in overseeing this necessary research, we must never relax our vigilance.

The breathtaking advances in science and technology demand that we always keep our ethical watchlight burning. No matter how rapid the pace of change, it can never outrun our core convictions that have stood us so well as a nation for more than 200 years now, through many different scientific revolutions.

I believe we will meet the test of our times -- that as science and technology evolve, our ethical conscience will grow, not shrink. Informed consent, community right-to-know, our entire battery of essential human protections -- all these grew up in response to the health and humanitarian crises of this 20th century. They are proof that we are equal to our challenges.

Science is not ever simply objective. It emerges from the crucible of historical circumstances and personal experience. Times of crisis and fear can call forth bad science, even science we know in retrospect to be unethical. Let us remember the difficult years chronicled in this report, and think about how good people could have done things that we know were wrong.

Let these pages serve as an internal reminder to hold humility and moral accountability in higher esteem than we do the latest development in technology. Let us remember, too, that cynicism about government has roots in historical circumstances. Because of stonewallings and evasions in the past, times when a family member or a neighbor suffered an injustice and had nowhere to turn and couldn't even get the facts, some Americans lost faith in the promise of our democracy. Government was very powerful, but very far away and not trusted to be ethical.

So today, by making ourselves accountable for the sins of the past, I hope more than anything else, we are laying the foundation stone for a new era. Good people, like these members of Congress who have labored on this issue for a long time, and have devoted their careers to trying to do the right thing, and having people justifiably feel confidence in the work of their representatives. They will continue to work to see that we implement these recommendations.

And under our watch, we will no longer hide the truth from our citizens. We will act as if all that we do will see the light of day. Nothing that happens in Washington will ever be more important in anyone's life affected by these experiments, perhaps, than these reports we issue today. But all of us as Americans will be better off because of the larger lesson we learned in this exercise and because of our continuing effort to demonstrate to our people that we can be faithful to their values.

Thank you very much. (Applause.)

END 11:23 A.M. EDT