

 **Baxter**

5 0 9 1 '99 FEB 19 A9:10

February 18, 1999

Docket Number 95S-0158  
Dockets Management Branch (HFA-305)  
Food and Drug Administration  
12420 Parklawn Dr. Rm 1-23  
Rockville, MD 20857

**RE: Investigational New Drug Application #6859**

Dear Sir or Madam:

In accordance with 21 §50.24, and 21 §312.130 concerning Baxter Healthcare Corporation's Investigational New Drug Application #6859, we are enclosing copies of information concerning public disclosure following the completion of the clinical investigation of Diaspirin Crosslinked Hemoglobin (DCLHb) involving an exception to informed consent.

Baxter has contacted the 18 clinical sites involved in its trauma trial which completed pre-study community consultation/public disclosure activities and received investigation product (DCLHb) to ensure completion of post-study notification activities. Each of these sites has received a copy of the final study report synopsis and all IRB's have completed or are in the process of completing their post-study disclosure activities.

This submission includes post-study information from the Oregon Health Sciences University (Portland, OR), the University of Louisville Hospital (Louisville, KY), Vanderbilt University Medical Center (Nashville, TN), the University of Pittsburgh Medical Center (Pittsburgh, PA), Methodist Hospital (Indianapolis, IN), Hershey Medical Center (Hershey, PA), Christiana Care Health Services (Newark, DE), St. Anthony Central Hospital (Denver, CO), MetroHealth Medical Center (Cleveland, OH), and Allegheny University-Medical College of Pennsylvania (Philadelphia, PA). This submission also includes recent "national" press coverage pertaining to the DCLHb Trauma Study .

95S-0158

SUPIS  
RPT/B

The post-study public disclosure information from the Oregon Health Sciences University includes a July, 1998 letter sent to the four survivors enrolled in the DCLHb study at OHSU (Attachment 1), a printed advertisement published in July, 1998 in the three local newspapers (*The Oregonian*, *The Columbian*, and *The Scanner*) utilized for public disclosure at the initiation of the study (Attachment 2), a wire service article published on April 2, 1998 in *The Oregonian* announcing termination of the study (Attachment 3), and a July, 1998 letter sent to approximately 500 recipients, including trauma surgeons, emergency physicians and EMS personnel within greater Portland, department chairs and chief administrators at OHSU, and numerous community and patient advocate groups (Attachment 4). These recipients also received the initial public notification letter sent at the beginning of the study.

The post-study public disclosure information from the University of Louisville includes an April, 1998 post-study press release (Attachment 5) and a May, 1998 post-study letter sent to this site's community consultation contacts (Attachment 6). In addition, a local television station, WHAS, reported on the study closure in a follow-up report in December of 1998 (video/transcript not available).

The post-study public disclosure information from the Vanderbilt University Medical Center includes a January, 1999 summary of the IRB's post-study activities (Attachment 7) which included a presentation to the Vanderbilt Community Committee in May, 1998.

The post-study public disclosure information from the University of Pittsburgh Medical Center includes a June, 1998 press release (Attachment 8) and a July, 1998 advertisement sent to the same newspapers used for community notification at the start of the study (Attachment 9).

Post-study public disclosure activities at the Methodist Hospital in Indianapolis included informing all clinical personnel involved in the study, contacting study patients and/or their families, briefing Indiana state offices which had been contacted during the pre-study disclosure, and following local press coverage (Attachment 10).

Post-study public disclosure activities at Hershey Medical Center included personal calls to members of their community group (Attachment 11).

The post-study public disclosure information from Christiana Care Health Services includes an April, 1998 article from the *Delaware News Journal* (Attachment 12), an October, 1998 *Delaware Today* magazine article on clinical investigations which discussed informed consent issues and the DCLHb trial (Attachment 13), and a December, 1998 public notice published in the *Delaware News Journal* (Attachment 14).

The post-study public disclosure information from St. Anthony Central Hospital in Denver includes an informational letter sent to each of the Area Trauma Advisory Councils (ATAC) that were initially informed of the study (Attachment 15) and a Feb. 7, 1999 notice published in the *Denver Post* (Attachment 16).

The post-study public disclosure information from MetroHealth Medical Center in Cleveland includes a January, 1999 public advertisement which was published in *The Plain Dealer* (Attachment 17) and a local African American newspaper, *The Call and Post*. A Spanish translation was placed in a local Hispanic newspaper, *Nueves Horizontes*.

The post-study public disclosure activities at Allegheny University – Medical College of Pennsylvania, a site which did not enroll any patients, included two letters to community and research council members (Attachment 18). A March, 1998 letter informed the members that the DCLHb clinical study had been terminated due to the mortality imbalance. A February, 1999 letter summarized the study results and included a copy of the study synopsis.

Recent national press coverage on the waiver of informed consent issue includes a Jan. 17, 1999 article from the *Chicago Tribune* (Attachment 19), a related *Associated Press* release (Attachment 20); and transcript of an *ABC Good Morning America* television segment (Attachment 21). Dr. Edward P. Sloan presented a “Clinical Update of the DCLHb Traumatic Hemorrhagic Shock Program” at the 6th Annual IBC Conference on Blood Substitutes and Oxygen Therapeutics on November 20, 1998 in Washington, D.C. (Attachment 22).

If there are any questions concerning this submission, please contact me at (303) 541-3320.

Sincerely,



Todd Marshall  
Associate Director of Regulatory Affairs  
BAXTER Hemoglobin Therapeutics

**Oregon Health Sciences University**

- Attachment 1: Letter to surviving study patients
- Attachment 2: Notice printed in local newspapers (*The Oregonian*, *The Columbian*, *The Scanner* - July 1998)
- Attachment 3: Article in *The Oregonian* (April 2, 1998)
- Attachment 4: Letter to research and community members

**University of Louisville Hospital**

- Attachment 5: Press release (April 17, 1998)
- Attachment 6: Letter to community consultation contacts

**Vanderbilt University Medical Center**

- Attachment 7: IRB Summary

**University of Pittsburgh Medical Center**

- Attachment 8: Press release (June 15, 1998)
- Attachment 9: Notice printed in local newspapers (July, 1998)

**Methodist Hospital in Indianapolis**

- Attachment 10: Site summary

**Hershey Medical Center**

- Attachment 11: Site summary

**Christiana Care Health Services, Newark**

- Attachment 12: Article in *Delaware News Journal* (April 2, 1998)
- Attachment 13: Article in *Delaware Today* (October, 1998)
- Attachment 14: Notice printed in *Delaware News Journal* (Dec. 5/6, 1998)

**St. Anthony Central Hospital, Denver**

- Attachment 15: Letter to Area Trauma Advisory
- Attachment 16: Notice printed in *Denver Post* (Feb. 7, 1999)

**MetroHealth Medical Center, Cleveland**

Attachment 17: Notice in the *Plain Dealer* (Jan. 9, 1999)

**Allegheny University-Medical College of Pennsylvania, Philadelphia**

Attachment 18: Letters to community and research council members

**National Press Coverage**

Attachment 19: Article in *Chicago Tribune* (Jan. 17, 1999)

Attachment 20: Release by *Associated Press* (Jan. 18, 1999)

Attachment 21: Transcript of *ABC Good Morning America*

**Research Community**

Attachment 22: Presentation at IBC Conference (Nov. 20, 1998)

Attachment I

May 10, 1998

John Doe  
1234 SW Main St.  
Portland, OR 97123

Dear Mr. Doe,

Last year you participated in a study sponsored by Baxter Healthcare entitled "The Efficacy Trial of Diaspirin Cross-Linked Hemoglobin (DCLHb) in the Treatment of Severe Traumatic Hemorrhagic Shock." The purpose of the study was to determine if DCLHb could decrease the rate of illness and death associated with severe traumatic injuries. Oregon Health Sciences University was one of 17 hospitals participating in this research.

Baxter Healthcare terminated the DCLHb Trauma Study on March 30, 1998 due to a higher death rate nationally among patients receiving the drug than those who did not receive DCLHb. Overall, the patients at OHSU who received DCLHb did better statistically than patients at other centers. To date no immediate or long-term effects of the drug have been identified.

We thank you for your participation in this research. If you have comments or questions, please contact me at (503) 220-8262, ext. 55432.

