

Despite Undisclosed Deaths, 10 Heart Attacks FDA Allows Blood Substitute Experiment With No Consent

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The Wall Street Journal reports: "The FDA is allowing Northfield [Laboratories, Inc] to test its blood substitute without the consent of the trauma patients, who often are unconscious."

Blood substitutes may be needed on the battlefield. But does that justify testing blood substitutes in trauma patients in urban communities when life-saving blood could be tested inasmuch as it has been proven safe and more effective?

The FDA, beyond all comprehension of a possible rationale, approved Northfield's multi-site trial at 31 medical centers in December, 2003, under the stewardship of Dr. Mark McClellan—when the agency had knowledge that the product caused heart attacks in patients in a prior, unpublished clinical trial whose results have remained concealed:

"ten of 81 patients who received the fake blood suffered a heart attack within seven days, and two of those died. None of the 71 patients in the trial who received real blood were found to have had a heart attack."

What's more, the FDA remained silent as the company continued to hide this vital information from physicians conducting the trial, from patients, and the public, is approaching criminal behavior.

Dr. William Hoffman, chief of cardiac-surgery intensive-care, at Massachusetts General, says "blood substitutes made with hemoglobin as a starting point...are associated with heart attacks and strokes."

Human blood is proven safe and effective. Indeed, efforts by (at least) four companies—Baxter, Biopure, Hemosol, Northfield—to produce an artificial blood substitute have ALL demonstrated that there is no safe substitute for human blood. Artificial products are made with hemoglobin which binds nitric oxide. This causes basal constriction seriously raising blood pressure. The blood platelets become sticky and have been shown to adhere to vascular surfaces, causing blood vessels to become inflamed and occluded.

ALL of the tested blood products have demonstrated the same adverse effect profile: they caused hypertension crisis, myocardial infarctions, strokes, and kidney failure. In clinical trials, no artificial blood product has compared favorably to human blood.

Human blood requires refrigeration, which is not possible on the battlefield. To save soldiers' lives a blood substitute would potentially be useful. However, no safe blood substitute has been developed—certainly none whose use can be justified on civilians who are not far from hospital emergency rooms. Dr. John Hess, who headed the Army's blood-substitute programs before he shut it down in 1996 "after concluding that all the blood substitutes he evaluated were toxic. With hemoglobin, the lining of the blood-vessel wall becomes inflamed..."

Artificial blood experiments on trauma patients violate that first and foremost condition set forth in FDA's waiver of informed consent Rule.

In 1996, the FDA adopted a radical rule granting waiver from informed consent requirements for trauma patients but only under conditions specified, the first being:

"(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions."

[See: Protection of Human Subjects: Informed Consent and Waiver of Informed Consent Requirements in Certain Emergency Research; Final Rules. Federal Register: 51528-51533. Code of Federal Regulations, Part 50 section 50.24] Human blood is available, and its efficacy and safety is proven and satisfactory.

FDA's waiver of informed consent rule was first applied in 1998, by Baxter International (competitor to Northfield) when it conducted a similar trial to test its blood substitute, HemAssist, without informed consent. The Baxter trial was stopped when 24 of 52 patients given the blood substitute died compared to 8 of 46 who had real blood. This lethal experiment demonstrates that waiver of informed consent opens the gate to medical disasters.

At the same time, Northfield was conducting its own abdominal aortic aneurism trial on surgical patients who underwent elective surgery to repair it—these patients were able to give informed consent. After the suspension of the Baxter trial, the FDA ordered Northfield to expand its trial at 21 medical centers to a voluntary patient base of 600 from 240.

In August, 2001, that trial was abruptly suspended without the company ever disclosing the results—not even to participating trial investigators.

“Northfield restricted access to the full data” thereby keeping the participating doctors in the dark about the heart attacks and other serious adverse events.

The Wall Street Journal reports: “These events occurred in 54% of the PolyHeme patients versus 28% in the control group”. Overall, eight PolyHeme patients died versus four on the conventional therapy. An FDA official is quoted stating:

“the adverse-event profile in the aneurysm trial, while significant, was not a show-stopper”. How many preventable deaths does the FDA tolerate before it stops the “show”?

It is inconceivable how the FDA justifies its approval of the current PolyHeme trial being conducted on trauma patients in urban centers across the US —without informed consent: “In lieu of patient consent, the 31 medical centers testing the product are required to carry out community-awareness campaigns about the trials.”

