

Fraud and Ethics Charges Hit Stroke Drug Trial

AMSTERDAM, THE NETHERLANDS—It should have been a landmark study in stroke research, capable of changing the way the disease is treated. But the Second European Stroke Prevention Study (ESPS 2), a major clinical trial of a drug to prevent repeat strokes—involving almost 7000 patients in 13 European countries—has become mired in controversy. A paper describing promising results from the trial, published earlier this month in the *Journal of the Neurological Sciences*, was first turned down by *The Lancet* in part because of ethical concerns over the use of placebos. And it has been further tainted by allegations that a physician at one of the 60 centers originally involved in the trial fabricated data that led to the disqualification of information on more than 400 patients. Although none of the suspect data were included in the published paper, “this is bound to do damage to neurological research,” says neurologist Peter Koudstaal of Erasmus University in Rotterdam.

The trial was designed to study the effect of dipyridamole, also known by its brand name Persantin Retard, in preventing a recurrent stroke in patients who have already suffered a previous stroke or a transient ischemic attack, a very mild stroke with symptoms lasting less than 24 hours. Currently, aspirin is the only generally accepted drug for this purpose, but it prevents recurrent strokes in roughly one in five patients only. Researchers had failed, so far, to find any significant improvement on aspirin. The CAPRIE study, a huge multicenter trial published in *The Lancet* in November, showed that another potential drug, clopidogrel, was only marginally more effective than aspirin.

Like aspirin and clopidogrel, dipyridamole is an antiplatelet drug—it prevents blood from clotting and thus cerebral arteries from getting blocked—and has been a mainstay of the German drug giant Boehringer Ingelheim for more than 15 years in the treatment of all cardiovascular afflictions, although its efficacy has been debated for many years. The results of the Boehringer-sponsored ESPS 2 trial indicate, however, that the drug has great potential in preventing recurrent strokes. Dipyridamole alone reduced the risk of a new stroke by 16% dur-

ing the 2 years the patients were followed; aspirin, which was also tested, gave a risk reduction of 18%; but combined the two lessened the chances of a stroke by 37%, with relatively few side effects. The death rates in all three treatment groups were about the same, however, and did not differ significantly from that of the placebo group.

But the encouraging news in the ESPS 2 results was soured by the paper's guarded suggestions of data problems discovered during the study. The paper refers to “serious inconsistencies in patient case record forms and compliance assay determinations” at one center. Armand Lowenthal of Middelheim Hospital in Antwerp, Belgium, who chaired the trial's coordinating committee, says that a thorough examination by an independent lab revealed that some of the 438 patients enrolled in the trial at that center turned out

PROMISING COMBINATION			
Treatment	# of Patients	# of Strokes	# of Deaths
Placebo	1649	250	202
Aspirin	1649	206	182
Dipyridamole	1654	211	188
Both	1650	157	185

to be “entirely made up.”

Although Lowenthal declined to name the doctor at the center of the allegations, others have identified him as H. J. Gelmers of Twenteborg Hospital, a regional clinic in Almelo, the Netherlands. Gelmers was originally a member of the trial's protocol and publishing committee, but left the committee after the alleged fraud was discovered in 1993; his resignation is recorded in a 1995 paper by the ESPS 2 study group in the *Journal of the Neurological Sciences*. In this month's paper, Gelmers was not listed as one of the authors and Twenteborg Hospital was not listed among the 59 institutions whose data were used in the study.

Gelmers denied in a brief telephone interview with *Science* that he fabricated data in the trial and said of alleged problems with blood samples: “It's more probable that this happened elsewhere.” Gelmers said he was not allowed to comment further and referred questions to H. J. Sissingh, the director of Twenteborg Hospital. Sissingh says that he was notified of the case some time ago by

Boehringer Ingelheim. “We subsequently had some conversations and carried out an investigation, but we were unable to establish either guilt or innocence. So we left it at that,” says Sissingh.