Sincerely,

Patrick Brunett, MD  
Principal Investigator

Attachment 2

AN IMPORTANT MESSAGE FROM THE  
PHYSICIANS AND EMERGENCY MEDICAL STAFF AT  
OREGON HEALTH SCIENCES UNIVERSITY HOSPITAL

One year ago, we informed you of the initiation of a multicenter trauma study sponsored by Baxter Healthcare entitled "The Efficacy Trial of Diaspirin Cross-Linked Hemoglobin (DCLHb) in the Treatment of Severe Traumatic Hemorrhagic Shock." The purpose of the study was to determine if DCLHb could decrease the rate of illness and death associated with severe traumatic injuries. Oregon Health Sciences University was one of 17 hospitals participating in this research.

Baxter Healthcare terminated the DCLHb trauma study on March 30, 1998, due to higher mortality nationally among patients receiving the drug than those who did not receive DCLHb. Overall, the patients at OHSU who received DCLHb did better statistically than patients at other centers. To date, no immediate or long-term effects of the drug have been identified.

If you have comments or questions regarding this research, please contact the OHSU Hotline at (503) 494-1400.

*This message is provided in accordance with the U.S. Food and Drug Administration (FDA) regulation, effective November 1, 1996, "Exception from informed consent requirements for emergency research" (21 CFR 50.24).*



Attachment 3

*April 2  
The Oregonian*

### **Company abandons study of blood substitute in ERs**

HOUSTON — A pharmaceutical company abruptly halted its study of a blood substitute in U.S. emergency room patients after discovering they were dying at a higher rate than expected.

But tests are continuing with emergency care patients in Europe and with elective surgery patients in the United States because they have shown no evidence of a higher death rate.

Baxter Healthcare Corp. of Deerfield, Ill., ended the trauma patient study Tuesday after a review of the first 100 participants showed people given the artificial blood product, HemAssist, died at a greater rate than those who did not receive it, said Mary Thomas, a Baxter spokeswoman.

Baxter had anticipated that 40 percent of the severely injured patients given HemAssist would die. The

company refused to give the exact number of patients who died or the exact number of those who received HemAssist.

Thomas would only say Wednesday that "about half" of the 100 were given the blood substitute and "slightly more than 40 percent" of those died.

The company stressed that those tested were among the most gravely ill trauma patients and that only 3 percent of the nation's emergency room patients could be eligible for the study, according to federal guidelines.

**Attachment 4**

May 10, 1998

John Doe  
1234 SW Main St.  
Portland, OR 97123

Dear Mr. Doe,

One year ago, we informed you of the initiation of a multicenter trauma study sponsored by Baxter Healthcare entitled "The Efficacy Trial of Diaspirin Cross-Linked Hemoglobin (DCLHb) in the Treatment of Severe Traumatic Hemorrhagic Shock." The purpose of the study was to determine if DCLHb could decrease the rate of illness and death associated with severe traumatic hemorrhagic shock. Oregon Health Sciences University was one of 17 hospitals participating in this research. The U.S Food and Drug Administration guidelines require us to apprise you of the completion of the study with the following information.

Baxter Healthcare terminated the DCLHb Trauma Study on March 30, 1998 due to a higher death rate nationally among patients receiving the drug than those in the control group.

Eight patients were entered in the study at OHSU out of approximately 100 patients nationwide. Their ages ranged from 28 to 83 years. Two patients were African-American and 6 were Caucasian. Two were female. Five patients were injured in motor vehicle accidents, two from gun shot wounds and one from multiple stab wounds. Five patients received DCLHb and three received saline. Three of the five patients in the DCLHb group survived and one of the three in the saline group survived.

If you have comments or questions, please contact me at (503) 220-8262, ext. 55432 or the OHSU Hotline at (503) 494-1400. You may also address comments via email to [brunettp@ohsu.edu](mailto:brunettp@ohsu.edu).

Sincerely,

Patrick Brunett, MD  
Principal Investigator

Attachment 5

April 17, 1998

FOR IMMEDIATE RELEASE  
Randi Hansen**BAXTER, U OF L CALL HALT  
TO ARTIFICIAL BLOOD TRIAL**

LOUISVILLE, Ky.--The University of Louisville and U of L Hospital no longer are participating in a national study of a modified blood product. Baxter Healthcare Corp. announced this month it has stopped the trial of Diaspirin Cross-linked Hemoglobin (DCLHb) in American trauma centers.

The clinical trial targeted trauma patients suffering from severe blood loss. Besides standard care for such cases, participants received either DCLHb or a control saline solution early in their hospital stay.

Enrollment in the study was suspended Jan. 2 in order to collect and analyze full data on all patients enrolled to date. National data showed an increased mortality rate in the DCLHb group when compared with the control group. Baxter and its clinical investigators are studying the data to understand better the difference in mortality rates. Complete data will be reported when that study has been completed.

Eight adult patients at U of L Hospital were treated in the study, which began last summer. Two died -- one who received DCLHb and one who received the saline solution. Neither fatality resulted from DCLHb use, said Mary Nan Mallory, emergency physician and the Louisville study's principal investigator.

Baxter continues two other clinical trials of DCLHb. A European trial is ongoing in patients with profiles similar to the one just ended here. In that study, however, the DCLHb is administered by physicians at the trauma scene rather than after the patient has been transported to the hospital, as in the U.S. trial. After the interim analysis of that study, an independent data monitoring committee recommended that Baxter continue it. Another study, which uses DCLHb in elective surgeries, also will continue. The medication is prepared from chemically modified human red blood cells.

U of L was one of 17 institutions nationwide to test the product using a waiver of informed consent approved in 1996 by the U.S. Food and Drug Administration. The waiver allows physician researchers to administer treatment under strict guidelines to patients unable to consent because of the sudden and severe nature of the injury or illness. Patients and/or family members then are informed and given the choice to opt out of the study. The waiver was used for all patients in the U of L Hospital study, and in all cases the patients or their family members agreed to continue in the study.

In addition to the FDA, U of L's Human Studies Committee supervised local DCLHb study participation and enrollment. Richard Miller, who heads the Human Studies Committee, said the group scrutinizes the studies and sometimes imposes more extensive patient protection measures than the FDA. The DCLHb study investigators followed those procedures to the letter, he said.

For more information about the treatment trial or its termination, call Mallory at (502) 852-5689 or Miller at (502) 852-5188.

###

Attachment 6

# UNIVERSITY of LOUISVILLE

May 6, 1998

Dear Community Consultation Contacts,

The University of Louisville Hospital and U of L are no longer participating in the national study of Diaspirin Cross-Linked Hemoglobin (DCLHb). Baxter Healthcare Corp. announced this month it has stopped the trial of DCLHb in the American trauma centers.

Enrollment in the study was suspended January 2 in order to collect and analyze data on all patients enrolled to date. National data showed an increased mortality rate in the DCLHb group when compared with the control group. Baxter and its clinical investigators are studying the data to understand better the difference in mortality rates. Complete data will be reported when that study has been completed.

At the University of Louisville Hospital we treated eight adult patients. Two of these patients died – one who received DCLHb and one who received that saline solution. Both deaths were injury related.

Baxter continues two other clinical trials of DCLHb. A European trial is ongoing in patients with profiles similar to the one just ended here. In that study, however, the DCLHb is administered by physicians at the trauma scene rather than after the patient has been transported to the hospital, as in the U.S. trial. After the interim analysis of that study, an independent data monitoring committee recommended that Baxter continue. Another study, which uses DCLHb in elective surgeries, also will continue.

U of L was one of 17 institutions nationwide to test the product using a waiver of informed consent.

We want to thank you for your support and participation in the Community Consultation and Public Disclosure portion of this new waiver. It is paramount that research and such waivers continue to learn new and better options for our healthcare needs.

If you have any questions and need more information, please call Dr. Mary Nan Mallory at (502) 852-5689.

Sincerely,  
Dr. Mary Nan Mallory &  
University of Louisville Research Team

Attachment 7

January 12, 1999

RE: IRB # 8618/Standard-Emergency Research and Waiver of Consent/The Efficacy Trial of  
Diaspirin Cross-Linked Hemoglobin (DCLHb) in the Treatment of Severe Traumatic  
Hemorrhagic Shock/Baxter Healthcare Corporation

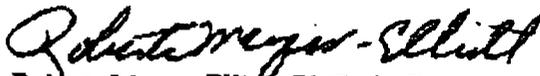
To Whom It May Concern:

In accordance with 21CFR50.24 (Emergency Research and Waiver of Consent), the following actions were taken to inform the community of the closure of the above-mentioned study.

1. The Vanderbilt Community Committee met on May 29, 1998, at which time Dr. John Morris presented a summary of the study and the reasons for closure of the study. The Committee recommended that follow-up letters be sent to the committee members summarizing the meeting discussion. No further recommendations were made.
2. The Vanderbilt Office of News and Public Affairs was notified.