How do FDA officials explain the agency turning a blind eye to fact that participating hospitals were misleading the community about the safety of the substitute blood? “Several hospitals have told community meetings that previous trials showed PolyHeme to be safe, failing to mention the 10 heart attacks [associated with PolyHeme] in their printed materials.”

Moreover, the community was not informed that type 0 negative blood could be used in ambulances—as is done in Israel. If the blood is proven beneficial in trauma victims, and more lives are saved, logistical problems can surely be worked out.

This experiment demonstrates why FDA’s waiver of informed consent Rule leads to abuse of vulnerable unconscious patients. The experiment turns the inalienable right of informed consent on its head by PRESUMING consent unless one wears a blue band on one’s wrist when one happens to be in an accident. This PolyHeme experiment increases the risk of death for trauma patients. It is unconscionable, and should have never been approved since the FDA had knowledge of the hazardous adverse events from prior clinical trials—and an existing, safe treatment is available.

How many patients have been subjects of trials testing an artificial blood product?

How many companies have tested such products?

How many patients who received the artificial blood suffered:

----- myocardial infarction compared to controls?

----- stroke compared to controls?

----- renal failure compared to controls?

What was the survival rate of those receiving the artificial product compared to those receiving human blood?

If the purpose of developing an artificial blood product were to improve mortality by getting oxygen carrying products to trauma patients in the ambulance, why not test blood type 0-negative—which is a universal donor? There is no question that 0-negative blood is safer than any artificial product and can accomplish the same goals.

Surely, we should not be increasing mortality in order to save the cost of refrigeration in ambulance!

Did the FDA Commissioner approve and sign-off on the PolyHeme experiment on trauma patients?

If so, the Senate Finance Committee may want to hear what the stated justification was for this devaluation of living human beings.

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Red Flags

Amid Alarm Bells, A Blood Substitute Keeps Pumping

Ten in Trial Have Heart Attacks, But Data Aren't Published; FDA Allows a New Study Doctors' Pleas Are Ignored

By THOMAS M. BURTON

February 22, 2006; Page A1

Several years ago a clinical trial of a blood substitute called PolyHeme finished with worrisome results. Ten of 81 patients

who received the fake blood suffered a heart attack within seven days, and two of those died. None of the 71 patients in the trial who received real blood were found to have had a heart attack.

PolyHeme's maker, Northfield Laboratories Inc., quietly shut down the trial and didn't publicly disclose the results, which are described in internal documents viewed by The Wall Street Journal. It decided the heart attacks might have been due to doctor inexperience in using PolyHeme, not a problem with the product itself.

Now Northfield is in the middle of a new trial. A Food and Drug Administration official, Jay Epstein, calls the earlier data "alarming" but not sufficient to stop Northfield from trying out its product on hundreds of trauma patients.

The FDA is allowing Northfield to test its blood substitute without the consent of the trauma patients, who often are unconscious. In lieu of patient consent, the 31 medical centers testing the product are required to carry out community-awareness campaigns about the trials. Several hospitals have told community meetings that previous trials showed PolyHeme to be safe, failing to mention the 10 heart attacks in their printed materials.

Some veteran doctors are concerned about the push by Northfield, of Evanston, Ill., to test its product without publicly disclosing earlier results. Ronald M. Fairman, chief of vascular surgery at the Hospital of the University of Pennsylvania, says he repeatedly urged the company to publish the data but got nowhere. "Even now, it remains frustrating the multicenter results were not disclosed," he says.

Northfield's chief executive, Steven A. Gould, argues the heart attacks could well have been caused by doctors pumping too much total fluid -- PolyHeme plus real blood -- into patients. He says PolyHeme could help many people, such as those in an ambulance who don't have access to human blood. "Our experience suggests the risk-benefit balance is in the patient's favor," Dr. Gould says.

In a statement, Northfield denies it "resisted publication" but says: "We did not allocate resources to publication. In retrospect, reporting the full study results earlier would have been better."

Northfield says any American who doesn't wish to participate in the current PolyHeme trial should ask the company for a blue plastic wristband that would alert paramedics. Those who fail to get a wristband and find themselves in a hospital trauma unit "can withdraw from the study, without prejudice, at any time," the company says.

