HEADLINE: Trials--and Errors

BYLINE: By Sharon Begley and Donna Foote; With Erika Check

HIGHLIGHT: Experiments on human volunteers are crucial to biomedical progress. But do they pose an unacceptable risk?

BODY: Gretchen Stewart thought she was doing the best thing for her 3-month-old boy when she allowed the doctor to include him in a human experiment. Little Gage was a fussy baby who seemed to be filled with as much gas as a balloon. The doctor, Susan Orenstein of Children's Hospital in Pittsburgh, said he was suffering from gastroesophageal reflux disorder, a painful condition that causes babies to vomit during or after feedings. Although the problem usually disappears by the 2d birthday, in severe cases it can result in what pediatricians call "failure to thrive." Orenstein was therefore conducting a clinical trial to see whether a combination of the heartburn drug Propulsid and the ulcer drug Tagamet could help children like Gage. On May 27, 1999, Stewart signed the informed-consent document to enroll Gage in Orenstein's 100-patient trial. Every day, he received baby-size oral doses of the two drugs. Six months later, on the day before Thanksgiving, Gage's grandmother gave him his usual medicines and laid him down for his nap. He never awoke.

At first the Allegheny County coroner attributed Gage's death to sudden infant death syndrome. But when he learned of the baby's drug regimen, he changed his opinion. "Though the exact cause of Gage Stevens' death cannot be determined morphologically, it most probably was due to a cardiac arrhythmia," reads his report. "Based upon the anatomic findings described above, the clinical history, and the documented reports of adverse reactions associated with [Propulsid] (especially when this drug is taken simultaneously with [Tagamet]), the death of the nine-month-old infant is determined to be directly related to the therapy."

The death of a baby is tragedy enough, of course. But last year federal investigators concluded that Gage's parents were not adequately informed of all the risks in the clinical trial that Stewart signed him up for. The four-page consent form stated that Propulsid had just been approved for use in infants; it hadn't. The form listed the most serious side effects of the drugs as headache or dizziness. Under "New Information," it stated that "heart rhythm problems have been reported in a tiny fraction of infants taking [Propulsid]... A few babies have died." In fact, the drug was associated with some 80 fatalities, including 19 children, say regulators. Orenstein, charged the government, had failed to inform the hospital's institutional review board, the panel that oversees all experiments on people, of previous serious adverse events in the trial. Four months after the baby's death, Children's Hospital aborted the trial and Jannsen Pharmaceuticals, manufacturer of Propulsid, pulled the drug off the market. The baby's parents filed a lawsuit against Janssen, the hospital and Orenstein. Both of the latter deny that the drug or the clinical trials killed Gage. A spokesman for Janssen told NEWSWEEK: "This was
not a Janssen trial. This was an investigator-initiated trial."

The Propulsid trial is just one of dozens of human studies that, according to federal investigators, have violated laws meant to protect people who volunteer to test experimental drugs and surgeries. In the worst recent case, Ellen Roche, 24, died in June from an experiment, at Johns Hopkins Medical Center, on how healthy lungs respond to asthma triggers. After an investigation, the Office for Human Research Protections (OHRP), the watchdog agency for clinical trials, temporarily suspended all human studies at Hopkins except those whose interruption would harm patients (NEWSWEEK, July 30). But Hopkins, one of the nation's leading biomedical-research centers, is hardly alone:

In 1996, student Nicole Wan, 19, volunteered for an experiment at the University of Rochester on the effects of smoking and air pollution. After undergoing a bronchoscopy to collect lung cells, Wan died; when she had complained of pain, a toxic amount of the anesthetic lidocaine had been mistakenly sprayed into her throat. Rochester has since reformed its human studies.

Last November, OHRP shut down a trial at the National Institute of Child Health and Human Development that was measuring insulin sensitivity, energy output and body composition in obese children and in normal kids of obese parents. For several hours the children had two IV lines dripping insulin and glucose into them. Although the children suffered no lasting harm, "this research involves greater than minimal risk," concluded OHRP, and so "does not represent the category of research involving children [that is] permissible."

In December, OHRP found that the National Institute of Mental Health had experimented on four children, giving them the antipsychotic drug olanzapine, with neither review-board approval nor their parents' informed consent.