My apology for the delay in submitting this information. Should you need additional information, please feel free to contact Virginia Wiley, R.N. or me at (615) 322-1918.

Very sincerely yours,



Roberta Meyers-Elliott, Ph.D., M.B.A.  
Acting for the Chair, Richard Hoover, Ph.D.  
Institutional Review Board-Health Sciences Committee

RMW/vw

Attachment 8



University of Pittsburgh  
Medical Center

News Bureau

**CONTACT:** Frank Raczkiwicz  
Susan Manko  
**PHONE:** (412) 647-3555  
**FAX:** (412) 624-3184  
**E-MAIL:** raczki@a1.isd.upmc.edu  
manko@a1.isd.upmc.edu

**FOR IMMEDIATE RELEASE**

**BLOOD SUBSTITUTE STUDY IN TRAUMA PATIENTS IS CANCELED**

**PITTSBURGH, June 15** -- UPMC Health System was one of about 40 sites nationwide that was asked to determine the effectiveness of a new treatment for trauma victims with severe blood loss. The study involved a patented, experimental blood substitute that was given to adult patients with life-threatening injuries. The blood substitute, developed by Baxter Healthcare Corp., was given for emergency treatment along with standard therapy, including blood.

Recently, Baxter decided to terminate the study, which had enrolled approximately 100 of its expected 850 participants from Oct. 1, 1997 to Dec. 22, 1997 at 16 sites in the United States. An interim data review by the study's independent data monitoring committee found that patients in the study treatment group had significantly increased mortality compared to those in the control group. Although the data do not yet indicate why the treatment group had a higher mortality rate than the control group, Baxter decided to cancel the study out of concern for patient safety. Further analysis of the data is ongoing to determine what factors contributed to the higher mortality rate in the treatment group.

-more-

Page -2-

Principal investigator in the study is Andrew Peitzman, M.D., professor in the department of surgery. Other investigators include: Marilyn J. Borst, M.D., a fellow in trauma/surgical critical care; Donald Yealy, M.D., associate professor in the department of emergency medicine and the department of medicine; and W. David Watkins, M.S., Ph.D., M.D., a professor and director of the clinical trials program in the department of anesthesiology and critical care medicine.

For additional information about UPMC Health System, please access <http://www.upmc.edu>.

# # #

kg\6-15-98

Attachment 9

Published 7-16-98

rience for the 115 Cub Scouts  
who attended. God Bless  
You. ★

ALCOLA — Clarion County  
Fair officials announce the results  
from last week's sheep leadline

**LOGUE & SON MONUMENTS**  
Over 100 Years in Business  
Phone 814-745-2401 • Sigo, PA

## Research study of blood substitute canceled

UPMC Health System in Pittsburgh, Pa., was one of about 40 sites nationwide that were asked to help determine the effectiveness of a new treatment for trauma victims with severe blood loss. The research study involved a patented, experimental blood substitute that was given to adult patients with life-threatening injuries. The blood substitute, developed by Baxter Healthcare Corp. (Baxter), was given for emergency treatment along with standard therapy, including blood.

Recently Baxter decided to end the study, which had enrolled approximately 100 of its expected 850 participants from Oct. 1, 1997, to Dec. 22, 1997, at 16 sites in the United States. An interim data review by the study's independent data-monitoring committee found that patients in the study treatment group had significantly increased mortality compared with those in the control group. Although the data do not yet indicate why the treatment group had a higher mortality rate than the control group, Baxter decided to cancel the study out of concern for patient safety. Analysis of the data is ongoing to determine what factors contributed to the higher mortality rate in the treatment group.

Please address comments to:

Andrew Peitzman, MD  
Department of Surgery  
UPMC-Presbyterian, Room A-1010  
UPMC Health System  
200 Lothrop Street  
Pittsburgh, PA 15213-2582  
or call (412) 648-9560

or

Dennis Swanson, MS  
University of Pittsburgh  
Institutional Review Board  
1212 Lilliane S. Kaufmann Building  
3471 Fifth Avenue  
Pittsburgh, PA 15213-3221  
or call (412) 692-4370



**UPMC HEALTH SYSTEM**



Todd Marshall  
Regulatory Affairs  
Baxter Hemoglobin Therapeutics Office  
2545 Central Avenue  
Boulder, Colorado 80301-2857  
Fax 303-443-7343

January 7, 1999

Dr. Mr. Marshall,

This letter is in response to a request made by Dr. Max Koenigsberg, Baxter medical consultant, to summarize actions taken at the Methodist Hospital, Indianapolis, Indiana study site as participant in the Baxter trial entitled:

***"The Efficacy Trial of Diaspirin Cross-Linked Hemoglobin (DCLHb) in the Treatment of Severe Traumatic Hemorrhagic Shock".***

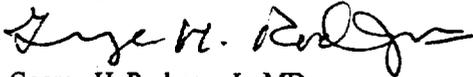
These actions disclosed results of the study to the research and public community in consultation with our hospital's Institutional Review Board.

1. All hospital clinical department heads and clinical staff directly involved in the study were informed of the results of the trial that led to the study's termination. This action was initiated by personal phone call and discussion led by Dr. Rodman, this site's principle investigator, and Maureen Misinski, RN, the site's study coordinator.
2. All patients and/or families were contacted by phone and personally informed of the results of the study by this site's study coordinator. All but one of the patient's and/or their immediate families were reached by phone. All patients/families contacted expressed gratitude for the follow-up discussion.
3. The Indiana State's Attorney General's office and the Office of Commissioner of the State Board of Health were contacted and briefed about the study's results and reason for termination of the trial. These offices had been part of this study site's pre-study disclosure process pursuant to 21 CFR 50.24, exception to informed consent requirements for emergency research.
4. The local newspaper, The Indianapolis Star, carried a story on or about March 31, 1998, after the press release from Baxter, describing the results of the study and its early termination. Likewise, the Indianapolis Business Journal in association with WISH-TV, a local television station, published in its daily news release an announcement of Baxter's decision to terminate the study due to the fact that "more patients died in its treatment group than in its control group".
5. Finally, having recently received a 'Synopsis' of the final study report attached to a Baxter letter dated November 19, 1998, I am forwarding a copy of the synopsis to relevant members of our research community, and our hospital's Institutional Review Board.

We feel that we have exercised full compliance with the intent of 21 CFR 50.24, exception from informed consent requirements for emergency research. We take this disclosure responsibility very seriously and we anxiously await the final step of publication of the results of this important study in the peer reviewed scientific literature.

If I can be of further assistance, please call me at 317-929-3940.

Sincerely,



George H. Rodman, Jr. MD  
Director, Trauma Services

cc: James Lingeman, MD, Chm., Methodist Hospital Institutional Review Board  
Max D. Koenigsberg, MD, University of Illinois





**PennState Geisinger**

**Health System**

**Section of Trauma/Critical Care Surgery**

M.C. H070

P.O. Box 850

Hershey, PA 17033-0850

717 531 6241 Tel

717 531 4404

717 531 3649 Fax

December 14, 1998

Jaime Houghton  
Clinical Project Manager  
Hemoglobin Therapeutics  
Baxter Healthcare Corporation  
25212 West State Route 120  
Round Lake, Illinois 60073-9799

J Stanley Smith, Jr., MD, FACS, FCCM

Robert N. Cooney, MD, FACS

Sandralec Blosser, MD, FCCP, FCCM

Dear Jaime:

Regarding the shutdown of the DCLHb Trial and the Waiver of informed Consent, I held a series of calls to members of our community group and filed a report with our IRB.

We enrolled 3 patients for this trial. 2 patients received placebo and one was randomized to DCLHb but never received the test article because of an early death in the OR. Thus, no one from our site received any DCLHb. We closed the study immediately upon learning that there was a problem.

Our community group understood the reasons for closure based upon the interim data set. They do not necessarily understand the reasons that this test article when given for other studies seemed safe but may have caused this problem in trauma. They also understood that no one from Central Pennsylvania had received the test article and that the one death resulted from the traumatic injuries, not the test article.

Our community group consists of lay people from the IRB and lay citizens from local churches. There is also a "Holocaust Survivor" on this group. They thought this study had a lot of potential and understand why research such as this needs to be done to confirm theoretical potential.

Sincerely,

J Stanley Smith MD

Professor of Surgery

M S Hershey Med Center

PO Box 850

Hershey, PA 17033

Attachment 12

4/2/98

# Substitute blood tests suddenly are halted

## High death rate prompts firm to end U.S. study

By TERRI LANGFORD  
Associated Press

HOUSTON — A pharmaceutical company abruptly halted its study of a blood substitute in U.S. emergency room patients after discovering they were dying at a higher rate than expected.