Chris Verhorst, medical director of Boehringer Ingelheim Netherlands, says the trial's organizers first became concerned about the large number of patients enrolled by a single physician and the unusual dedication with which they took their daily medication. Suspicions grew, says Lowenthal, when blood pressure data submitted by the physician turned out to be distributed along a perfect Gaussian curve—which is highly unlikely in a patient sample of this size.

According to the trial protocol, patient compliance was tested by assaying drug levels in plasma from 15% of the patients. Lowenthal says analysis of the suspect samples showed that all of them came from just two individuals, and all contained both drugs, which would have been very unlikely because only one in four patients got a combination of both drugs. The concentrations of the drugs also varied widely, reaching impossibly high levels in some of the samples, Lowenthal said.

Asked why the problems with the data went undetected for years, Verhorst says this was an old study, and “monitoring was less careful and less frequent than it would be today. ... But we did discover the irregularities thanks to the monitoring.” Verhorst says Boehringer Ingelheim paid participating centers about \$1500 for each patient who completed the trial, which would have amounted to about \$640,000 for the suspect data. Verhorst says that payments were stopped after the alleged fraud was discovered, and as far as Boehringer Ingelheim is concerned, the case is closed—the company decided not to claim its money back.

The Dutch Association for Neurology may not let the matter rest, however. It is intending to set up an independent committee to investigate, says Marianne de Visser, chair of the association. “This is something that bears on the reputation of Dutch neurology,” she says. “There may be something wrong, but we will investigate the matter very carefully before drawing conclusions.”

While the neurology association investigates the implications of the alleged fraud for Dutch neurology, researchers in several countries have expressed ethical concerns about the ESPS 2 trial. During the trial, patients were divided into four groups, which were given different treatments: dipyridamole alone, aspirin alone, a combination of the two, and a placebo. A placebo is generally used only when there is no proven effective drug to test against, but critics argue that aspirin had already been proven effective in reducing the risk of recurrent stroke.

Clinical epidemiologist Michael Gent of

SOURCE: H. C. DIENER ET AL., *J. OF THE NEUROLOGICAL SCIENCES*

Canada's McMaster University in Hamilton, Ontario, who was the principal investigator in the CAPRIE study, says that "When they started this study in 1988, there was clear evidence from a number of published studies that antiplatelet drugs, particularly aspirin, prevented stroke ... in these patients." The 1649 people in the placebo group were unnecessarily exposed to a higher risk, he says.

Erasmus's Koudstaal says that there may have been room to doubt aspirin's efficacy at the beginning of the trial. But later studies, such as the 1991 Swedish Aspirin Low-dose Trial (SALT) and the "aspirin papers," a series of meta-analyses published in the *British Medical Journal* in 1994, "convincingly proved" that aspirin worked, he says, and should have been reason to stop the placebo arm of the trial. Yet, the study continued until March

1995. "It was probably a mistake at the time," adds Charles Warlow, a neurologist at Western General Hospital in Edinburgh, U.K. "I personally wouldn't have put people in the trial. But there are many perfectly respectable people who did. People vary in what they regard as definite evidence."

Verhorst and Lowenthal dismiss these criticisms, arguing that the efficacy of aspirin, as well as the optimal dosage, was not known when the trial started. Says Verhorst: "The study was submitted to ethical committees in every center. If 59 ethical committees approve, then there is no ethical problem." And Lowenthal says that the trial was monitored by a central ethics committee, which discussed the study each year. It reported in 1995 that use of placebos was justified because of doubts about aspirin's efficacy and

side effects. However, Verhorst confirms that the study was turned down by *The Lancet* largely due to ethical concerns.

Neurologists are now debating whether the results of the study should guide clinical practice. Some previous studies have found no benefit from the combination of dipyridamole and aspirin compared with aspirin alone in stroke prevention, although one other study, published 10 years ago by the same group, reported very positive results with a smaller number of patients. A meta-analysis of all relevant trials will be needed to give a definitive answer. "There is some discomfort about this," says Gent, "but the results are interesting."

—Martin Enserink

Martin Enserink is a science writer based in Amsterdam.