In June, OHRP completed its investigation of the death of Tyler Shelton, 3, at the University of Arkansas and Arkansas Children's Hospital. In May 1997 the little boy was diagnosed with a kidney cancer called Wilms' tumor. Oncologist David Becton urged the boy's mother, Annette, to enroll her son in the National Wilms' Tumor Study, a multisite clinical trial. She did. But things began to go wrong immediately, found OHRP. Although the pathology report said that Tyler's tumor was an aggressive "stage II," Becton grouped the boy with patients who had stage I tumors and so received less aggressive therapy. By June or July, found OHRP, "Becton realized that [Tyler] had been placed in the wrong arm of" the trial but, he wrote in a September letter to Tyler's new doctor, "this made no change in his protocol therapy." In other words, Becton kept Tyler on the same, nonaggressive regimen. On March 25, 1999, the boy died from the spread of advanced Wilms' tumor.

OHRP concluded that the therapy Tyler received "may have contributed to [his] premature death." The university and hospital agreed with OHRP that assigning Tyler to "the wrong arm" of the study was a "significant" violation. In an affidavit, however,
Becton "den[ies] that I was guilty of any negligence." He said leaving Tyler in the other arm of the trial was "a medical judgment," and that the child's cancer may have been too far gone even then for any therapy to have helped him. The hospital and university agreed to make changes in their clinical trials, instituting random audits, beefing up review-board staff and requiring scientists running trials to undergo mandatory education about their responsibilities to human subjects.

Tyler's case is surely atypical, but no one knows how atypical. Documents submitted to OHRP and obtained by Dr. Adil Shamoo, a member of the National Human Research Protection Advisory Committee, list 878 "incidents"—adverse reactions by volunteers—in the 10 years ending in 2000, including eight deaths. But there is strong evidence that those are underreports. In 1999 Jesse Gelsinger, 18, died in a gene-therapy trial at the University of Pennsylvania. In the ensuing uproar, 921 "adverse events" associated with gene therapy were reported to the government from February to June 2000—10 times more than in the entire decade before. "Deaths in the thousands are never reported, and adverse events in the tens of thousands are not reported," says Shamoo. Dr. Greg Koski, director of OHRP, also has concerns. "I don't think there is any way to measure the scope of the problem," he told NEWSWEEK. "Clearly, there have been more than eight deaths in clinical trials. The question is: how many were actually killed as a direct result of the study? We don't know that answer. But to the best of our knowledge, the number is very small."

The system can break down anywhere along the line—-with investigators who mislead review boards, with review boards that don't do their jobs. A 1998 report by the inspector general of the Department of Health and Human Services found that institutional review boards "review too much, too quickly, and with too little expertise." Johns Hopkins, for instance, had three review boards to monitor thousands of human experiments. Continuing review of clinical trials, concluded an HHS follow-up last year, is a low priority of many review boards, which "know little of what actually occurs during the consent and research process."

An early tip-off, says one worried doctor, came when he saw a little Mexican boy at Tampa General Hospital. Each of the child's eyes had undergone a different operation: one had received a cornea transplant with the standard technique, in which the cornea from a cadaver is stitched into the eye, while the other eye had received an experimental transplant, using a cutting device that surgeon James Rowsey named the Tampa trephine. "I knew there had been very little testing of the device on animals," says the doctor. "And when I saw this little boy, who had one eye done with the conventional procedure and the other with the trephine, I thought to myself, 'He's experimenting on these people.'" The doctor never saw the boy again. But he alerted hospital officials about his suspicions and then, being told Rowsey had permission to experiment with the trephine, got the American Academy of Ophthalmology to launch an investigation.

Rowsey had told the University of South Florida, whose ophthalmology department he chaired, that the patented new device would advance the field of cornea transplants, and could bring the university millions in licensing revenue. But he never finished testing it in
cats before trying it on people, say university and federal investigators; none of his patients was ever told they were receiving unapproved surgery. The hospital's institutional review board acquiesced when Rowsey insisted he was providing "standard therapy" that did not require its involvement, according to minutes of an October 1995 meeting. Last September OHRP concluded that Rowsey's operations were indeed experimental. It cited him for doing research without review-board approval, for subjecting patients to greater than minimal risk and for failing to get their consent.

Since then, two of Rowsey's patients have filed suit against him, an assistant surgeon, the hospital and the university, alleging malpractice, fraud and abuse. One is Harry Rogers, 86. After Rowsey performed the trephine surgery on him in 1995, Rogers became legally blind. He cannot drive, garden or walk down the block unaided, and needs a magnifying glass to read the newspaper. Rowsey, who resigned as department chair in 1997 and is now in private practice, denies his surgeries were experimental. The university has overhauled its program of human experiments and today considers it a model.

Clinical trials have become so "commercialized and competitive," found the HHS inspector general last year, that they have spawned "disturbing" recruitment practices. Vulnerable or ineligible patients sometimes enlist because their doctor (who may also be an investigator) pressures them to do so. In one case, a nursing-home resident was threatened with eviction if she refused to join a trial. More and more, investigators stand to gain financially. In the trial that enrolled Jesse Gelsinger, the chief scientist was founder and 30 percent shareholder of the biotech firm licensing the technology in the study. Penn held equity in the company, too.