But tests are continuing with emergency care patients in Europe and with elective surgery patients in the United States because they have shown no evidence of a higher death rate.

Baxter Healthcare Corp. of Deerfield, Ill., ended the trauma patient study Tuesday after a review of the first 100 participants showed people given the artificial blood product, HemAssist, died at a greater rate than those who did not receive it, said Mary Thomas, a Baxter spokeswoman.

Baxter had anticipated that 40 percent of the severely injured patients given HemAssist would die. The company refused to give the exact number of patients who died or the exact number of those who received HemAssist.

Thomas would only say Wednesday that "about half" of the 100 were given the blood substitute and "slightly more than 40 percent" of those died.

The company stressed that those tested were among the most gravely ill trauma patients, and that only 3 percent of the nation's emergency room patients could be eligible for the study, according to federal guidelines.

The race to find a blood substitute has been intense because artificial blood could ease shortages, eliminate the time-consuming process of matching blood types and wipe out the risk of contamination. In addition, members of some religious groups refuse to accept transfusions of human blood.

The study, originally slated to include 850 patients, involved critically injured patients taken to hospital emergency rooms.

The study was discontinued in Phase III testing, usually the last stage before a drug is considered for approval by the U.S. Food and Drug Administration.

Studies of HemAssist in elective surgery patients and in severely injured patients in Europe are continuing because no abnormal mortality rates have been detected in those trials, Thomas said.

Experts cannot explain the difference between the U.S. and European trauma patient studies, but speculate that the way emergency care is provided may be a factor.

"In Europe, physicians actually ride with the ambulances, and HemAssist is administered more quickly," Thomas said. "In the United States, patients are treated after they arrive at the hospital. They have been in shock longer."

Attachment 13

# The Science of Hope

Medical research provides Christiana Care physicians a chance to distinguish themselves and their employer. It also provides patients with cutting-edge therapies when nothing else seems to work.

by Mark R. Nardone

**I**lene Nusblatt's water had broken — again. Her obstetrician at Jefferson Medical College in Philadelphia told her, "You're done."

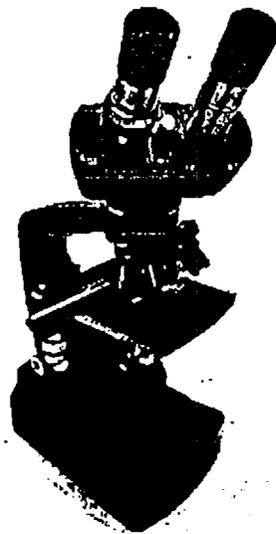
Nusblatt, 34, was 17 weeks into her sixth pregnancy. The previous five had failed, and though the fetus she was carrying was still healthy, she knew that the chances of delivering a normal child before 28 weeks were slim. Her husband Jay pushed the doctor. "That's no good," he said. "Get creative."

The obstetrician made some calls. One was to a colleague from Jefferson who

was also the director of research for the department of obstetrics and gynecology at Christiana Hospital. He was working on an experimental technique and had seen some good results. The procedure was risky, Ilene's doctor explained, but it just might help.

With 8,000 employees and 1,000 beds, Christiana Care is one of the largest health systems in the country. It is also one of the largest sites for clinical research, "one that does more research than most university hospitals," says president and CEO Dr. Charles Smith. "It's part of our mission, it's

Digital photography by Carlos Alejandro





integral to improving the health of the community. And we've established a reputation."

But the Nusblatts, of Yardley, Pennsylvania, didn't know that. As they raced to Newark, Ilene knew only that she couldn't tolerate losing the baby, of losing the ability to ever bear children. Even if her best hope was slim, it was still her only hope.

**R**esearch is the science of hope. Participating in clinical trials gives Christiana Care patients an opportunity to receive today the treatment of tomorrow.

As of August, Christiana Care was participating in nearly 700 clinical trials. Areas of research include cancer, cardiology and cardiac surgery, perinatology and neonatology, infectious disease, radiology, hypertension, trauma, dentistry and exercise physiology. It also participates in studies of health care delivery and medical education. Many of the studies are national in scope. And some are linked to major research hospitals such as Mayo Clinic and Johns Hopkins University. "We get the same drugs here as at (Memorial) Sloan-Kettering (Cancer Center) because we're part of the same studies," Smith says.

The largest research programs correspond directly with Delaware's major health problems — cancer, heart disease and infant mortality, to name a few — partly because they are the largest problems and partly because there is a large

pool of patients to enroll in studies. Christiana Care surgeons will perform 2,000 angioplasties this year, for example, and they routinely do more critical heart surgeries than any hospital in Philadelphia. "We recognize that this is a need for this population," says Angela DiSabatino, coordinator of cardiac research. "We have a large population. Let's find out why and help them."

About 80 Christiana Care patients are diagnosed with heart attacks each month, which helped make Christiana Hospital in Newark the No. 1 patient enroller in the country two years ago for GUSTO III, a trial of a then-new clot-busting drug called Retevase. (Retevase has since been approved by the Food and Drug Administration.) Other cardiac trials over the past 10 years have tested different drugs, various types of stents (small cylindrical cages inserted in arteries to keep them from closing), various types of balloons for angioplasties and a tool for shaving cholesterol plaque from the walls of arteries.

As principal investigator for the CADILLAC trial (Controlled Abciximab Device Investigation to Lower Late Angioplasty Complications), cardiologist James Ritter predicts one of the biggest breakthroughs in the treatment of heart attack victims since clot-busting medications, or lytic therapy, revolutionized treatment two decades ago. Angioplasty — opening blocked arteries by inflating balloons inside them — was first reported in the late 1970s, and it caused a dramatic increase in the number of heart attack sur-

vivors. Then came stenting. But stents can also clog with cholesterol plaque. About 15 percent of angioplasty patients suffer recurring problems during their hospital stays, and 30 percent to 50 percent experience a narrowing of their arteries within three to six months after surgery. CADILLAC is testing whether or not stenting combined with a drug called Reopro, which inhibits clotting, is better than standard therapies. "This stands to be a landmark trial," Ritter says.

Christiana Care's Cardiology Research Office was established in 1991, though individual doctors like Ritter had already been doing research there for several years. Similarly, Christiana Care (formerly the Medical Center of Delaware) had been involved in cancer research "since the early days" when there were only four medical oncologists in Wilmington, says Dr. Irving Berkowitz, principal investigator for cancer research. In the early 1970s, for example, the old Wilmington General Hospital was the first in the country to test tamoxifen, which was made in Delaware by ICI Americas. Tamoxifen was found to prevent a recurrence of breast cancer by blocking the body's production of the female hormone estrogen. A recent national study, in which Christiana Care took part, tested whether or not tamoxifen will prevent breast cancer in high-risk women. Researchers await the results. Since then Christiana Care has applied to take part in another study of tamoxifen.

With a grant from the National Cancer Institute in 1987, the medical center became a Community Clinical Oncology Program. It is now among the largest of the 50 CCOPs in the country, according to Pamela G. Eppes, clinical trials coordinator for oncology research. Trials coordinated through Christiana Care include patients from every private hospital in Delaware, some in New Jersey, Anderson Cancer Center in Texas and the duPont Hospital for Children. At any time about 300 patients are participating in 150 trials, and Christiana Care tracks about 2,500 patients going back 25 years. There are now 12 medical oncologists on staff. Nearly all of them are involved in research.

"The amount of resources committed to clinical cancer research — that's a lot of money," says Dr. Peter Hulick, director of the cancer program for the radiation oncology department. "That's a huge amount for any community hospital."

**B**y contrast, serious research into women's health began only five to 10 years ago, says Dr. Tony Sciscione, director of research for the department of obstetrics and gynecology at Christiana Hospital. "A teacher once told me, 'Do you know what maternal-fetal medicine is all about? It's about making decisions without information.' That's what I want to see if I can do something about."

As in all research, research into female health is fraught with ethical concerns. Research in maternal-fetal medicine is further complicated by concern not only for the safety of the mother, but also the safety of the fetus. Ensuring the safety of the subjects and making sure proposed trials meet federal guidelines for research are the main duties of Christiana Care's Institutional Review Board. "As bio ethics merge with medical ethics, research ethics is emerging as its own branch," says Paul Durbin, an IRB member and professor of philosophy at the University of Delaware. "Nobody wants to see another Tuskegee."