AIDS POLICY

Baltimore to Head New Vaccine Panel

With powerful new cocktails of AIDS drugs beginning to make headway against HIV (see p. 1988), researchers and AIDS activists alike are turning more attention to a research area that has been something of a stepchild: development of a preventive vaccine. William Paul, head of the Office of AIDS Research at the National Institutes of Health, announced on 12 December that the NIH AIDS vaccine budget would be raised from \$109.5 million to \$129 million in fiscal year 1997, and that Nobel Prize-winning retrovirologist David Baltimore will head a new AIDS vaccine panel to help coordinate the effort. "The NIH has often been accused by others of not taking AIDS vaccine development seriously," says Paul. "We think this appointment, aside from its scientific value, is saying to the nation and the pharmaceutical industry we are taking it seriously."

Baltimore, a researcher at the Massachusetts Institute of Technology (MIT), well knows that reinvigorating the AIDS vaccine field—which has suffered from industry's lackluster interest and a sobering list of scientific obstacles—is a tall order. "The major challenge is to create more scientific opportunities and to produce a vaccine preparation that will give such an exciting result in preclinical testing that industry will say, 'Yes, this is something we want to do,'" says Baltimore. But no one, including Baltimore, yet knows how he and his panel—which will mix extramural researchers and representatives from various branches of NIH—will accomplish this.

The idea for the panel stems from a task force, consisting of 100 extramural researchers, who just this spring completed a massive review of NIH's AIDS research portfolio (*Science*, 15 March, p. 1491). The report concluded that "the entire AIDS vaccine research

effort of the NIH should be restructured"—although it didn't say how—and overseen by an AIDS Vaccine Research Committee (AVRC). The AVRC, it stipulated, should coordinate direction for all the AIDS vaccine research—intramural and extramural—funded by NIH. Although Baltimore won't have any formal authority, he will advise Paul, NIH Director Harold Varmus, and NIH institute directors on what his committee believes should be done to stoke the vaccine effort. "Having someone of David's breadth of experience and extraordinary creativity and intelligence cannot help but be a positive thing," says Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases.

Baltimore, who first surfaced as a candidate for the job this summer (*Science*, 20 September, p. 1647), says he thought about the offer long and hard. "When I was first asked, I decided I had to look carefully at whether I believed it was possible to make a vaccine," says Baltimore. After considering data from several promising studies, including one showing that monkeys given a live, but weakened, AIDS virus vaccine were protected from subsequent challenge with lethal virus, Baltimore decided that it would be. "At that point," he says, "I was honored and excited by the possibility that I could contribute to that."

Baltimore acknowledges that he was also hesitant to take the job until after the national elections in November. Had the Democrats reestablished a majority in the House, Representative John Dingell (D-MI)—with whom Baltimore had battled over charges that a co-

author on one of his papers had falsified data—likely would have once again chaired the subcommittee that oversees scientific misconduct. "I certainly did feel if the House became Democratic, I had to come to some understanding with him before I could take the job," says Baltimore.

Baltimore's appointment is being received enthusiastically—although with some reservations. "Clearly, David is one of the best and brightest scientists that the United States has," says Margaret Johnston, scientific director of the Rockefeller Foundation's International AIDS Vaccine Initiative. "That said, he's got some things to learn about vaccine development, and there are very serious issues that need to be taken on by NIH." Johnston points to what she believes is a need to direct some areas of AIDS vaccine development, such as launching a targeted program to determine which immune responses protected the monkeys in the 1992 vaccine experiment Baltimore cited.

Another serious issue, as highlighted in a report issued this month by the AIDS Vaccine Advocacy Coalition, a new group of AIDS policy analysts, is the low-level interest of industry. The report concludes that it is "extremely troubling that only a handful of companies are actively attempting to develop an AIDS vaccine."

Baltimore, who will devote about 20% of his time to the vaccine effort, intends to survey people in the field over the next few months to figure what, exactly, he'd like his committee to do. "I may find 2 years down the road that it's all frustration," says Baltimore. "But I doubt it."

—Jon Cohen



Vaccine chief. MIT's David Baltimore.