Northfield has raised \$194 million in stock offerings since going public on the Nasdaq Stock Market in 1994. Its market value stands at \$334 million on hopes that PolyHeme, its sole product, could be the first blood substitute approved by the FDA. Results of the new study are expected this year.

Scientists have been hunting for a safe, workable blood substitute for more than half a century. Unlike donated human blood, artificial blood may reduce the risk of hepatitis or HIV infection. It eliminates the need to match blood types of donor and recipient, and has a far longer shelf life without refrigeration.

One use for artificial blood is in the military. Blood needs to be refrigerated and usually can't be carried into combat. It goes bad in about 42 days, whereas PolyHeme lasts a year or more. Soldiers who would otherwise bleed to death on the battlefield might be saved if a medic could quickly infuse them with an oxygen-carrying blood substitute.

But companies seeking this lifesaver have often met with disappointment. Baxter International Inc. halted a U.S. study of its blood substitute HemAssist in 1998, because 24 of 52 trauma patients, or 46%, given HemAssist died compared with only eight of 46, or 17%, who received standard therapy. Study doctors said the product may have dangerously raised blood pressure. Shortly before HemAssist failed, Baxter spent \$190 million to buy another company with a blood substitute. It ultimately abandoned that product, too, after throwing a total of \$500 million into its blood-substitute ventures.

Today there are several companies remaining in the blood-substitute race, but Northfield is the only one known to be in final-stage clinical trials.

Northfield was founded in 1985. Among its founders was former Navy surgeon Gerald S. Moss, later dean of the University of Illinois at Chicago College of Medicine. He had worked on a blood substitute beginning in 1969 under a contract with the Army and Navy. Later he worked with Dr. Gould, a surgeon, and the two were among those who started the company.

The making of PolyHeme begins with outdated donor blood. A protein called hemoglobin in red blood cells delivers oxygen throughout the body. Northfield bursts open red cells in giant metal vats, freeing the hemoglobin molecules inside.

Hemoglobin molecules are known to be dangerous if they aren't held within red blood cells. The molecules tend to seep into the walls of blood vessels and cause inflammation. Most relevant to heart attacks, they can constrict blood vessels and cause clotting. Northfield chemically links one hemoglobin molecule to another in a process called polymerization.

Dr. Gould says this removes hemoglobin's toxicity.

John R. Hess, a University of Maryland research doctor, is skeptical. He once headed the Army's blood-substitute program but shut it down in 1996 after concluding that all the blood substitutes he evaluated were toxic. With hemoglobin, Dr. Hess says, "the lining of the blood-vessel wall becomes inflamed....There's no reason the modification should change this."

Northfield has voiced optimism for years. In May 1997, a company news release said, "PolyHeme is in the home stretch with market introduction planned for sometime during 1999." The company's then-chief executive, Richard DeWoskin, said, "We have advanced to the point that the question of science is now being replaced with the question of size and scope of the commercial market for our product."

At the time, Northfield was starting what was to be its pivotal trial. Patients were randomly assigned to a group receiving PolyHeme or a control group receiving real blood. This type of study is the gold standard in medicine. The patients in the trial were undergoing surgery to repair aneurysms, or ballooned sections, in their aortas. They gave their consent before participating.

After the Baxter product was implicated in deaths in March 1998, the FDA ordered Northfield's study enrollment target expanded to 600 patients from the original 240. Northfield remained upbeat. An August 1999 news release spoke of PolyHeme's "excellent safety profile." A news release in April 2000 said the study was "producing very important results" but was taking a long time to enroll enough patients. Then in the second half of 2001, Northfield abruptly shut down the study, explaining in a Securities and Exchange Commission filing that it was taking too long to complete.

In August 2001, Northfield tried a long-odds maneuver: It asked the FDA to approve PolyHeme based on earlier research on hospital trauma patients. In that research, PolyHeme wasn't compared with a control group receiving standard therapy. Instead, Northfield compared the results with other hospitals' historical experience with patients who needed blood but didn't get any. These patients were Jehovah's Witnesses who declined blood for religious reasons. In November 2001, the FDA refused to consider the application, citing concern about the validity of the comparison, according to a Northfield SEC filing.

Critical Question

The sudden halt to the big randomized PolyHeme trial left unanswered a critical question: What were the results? Doctors who had taken part were curious. In an arrangement that doctors often reject today, Northfield restricted access to the full data and individual doctors knew only what happened to their own patients.