Durbin refers to the Tuskegee Study of Untreated Syphilis in the Negro Male performed by the United States Public Health Service from 1932 to 1972. Researchers wanted to understand what would happen to untreated syphilitics in order to improve treatment of them in the future. For 40 years government doctors denied aid to a group of infected black men from Macon County, Alabama. "The idea was that they would really help these people once they understood the disease," Durbin says. "The research would benefit many people. But it didn't help the subjects."

The Tuskegee study was the "longest nontherapeutic experiment on human beings in medical history," according to the New York Times. Researchers eventually learned that syphilis could be easily treated with penicillin, but before then many of the study subjects died blind or insane. The study raised many questions about racism in medicine, government abuse of a vulnerable population and ethical misconduct in medical research. After a public uproar, federal guidelines were written in the 1970s to protect human subjects.

The most important factor in clinical trials is informed consent. Any patient presented with an opportunity to participate in a study or trial is fully advised of the possible benefits and risks. "Research is intru-

*see RESEARCH, page 89*

**"Research is  
intrusive.**

**We don't want  
to take  
advantage  
of people.**

**Now there are  
mechanisms to  
make SURE  
that doesn't  
happen."**

**— Paul Durbin,  
Institutional  
Review Board**

## RESEARCH

continued from page 57

sive," Durbin says. "We don't want to take advantage of people. Now there are mechanisms to make sure that doesn't happen."

Most trials denied by the Institutional Review Board are poorly designed, Durbin says. Two years ago, for example, Christiana Care was asked to participate in a trial of a new blood substitute. The trial was designed to occur without the consent of its subjects. The maker of the blood substitute argued that trauma patients would have lost much of their blood before arriving at the emergency room and would therefore need their product to survive. The Institutional Review Board considered the proposal carefully before deciding to go along with the Food and Drug Administration, which had the requirement of informed consent. The product proved ineffective, and the maker withdrew after only a couple of months. The question remained: Should the trial have been conducted without the patient's informed consent?

Yet researchers admit that there are times when there is no scientific basis for

trying new therapies. Other times, a new treatment or medicine may be a patient's last hope. And, Durbin adds, "There is a lot of this that is just humanitarian."

As Ilene Nusblatt well knows.

Sciscione, 38, leans back in his chair and props his running shoe-clad feet on his desk. "The hardest thing is to see people who work so hard to have a baby and just can't," he says. "I know that God has different things in store for all of us. But people who lose 15 babies? That I just can't understand."

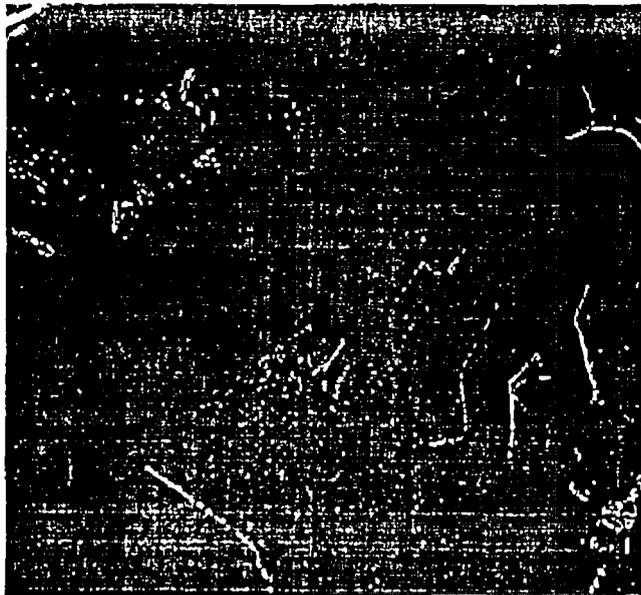
Sciscione is obsessed with understanding. His father, an engineer, never let him change a bad light bulb without making him explain why the bulb burned out in the first place. "Now I do the same thing to my kids," Sciscione says. When his wife started contractions 10 weeks before the expected due date of their first son, he questioned the conventional wisdom that the signaled premature labor even when the cervix — the gateway to the birth canal — had not started to open.

Sciscione devised an experiment: half the participants who experienced signs of

pre-term labor were admitted to the hospital and given medicines to stop the contractions; the other half were sent home to rest. "Do you know what we learned?" Sciscione says. "Nothing." The results were reported in the American Journal of Perinatology last year. When Sciscione's wife started pre-term contractions during her next two pregnancies, he refused to take her to the hospital.

"I ask my students: How do we learn in medicine?" Sciscione says. "The students always say, 'We do studies.' No. Someone makes an observation. Then we make an experiment."

For example, doctors had been using a device called a Foley bulb — a small balloon on the end of a catheter tube — to open the bladder of patients with blocked urinary tracts. Sciscione had heard enough anecdotal evidence to believe the Foley bulb might be used similarly to induce labor by stimulating dilation of a woman's cervix. During a normal labor, the cervix, a cartilage-like valve, softens in response to the change of hormones around it. Usually doctors wait for the dilation to occur naturally, but it can take many days, and waiting too long presents various risks; such



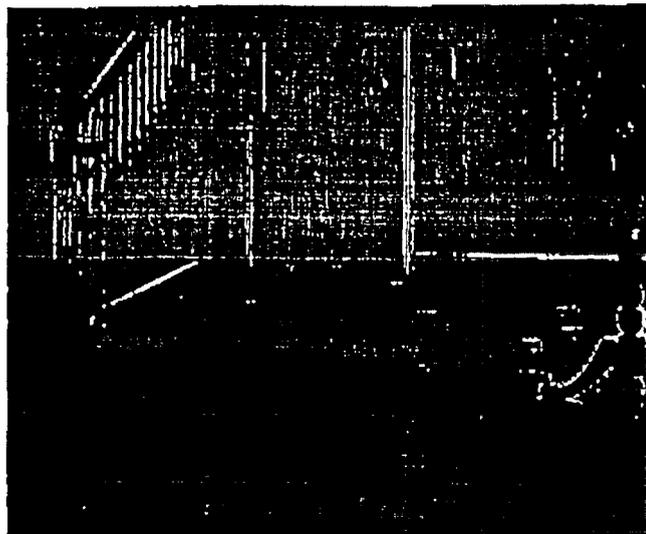
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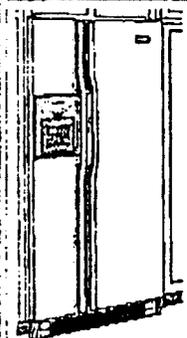
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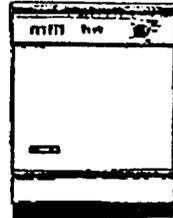
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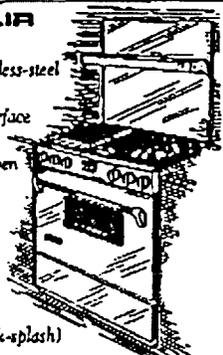
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women stand a greater chance of delivering by caesarean section, for example. Most obstetricians stimulate an uncooperative cervix using a special hormone gel. But after testing his technique on 150 women, Sciscione learned that a \$17 Foley bulb worked as well as a \$200 dose of gel, thus lowering the financial cost of giving birth, reducing the need for caesareans and shortening hospital stays for new mothers.

That result will soon be published in the American Journal of Obstetrics and Gynecology. The procedure is now encouraged by Christiana Care — and by new mom Jackie Boyer.

Boyer, 23, was eating a breakfast of scrambled eggs in her Christiana Hospital room on an August morning while her husband Peter, 27, cuddled their daughter Madison. Boyer participated in a second test of the Foley bulb technique. In the first experiment, all the participants were hospitalized after the bulb was inserted. In Boyer's experiment, half the women were sent home until labor began. "Inducement with Protosin (a brand of gel) would have taken three times as long," Jackie says. "I was ready." Eight hours after the bulb was placed, she began labor. The technique was so simple and painless, Boyer says, she hardly felt like she was contributing to the advancement of medical science.

Now Sciscione is testing whether the Foley bulb is superior to other therapies. Says IRB director Dr. Jerry Castellano, "The best research doesn't have to be complex."

What's neat about medicine is that you really can affect people positively," Sciscione says. "As researchers, we answer a lot of really neat questions."

Sciscione's greatest fascination is the induction of labor. The problem he's most interested in now is what causes a woman's water to break before full term. Most obstetricians suspect the rupture is caused by infection, but no one knows.

During a normal pregnancy, the cervix is plugged with a mucus-like barrier. Sometimes that barrier breaks down and washes free. When that happens the woman starts to lose amniotic fluid. The result to the fetus is usually devastating. The fluid protects the fetus by preventing it from twisting its umbilical cord and by shielding it from trauma; sometimes the sac that contains the fluid collapses, causing the fetus's

limbs to press against the uterus and disfigure. In ways doctors don't fully understand, the amniotic fluid is also critical to healthy development of the fetus's lungs. If a fetus was born before 24 weeks in the past, Sciscione says, it almost never survived.