Dr. Michael McGee thought the vaccine he had developed might help cure melanoma. So the ex-missionary, a researcher with the University of Oklahoma Medical Center in Tulsa, began to test the efficacy of his serum on more than 90 cancer patients. But there had been no consistent monitoring of the trial's safety or the vaccine's efficacy, found a private auditor last year, and the vaccine was manufactured on-site with virtually no quality control. The university's review board effectively turned over responsibility for the trial to the department chair. With staff lacking "background, training [and] experience" in such studies, found auditors, deficiencies "are so severe that it is beyond the scope of this report to advise corrective actions. Adequate precautions to protect the safety of patients have not been taken." When a nurse-whistle-blower told OHRP of her suspicions that the problems with human studies at Oklahoma went beyond the melanoma trial, the agency launched an investigation. The vaccine researchers, found OHRP, tried to cover up their lapses by withholding information from university and government overseers--as well as patients.

Last year OHRP shut down all federally funded research at the campus. McGee was fired. The dean of the school and head of research were forced to resign. Lawyers for the three deny patients were ever in harm's way; none was killed or hurt by the vaccine. They agree, however, that the trial did not comply with federal regulations. But the fault, they say, lies with the university, which had no system of oversight for such research. Indeed, one member of the Oklahoma review board in the years before the melanoma trial recalls
a system that rubber-stamped trials. "There was an assumption that these are people who do research for a living and know what they're doing," he told NEWSWEEK. "We were just there to make sure they crossed the t's and dotted the i's. There was not enough perspective to expose what might not have been in the best interests of the subjects." Neither McGee nor Oklahoma officials would speak with NEWSWEEK.

Other research centers, while not exactly welcoming federal scrutiny, acknowledge that good can come of it. In 1998 and 1999, three children died in a clinical trial at St. Jude Children's Research Hospital in Memphis, Tenn., each within the first six months of receiving an experimental treatment for acute lymphoblastic leukemia (ALL). The most common childhood cancer, it responds to standard therapy 80 percent of the time, but St. Jude hoped to do better, adding a round of intensive chemotherapy. The trial began in July 1998; the children died in October, December and the following June, two of infections and one from a seizure. After an investigation, OHRP charged that the trial's principal investigator failed to notify the hospital's review board of "multiple instances of unanticipated problems," that St. Jude needed to better protect the rights of its "vulnerable" patients--children--and that the hospital did not conduct "continuing review" of its human experiments. The informed-consent document for the ALL trial, found regulators, "appeared to minimize the potential risks," failing to emphasize that there was a "high likelihood [of]... life-threatening adverse side effects requiring prolonged hospitalization" and that death was a "significant risk." As a result of the OHRP investigation, says Dr. William Evans, deputy director of St. Jude, "we redoubled our commitment to be an example to the rest of the country" on clinical trials.

Most researchers believe that volunteers in clinical trials are well protected. According to the reported numbers, they're right: an estimated 60,000 clinical trials are underway every year, and only the tiniest fraction have problems. Dr. Wyndham Wilson chairs the National Cancer Institute's review board, which monitors 250 studies and meets once a month. "I think the federal regulations necessary to protect human subjects are in large measure there," he says. "Everybody I know in research is dedicated to making the system as safe as possible. A clinical trial is safe." But OHRP's Koski thinks they can be safer, especially given the problems that came to light after Gelsinger's death. He plans to increase his staff from 25 to 47, conduct more random audits and give researchers more help following regulations governing clinical trials. Without the patients who volunteer their bodies to science, biomedical progress would screech to a halt. The trials had better be as safe as we can humanly make them.

**GRAPHIC:** PHOTO: NAME: Harry Rogers, DIAGNOSIS: Became legally blind after receiving an experimental cornea transplant in 1995, FOLLOW-UP: Surgeon resigned from university, which reformed its clinical-trial system. Rogers is suing.; PHOTO: NAMES: DaWanna Robertson, Sydnee, DIAGNOSIS: Enrolled in Oklahoma trial of melanoma vaccine that hadn't been properly tested, PROGNOSIS: All trials at Oklahoma temporarily shut down. Robertson part of class-action suit.; PHOTO: NAME: Paul Gelsinger, DIAGNOSIS: His son Jesse, 18, died in a gene-therapy trial at Penn. Paul says he was never informed of the risks., FOLLOW-UP: Settled suit against Penn. Jesse's death led to revelations of hundreds of 'adverse events.'
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