At the University of Pennsylvania, Dr. Fairman says he and a colleague, Albert Cheung, repeatedly called Northfield's Dr. Gould. "We said, 'Let's sit down and write up the data,'" Dr. Fairman recalls. "He wouldn't do it." Dr. Cheung proposed a meeting in Philadelphia of doctors at the 21 hospitals that had taken part in the study. He says Dr. Gould agreed to the meeting, then canceled it at the last minute.

T.J. Gan, a Duke University anesthesiologist involved in the study, says he called Northfield three years ago to ask if results had been published. He says Dr. Gould told him, "Someone's working on it." Dr. Gan says, "Regardless of whatever the problem, you publish it and outline the results." In its statement, Northfield says company officials don't recall the specifics of any discussion with Dr. Cheung about a meeting or the conversation with Dr. Gan.

Dr. Gould says he did inform the FDA of the aneurysm trial's results. The company now says it plans to make public a medical abstract of the study in April.

Besides the heart attacks and deaths in those taking PolyHeme, the trial suggested the product was linked with other serious adverse events such as heart rhythm aberrations and pneumonia. These events occurred in 54% of the PolyHeme patients versus 28% in the control group, according to Northfield's internal documents. The higher rate of heart attacks and serious events was considered statistically significant, meaning there is minimal likelihood they happened by chance. Overall, eight PolyHeme patients died versus four on conventional therapy, a difference that wasn't found to be statistically significant.

Such a stark difference in serious adverse events would often be fatal for a drug or medical device under study. Still, Northfield persevered.

Dr. Gould says the company doesn't believe PolyHeme caused the heart attacks. Before surgery, patients had their own blood drawn for possible use during the operation. Dr. Gould says several hospitals gave patients both PolyHeme and real blood. Together, he says, the amount of fluid was too much. "It can't be determined," he says, whether the heart attacks were due to the "capability and experience" of doctors "or to the product."

William D. Hoffman, chief of the cardiac-surgery intensive-care unit at Massachusetts General Hospital in Boston, says blood substitutes made with hemoglobin as a starting point, a class that includes PolyHeme, are associated with heart

attacks and strokes. "It is self-serving and potentially misleading to associate harmful effects with something other than the test drug," says Dr. Hoffman, who used to work for another artificial-blood company but left after a dispute with executives there.

The FDA's Dr. Epstein, who is director of the agency's blood-products office, sides with Dr. Gould, calling Northfield's theory a plausible one. "Of course it's alarming there were excess deaths in the treatment group," he says. "We are highly mindful of the adverse events." But, he goes on, "the adverse-event profile in the aneurysm trial, while significant, was not a show-stopper." The FDA's review suggested that "volume overload" rather than "any intrinsic toxicity of the product" was responsible for the cardiac events, he says.

As a result, Northfield was able to embark on a big new trial -- this time in trauma patients such as victims of shootings or car accidents. It started signing up trauma centers in December 2003 and as of early this year about 600 people had taken part. Half get PolyHeme and the other half get saline solution plus real blood. The study measures the death rate at 30 days. Northfield's hope is that PolyHeme will be found equivalent to -- or at least not provably worse than -- the standard therapy. As of late last year, an independent data monitoring board hadn't found any statistical differences between the two groups large enough to warrant halting the study.

Dr. Gould says Northfield typically pays hospitals around \$10,000 a patient to participate. Northfield agreed to pay \$336,000 to the University of Texas Health Science Center at Houston and \$132,468 to the University of Kentucky Medical Center, hospital records show. The hospitals say the money merely covers costs in collecting the data. "This is not a profit-making endeavor -- it is a scientific one," says University of Kentucky surgeon Andrew C. Bernard. Others participating include the Mayo Clinic, Duke University and Lehigh Valley Hospital in Allentown, Pa.

In the trauma study, patients are in hemorrhagic shock, meaning they are bleeding so profusely that their blood pressure plummets. The typical patient can't offer the informed consent that normally is required for clinical trials. A 1996 FDA rule says it is acceptable to give trauma patients experimental treatments without their knowledge. Without the rule, the agency says, trials would be impossible and society wouldn't benefit from advances in trauma care.

Playing Down Risks

In place of individual consent, the FDA has required Northfield and the hospitals participating in the trauma trial to hold public meetings at churches, city halls and the like in their communities. Materials used at the meetings and filed to the FDA often played down the risks of PolyHeme.