These were among the risks Ilene Nusblatt faced when she was admitted to Christiana Hospital in August last year. "They were afraid that, even if the baby was born, it wouldn't be able to breathe," she says. "Even if we made it to viability, we could deliver a baby that wouldn't live."

The matter was further complicated by other factors. During her fifth pregnancy, Nusblatt had been given a cervical cerclage, a stitch made to keep her cervix closed until she began labor. That pregnancy lasted 16 weeks before her water broke. But because it had lasted far longer than the previous four, she was hopeful. During her sixth pregnancy, her doctor gave her an abdominal cerclage to close her cervix permanently. That pregnancy lasted 17 weeks. Sciscione had used a similar technique on another patient. When it failed, he came up with a new idea.

The "why" of things is Sciscione's obsession, but why is sometimes outweighed by "how." No one knew why Nusblatt had so many miscarriages. (The Nusblatts later learned that Ilene was affected by a synthetic hormone her mother had been given to prevent a miscarriage.) "How" Sciscione planned to help Nusblatt was by damming her cervix with a glue made of fibrin.

Fibrin is an insoluble protein formed from an enzyme that causes blood to clot and a protein found in blood plasma. Fibrin glue had been used effectively in cosmetic, urologic and cardiovascular surgery since the 1960s. Sciscione suspected that, like the Foley bulb, fibrin might have other applications.

When Sciscione was recommended to Nusblatt, he had tested the glue on only 10 women. "The first five times it failed miserably," he says. He changed the composition of the glue and tried it on five more women. "Two of the women delivered beautifully," he says.

But the glue was far from perfect, and he warned the Nusblatts that their chance of the pregnancy going to term was "dismal."

"It's important not to put up these quote-unquote 'medical barriers.' I think it sets the person up for disappointment," Sciscione says. "I explain to them that I'm not God; I'm just a human who has



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worked hard at this. But I also explain that all my training was done to help them."

"For two days we didn't do anything," Ilene says. "I thought, 'This is ridiculous. Take the baby.' Then I thought I couldn't do that again. I couldn't make that decision again. I didn't know if I could handle that loss. It wasn't just the loss of the pregnancy. It was the loss of not being able to have children. I couldn't deal with it, so I refused to." Jay Nusblatt remained optimistic, however, and his attitude buoyed Ilene. "It was a crossroads for us," she says. "We wanted to do everything we could so that we wouldn't have any regrets. We were totally involved, and we were working together. It was new to (Sciscione) and to us."

After testing Ilene for infection and ascertaining that the fetus was still healthy, Sciscione applied the glue. It washed free a short time later. He changed the composition and applied the glue again. Again it washed.

Sciscione could not understand why the glue kept failing. Then, while he was jogging one afternoon, the answer hit him: There was something in Ilene's amniotic fluid that was eroding the plug. He altered the glue again, this time using Ilene's own blood agents. The blood platelets would reduce the risk of infection and stand up to the flood of chemicals released during pregnancy. The next plug stayed in place 2 1/2 weeks.

Ilene stayed on bed rest for 101 days: no bathroom privileges, no showers. Intravenous antibiotics burned up her veins. Sciscione replaced the fibrin plug five times.

Ilene doesn't remember much of the day 3-pound, 2-ounce Ava Rose Nusblatt entered this world. Ilene was in pain. Sciscione feared that the stitch in Ilene's abdomen would cause her uterus to rupture. She delivered by caesarean, and she lost much blood. But it worked out.

"The kid comes out," Sciscione says, "and the kid is absolutely cool."

Sciscione calls Ilene the hero in this drama. He sees himself only as someone with some special knowledge who considers research important and finds that helping people makes him feel good. Ilene sees it differently.

"I don't think we solved anything," she says. "I don't think Tony knows the answer. But he knows more than he did going into it. He says he didn't do a lot. He did do a lot, but not only that, he gave us a chance where most doctors wouldn't." ♦



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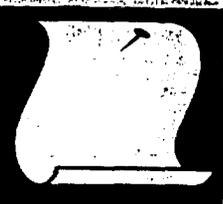
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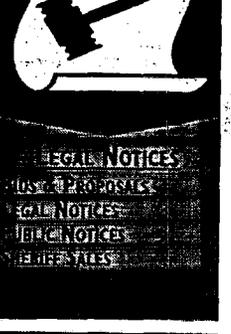
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**LEGAL NOTICES**

**Name Change**  
IN THE COURT OF COMMON PLEAS FOR THE STATE OF DELAWARE IN AND FOR NEW CASTLE COUNTY IN RE: CHANGE OF NAME OF Patrick Gagai, PETITIONER(S) TO Phethuvuyo Gagai. NOTICE IS HEREBY GIVEN THAT Patrick Gagai intends to present a Petition to the Court of Common Pleas for the State of Delaware in and for New Castle County, to change his name to Phethuvuyo Gagai. Patrick Gagai Petitioner(s)

DATED: 12-3-98  
12/5, 12/19-NJ O986394

**Register Order**  
Estate of RICHARD J. LEE, Deceased. Notice is hereby given that Letters of Testamentary upon the Estate of RICHARD J. LEE who departed this life on the 29th day of OCTOBER, A.D. 1998, late of 80 VERSAILLES COURT, NEWARK, DE 19702, were duly granted unto JOYCE M. LEE on the 16th day of NOVEMBER, A.D. 1998, and all persons indebted to the said deceased are requested to make payments to the Executrix without delay, and all persons having demands against the deceased are required to exhibit and present the same duly probated to the said Executrix on or before the 29th day of JUNE, A.D. 1999, or abide by the law in this behalf. Address: CHARLES S. KNOTHE, ESQ. 3516-14 SILVERSIDE RD. WILM., DE 19810 JOYCE M. LEE

12/5/98 pm

**PUBLIC NOTICE**

The blood substitute clinical trial which involved the administration of a blood solution for the treatment of severe hemorrhagic shock has ended. Baxter Healthcare Corporation, the sponsor of the trial, decided to stop the trial following an interim data review by the trial's independent monitoring committee.

Patients enrolled into the clinical trial were gravely ill, victims of severe trauma, such as motor vehicle accidents, knife and gunshot wounds, which have a high expected mortality.

Analysis of interim patient data by the committee, using a published model (Trauma Injury Severity Score (TRISS)) of predicting outcomes in trauma patients combining physiologic and anatomic indicators of severity and age, indicate the predicted death rate in the treatment group (received DCLHB) was 42.6 percent (24 of 52 patients.) The predicted death rate in the control group (received placebo of saline) was 35.5 percent with an observed death rate of 17.4 (8 of 46 patients.) Some differences were noted between the two groups (DCLHB or placebo,) none were significant enough to verify why the treatment group (received DCLHB) had a higher death rate than the control group (received placebo, saline.) Further analysis of data is ongoing.

Approximately 100 patients of the expected 850 participants were enrolled nationwide. Christiana Care enrolled six participants, five males and one female. Two patients received DCLHB, and four patients were evaluated as control patients (received placebo, saline.) One patient who received DCLHB, expired and was found to have injuries incompatible with life. The other five participants were treated for various serious injuries and subsequently were discharged from Christiana Care.

All cases were thoroughly reviewed by Dr. Glen Tinkoff, director of trauma, the Principal Investigator and the Institutional Review Board which approved the study with the waiver of informed consent, and none, through the administration of DCLHB or placebo, were related to outcome.

Baxter is releasing this clinical information prior to its final analysis to fulfill its responsibilities according to regulations pertaining to waiver of informed consent.

**Christiana Care Health Services**

The 1998 Annual Meeting of The New Century Club Corporation will be held on Wednesday, December 9, 1998 at 11 A.M. the location being 1912 Marsh Rd., Farwood Manor. Secretary, Helen Parry 12/4,5,7,8,9-NJ O986579

**BIDS & PROPOSALS**

**ATTENTION SMALL MINORITY AND/OR WOMAN OWNED ENTERPRISES (DBE, SBE, MBE, WBE) EQUAL EMPLOYMENT OPPORTUNITIES FULL OPPORTUNITY IS BEING AFFORDED FOR YOUR SUBMISSION OF BIDS TO BUNTING & MURRAY CONSTRUCTION CORPORATION SELBYVILLE, DE FOR THEIR CONSIDERATION FOR THE WEST REHOBOTH EXPANSION OF THE DEWEY BEACH SEWER DISTRICT SUSSEX COUNTY, DE COLLECTION AND TRANSMISSION SEWER SYSTEM CONTRACT WIII-3 FIVE POINTS NORTH YOUR PRICING IS BEING SOLICITED FOR THE FOLLOWING CONSTRUCTION SERVICES: FLOW CHANNELING, SURVEYING, ASPHALT PAVING/MARKING, MAINTENANCE OF TRAFFIC ELECTRICAL HOOK UP OF PUMP STATIONS. PLEASE DIRECT ALL INQUIRIES TO OUR ESTIMATING DEPT. NO LATER THAN 12/14/98 BY PHONE: (302)436-5144 BY FAX: (302)436-1753 12/4,5,6,7-NJ O9865724**

**GO FETCH.**

**WANT SOME?**

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**COUNTY COUNCIL**

**MONTHLY SCHEDULE DECEMBER (Subject to Change)**

Tues. Dec. 1	4:00 p.m.	Land Use Committee Rezonings, Plans, Code Amend. Etc.
Tue. Dec. 8	4:30 p.m. 7:30 p.m.	Finance Committee Council Meeting
Mon. Dec. 14	4:00 p.m.	Land Use Committee Rezonings, Plans, Code Amend. Etc.
Tue. Dec. 15	4:30 p.m. 7:30 p.m.	Finance Committee Council Meeting

All meetings will be in the 8th Floor Conference Room unless otherwise noted. Council's regular meeting in Chambers.

**REGULAR MEETING OF NEW CASTLE COUNTY COUNCIL**  
City/County Building, City/County Council Chambers  
800 French Street, Wilmington, Delaware 19801

**AGENDA**  
December 8, 1998  
7:30 p.m.

G. Introduction of Ordinances AN ORDINANCE TO: #98-132: AMEND THE PAY PLAN AND RATES OF PAY FOR CLASSIFIED SERVICE EMPLOYEES REPRESENTED BY LOCAL 1607 (HOUSING PROGRAM ASSISTANT).

I. Resolutions and Ordinances for Council's Consideration and Adoption

**CONSENT CALENDAR**  
R98-188: NEW CASTLE COUNTY COUNCIL EXPRESSING CONDOLENCES TO THE FAMILY OF WILLIAM L. KAPA.  
R98-189: RECOGNIZING JOHN W. SLACK FOR HIS

**TOWN OF CHARLESTOWN MARYLAND PROJECT NO. 98-FB-CONS FIRE BOAT PIER & ENTRANCE CHANNEL DREDGING ADVERTISEMENT FOR BIDS**

Sealed bids for Project No. 98-FB-CONS for the construction of a Fire Boat Pier and Entrance Channel Dredging will be received until 2:00 p.m. prevailing time, December 21, 1998 at the Town Hall. The contractor shall submit one bid for Entrance Channel Dredging and the Dredge Material Placement Work. A separate bid may be given for Pile Driving and Installation of the Pier. A quote may also be given for the Entire Project. Bids will be opened and read publicly. One set of drawings and specifications may be obtained between 9:00 a.m. and 5:00 p.m. Monday through Friday at the offices of the Town of Charlestown, P.O. Box 154, 241 Market Street, Charlestown, Maryland 21914, Cecil County, Maryland. Payment is \$25.00 per set. 12/5,6,7-NJ O986170

**GO FETCH.**

**WANT SOME?**

Sell your stuff in the classifieds.

**COUNTY COUNCIL**

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.. ANTHONY  
CENTRAL HOSPITAL

January 7, 1999

Jon M. Burch, MD  
Chair, DAATAC  
777 Bannock Street #206  
Denver, CO 80204

Dear Dr. Burch:

This is a letter to inform the DAATAC that the clinical study entitled "The Efficacy Trial of Diaspirin Cross-Linked Hemoglobin (DCLHb) in the Treatment of Severe Traumatic Hemorrhagic Shock" that was conducted at our site and sponsored by Baxter Healthcare has terminated.

In accordance with regulations issued by the U.S. Department of Health and Human Services and the U.S. Food and Drug Administration, Centura Health-St. Anthony Central Hospital (SAC), a Level I trauma center, is informing the community of the preliminary findings from this multi-center research study. Several hospitals throughout the U.S. participated in the research study, including SAC.

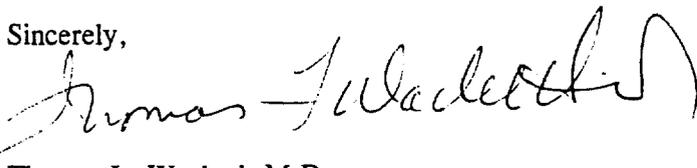
The research study included critically injured trauma patients admitted with severe blood loss. One patient from SAC was entered into the study. The study participants received an investigative hemoglobin solution in addition to the standard procedures for trauma care. The study compared the mortality of the group that received the investigative hemoglobin solution (treatment group) with the group that did not receive the investigative hemoglobin solution (control group).

The independent data monitoring committee found that patients in the treatment group had significantly increased mortality compared to those in the control group. As a result, the company decided to stop the study early. The company is continuing to analyze the data from the study and will publish a full report in the future. Included with this letter are the following enclosures:

1. Letter from Baxter Hemoglobin Therapeutics, dated 11/19/98, along with Clin Trials' synopsis of the study
2. Information downloaded from the study's website
  - a. Press Release from the company announcing the termination of the study
  - b. Clinical Update
  - c. Informed Consent Information

If you would like additional information about this study, or would want to make this an ATAC agenda item, please contact Thomas L. Wachtel, MD, principal investigator at 303-629-4222.

Sincerely,



Thomas L. Wachtel, M.D.  
Principal Investigator

Cc: St. Anthony Central Hospital IRB

Attachment 16

Sunday, February 7, 1999

THE DENVER POST GUARANTEED CLASSIFIED

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Trade (303) 223-4957  
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**Public Notice**

In accordance with regulations issued by the U.S. Department of Health and Human Services and the U.S. Food and Drug Administration, Centura Health-St. Anthony Central Hospital (SAC), a Level I trauma center, is informing the community of the preliminary findings from a multi-center research study that has ended. Several hospitals throughout the U.S. participated in the research study, including SAC.

The research study included critically injured trauma patients admitted with severe blood loss. One patient from SAC was entered into the study. The study participants received an investigative hemoglobin solution in addition to the standard procedures for trauma care. The study compared the mortality of the group that received the investigative hemoglobin solution (treatment group) with the group that did not receive the investigative hemoglobin solution (control group).

The independent data monitoring committee found that patients in the treatment group had significantly increased mortality compared to those in the control group. As a result, the company decided to stop the study early. The company is continuing to analyze the data from the study and will publish a full report in the future.

If you would like additional information about this study, you may contact Thomas L. Wachtel, MD, principal investigator and medical director of the trauma service, at 303-629-4222 or go to the Web site at <http://dclhb.er.uic.edu/>.

 **Centura Health**  
ST. ANTHONY CENTRAL HOSPITAL

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IT Corporation is soliciting THE BIGGEST DAY

Attachment 17

make suggestions about needed services or equipment such as computers.

belnogich, who was a lawyer in Serbia.

The local chapter of Interna-

couple of years as a result of the war in the former Yugoslavia, and it seems this trend will continue in the future."

The Plain Dealer - Jan 9, 1999



## Hemoglobin Therapeutics Research ends at MetroHealth Medical Center

MetroHealth Medical Center has ended a research study that was designed to evaluate a new treatment for seriously injured patients suffering from severe blood loss.

The study, conducted by 17 of the nation's leading trauma centers, was stopped by Baxter Healthcare, Inc., developers of the patented blood substitute product. According to officials at Baxter Healthcare, the Data Safety Monitoring committee overseeing the national research effort decided the study proved to be unlikely to show the product had a beneficial effect on increasing patient survival.

The hemoglobin therapeutics study was the first in the nation to use a new U.S. Food and Drug Administration (FDA) regulation that allows unconscious patients in danger of dying, and for whom no one was available to give consent, to receive an experimental treatment if no alternative treatment with a good chance of success exists. Public notification of the study's outcome is a requirement of the FDA.

While this particular project did not prove the product to be effective, researchers at MetroHealth Medical Center believe that data gathered from this study can contribute to future trauma studies.