The Lehigh Valley Hospital materials for local meetings said, "Past studies have shown that PolyHeme...has not caused organ damage." Materials from the Brooke Army Medical Center near San Antonio for meetings last July were even more categorical: "In clinical trials to date, PolyHeme has demonstrated no clinically relevant adverse effects. Up to now, PolyHeme has not caused any clinically bad problems."

"Aneurysm-surgery patients are vastly different from trauma patients," said Col. John Holcomb, a trauma doctor at Brooke. "I know that there are no safety issues." A doctor at Lehigh didn't return a phone call seeking comment.

Northfield did tell trauma doctors about the heart attacks in the earlier study but did so confidentially and with an explanation that it didn't believe PolyHeme was responsible, according to company documents and interviews with doctors. The University of Kentucky's Dr. Bernard says there is a limit on what the public can be told about the earlier trial results because "everything in the study is confidential."

Early last year, Keith Berman, a Pasadena, Calif., medical-products consultant who has studied blood substitutes, urged the FDA to make the earlier trial's results public. Last year, the agency required Northfield to mention on its Web site "serious cardiovascular adverse experiences" with PolyHeme. Five of the 31 hospitals in the trauma study followed suit, but well after many trauma patients had been treated.

Because Northfield needs only about 120 more people to complete its study, any individual's chance of being enrolled is low. However, those who are still worried can get the blue plastic wristband from the company to signal that they refuse to take part.

While Northfield says PolyHeme could be useful in rural ambulances, battlefields and other settings where real blood is out of reach for hours, it hasn't conducted a large-scale test focusing solely on that notion. It says assembling patients for such a trial would be too difficult and time-consuming. "We all recognize that doing the [trauma] trial in an urban setting was not ideal, but this was the only way to get the trial done," says a Northfield spokeswoman.

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FDA, Northfield Face Inquiry Over Study of Blood Substitute
Chairman of Senate Panel Opens Probe Questioning Methods and Disclosures
By THOMAS M. BURTON
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The chairman of the U.S. Senate Finance Committee has begun an inquiry into how federal health regulators and Northfield Laboratories Inc. handled a clinical study of a blood substitute used in hundreds of hemorrhaging trauma patients around the U.S.

Sen. Charles E. Grassley (R., Iowa), who has actively challenged the Food and Drug Administration's performance in recent years, raised questions about the conduct of the 720-patient trauma study in a draft of a letter being sent to acting FDA Commissioner Andrew C. von Eschenbach. The letter cited a page-one article in The Wall Street Journal on Wednesday on Northfield and its clinical studies. The Finance Committee has jurisdiction over federal Medicare and Medicaid insurance programs.

Sen. Grassley focused both on whether patients in the study were made aware of all adverse events with the product, and whether it was appropriate to conduct such a trial without the consent of patients. The study is being conducted at 31 hospitals in 18 states. Severely injured trauma patients are given either the blood substitute, called PolyHeme, or saline solution and human blood red cells.

The FDA occasionally allows exceptions to normal informed-consent rules under the rationale that it would otherwise be impossible to test a medical product used in trauma.

The Journal article noted that Northfield hadn't publicly disclosed the full results of an earlier study in aneurysm-surgery patients, in which 10 patients of 81 given PolyHeme had heart attacks, of whom two died. None of the 71 patients on more standard treatment suffered heart attacks, though Northfield said that an overload of fluid volume, rather than PolyHeme itself, may have been the cause. The article noted, too, that most people in America could be inadvertently drawn into the study unless they wear a light-blue Northfield wristband telling paramedics not to enroll them. Only about a 100 patients are still to be enrolled in the study. The wristbands are available from Northfield in Evanston, Ill.

"If you suffer a traumatic injury ... you may, without your consent, become a human research subject for an experimental blood product," Sen. Grassley wrote in his draft letter to the FDA. "That is, unless you happen to be wearing a light-blue wristband imprinted with the following: 'I decline the Northfield PolyHeme study.' "

The FDA and Northfield declined to comment.

Sen. Grassley said he is "skeptical that any participating medical centers managed to conduct effective, practical outreach to the community" before beginning the trauma study and requiring people to wear wrist bands to opt out.

Sen. Grassley's letter also asked the FDA to focus on whether "known adverse events" from earlier studies were "disclosed with the risks and expected benefits information."

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