Baxter Healthcare has established a website at <http://dclhb.er.uic.edu> to provide further information about the study. You may also direct questions or comments about the study to:

**DCLHb Study**  
c/o MetroHealth Medical Center  
Emergency Medicine  
2500 MetroHealth Dr.  
Cleveland, OH 44109-1998

Attachment 18

March 25, 1998

[REDACTED]

**Re: Termination of the Efficacy Trial of Diaspirin Cross-Linked Hemoglobin (DCLHB™) in the Treatment of Severe Traumatic Hemorrhagic Shock. Protocol #60292-02P**

Dear [REDACTED]:

An interim analysis after randomization of 113 patients was performed under the direction of the independent data safety monitoring board. Evaluation of the preliminary data prompted the safety board to request a hold on further patient accrual as of January 2, 1998. Further analysis of this data indicated an imbalance in mortality disfavoring the study agent. With these results, the sponsor has terminated this clinical program. The sponsor, Baxter Healthcare will release general information concerning this trial in the near future. In fulfillment of the new federal regulations for the exception of informed consent (21 CFR 50.24), each site is obligated to inform its community of the demographics and results of the study. Once the results of this study have been completely analyzed, the sponsor will make this information available to each investigator for their use in this public disclosure process. *Since our original approval on June 24, 1997, we have not enrolled any patients in this clinical trial.*

As principle investigator I will keep you abreast of the ongoing activities of this terminated clinical program.

Regards,

Thomas A. Santora, M.D.  
Associate Professor of Surgery  
Principle Investigator

**MCP HAHNEMANN UNIVERSITY  
DEPARTMENT OF SURGERY**

*Thomas A. Santora, M.D.  
Associate Professor of Surgery  
Associate Director, Regional Resource Trauma Center  
Program Director, Surgical Critical Care Fellowship  
Director, Surgical Intensive Care Unit*

*3300 Henry Avenue  
Philadelphia, PA 19129  
(215) 842-6567  
fax (215) 843-1095*

February 4, 1999

**Re: Post Study Disclosure - Trial of Diaspirin Cross-Linked Hemoglobin (DCLHB™) in the Treatment of Severe Traumatic Hemorrhagic Shock. Protocol #60292-02P**

Dear \_\_\_\_\_:

This is a follow-up letter concerning the Efficacy trial of Diaspirin Cross-linked Hemoglobin. You may recall that on the correspondence dated March 25, 1998, I informed you as a member of our research community counsel that this research study had been discontinued due to an imbalance in mortality disfavoring the DCLHB compound. Since the discontinuation of this protocol, the sponsor, working with the research investigators, have reviewed the data collected on the 112 patients randomized into the study prior to discontinuation. This information was sent to me in synopsis form on February 1, 1999. In fulfillment of the new federal regulations for the exception of informed consent (21 CFR 50.24), I am obligated to share with you, the community, the demographics of the patients enrolled and the results of the study.

On June 24, 1997, the Institutional Review Board of the Medical College of Pennsylvania approved patient enrollment into this trial. However, due to the restrictive entry criteria of the study and the conscientiousness of the investigators at the Medical College of Pennsylvania, we did not enroll any patients into this clinical trial. I have provided a synopsis of the study design and the results for your review. Definite conclusions as to the imbalance in mortality could not be drawn but, given the significant imbalance, the sponsor and the research investigators felt that this study could not and should not proceed.

Though this clinical trial did not show the benefit for our community as we had hoped it may, we stand convinced that clinical trials need to continue in the trauma patient population to test and improve the quality of care provided to our critically injured community members.

I appreciate the commitment that you have given to this research effort in response to your commitment to our community. I would encourage you to share this information with other members of the community. If I can be of any assistance to you or if further information is needed, please feel free to contact me through the Trauma Center at the Medical College of Pennsylvania.

Regards,

*Thomas A. Santora, M.D.  
Associate Professor of Surgery  
Associate Director, Regional Resource Trauma Center*

TAS/lh

**Meg McGoldrick**  
**Executive Director and Chief Executive Officer**  
**Medical College of Pennsylvania Hospital**

**Barbara Atkinson, M.D.**  
**Annenberg Dean, MCP Hahnemann University**

**Joel Roslyn, M.D.**  
**Professor and Chair,**  
**Department of Surgery**  
**MCP Hahnemann University**

**Stan Trooskin, M.D.**  
**Professor of Surgery**  
**Chief, Division of Trauma and Surgical Critical Care**  
**MCP Hahnemann University**

**Lewis J. Kaplan, M.D.**  
**Department of Surgery**  
**MCP Hahnemann University**

**John R. Clarke, M.D.**  
**Professor of Surgery**  
**MCP Hahnemann University**

**Rosemary Kozar, M.D.**  
**Department of Surgery**  
**MCP Hahnemann University**  
**MS# 413**

**Jan C. Harrow, M.D.**  
**Co-Chair, Committee for the Protection Human Subjects**  
**MCP Hahnemann University**  
**MS 310**

**Pamela Crilley, D.O.**  
**Co-Chair, Committee for the Protection of Human Subjects**  
**MCP Hahnemann University**  
**MS 412**

**Pat Baldrige**  
Vice President, Communications  
Medical College of Pennsylvania Hospital

**Vincent Cowell, M.D.**  
Department of Anesthesia  
Medical College of Pennsylvania Hospitals

**Reverend Doctor Florence Gelo**  
Chaplain, Medical College of Pennsylvania Hospitals  
3300 Henry Avenue  
Philadelphia, PA 19129

**Steven Woodside, Esq.**  
President East Falls Business Association  
1700 Market Street  
Suite 2628  
Philadelphia, PA 19103

**Reverend William King**  
United Church of Christ  
52 E. Slocum Street  
Philadelphia, PA 19119

**Reverend William DeHeyman**  
3300 W. Queen Lane  
Philadelphia, PA 19129

**Ms. Roberta Ginsberg**  
President, East Falls Community Development Corporation  
3709 Midvale Avenue  
Philadelphia, PA 19129

**Dr. Jesse Gardner**  
Principal, Germantown High School  
Germantown Avenue and High Street  
Philadelphia, PA 19144

**Mr. Charles Whiting**  
Principal, R.S. Walton Elementary School  
28th and Huntingdon Streets  
Philadelphia, PA 19132

**Officer Velma Dean  
Community Relations Officer  
39th District  
22nd and Hunting Park Avenue  
Philadelphia, PA 19140**

**Reverend Sligh  
Devereaux United Methodist Church  
26th and Allegheny Avenue  
Philadelphia, PA 19132**

2. SYNOPSIS

<b>Name of Company:</b> Baxter Healthcare Corporation	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Diaspirin Cross-linked Hemoglobin (DCLHb)		
<b>Name of Active Ingredient:</b> DCLHb		
<b>Title of Study:</b> The Efficacy Trial of Diaspirin Cross-linked Hemoglobin (DCLHb) in the Treatment of Severe Traumatic Hemorrhagic Shock		
<b>Investigators:</b> There were 19 principal investigators who were approved to enroll patients in this study. A total of 18 investigators at 17 sites enrolled patients in this study. See Panel 6:1 for a list of investigators and number of patients enrolled.		
<b>Study Center(s):</b> There were 20 study centers with one center not enrolling any patients and two other centers not initiated to enroll patients (see Panel 6:1)		
<b>Publication (reference):</b> None		
<b>Study period (years):</b> (Date of first enrollment): February 1997 (Date of last completed): January 1998	<b>Phase of development:</b> Phase III	
<p><b>Objectives:</b></p> <p><u>Primary Endpoints:</u> 28 day Mortality Reduction.</p> <p><u>Secondary Endpoints:</u> Morbidity reduction as measured by the multiple organ dysfunction (MOD) scores; 48 hour mortality reduction; and 24 hour lactate level.</p> <p><u>Pharmaco-economic Endpoints:</u> Blood utilization reduction; ventilator, dialysis, ICU and total hospital day reduction.</p> <p><u>Safety Endpoints:</u> (a) the incidence and severity of adverse events (AEs); and (b) changes from baseline in clinical laboratory results and summary of graded toxicities.</p>		
<p><b>Methodology:</b> This was a multicenter, randomized, normal saline procedure controlled, single-blind study in which trauma patients with persistent hypoperfusion despite aggressive pre-hospital therapy were randomized to receive up to 1000 mL of 10% DCLHb or up to 1000 mL of normal saline. Investigators evaluated patients clinically for 28 days following infusion.</p> <p>Investigators, IRBs, and Baxter complied with regulations 21 CFR 50.4 (Exception from informed consent requirements for emergency research, the regulations governing emergency research conducted with an exception from informed consent).</p>		
<b>Number of Patients (Planned and Analyzed):</b> Planned 850; Analyzed 112 randomized patients, 98 infused patients. Based on the recommendations of the Data Monitoring Committee the study was terminated early.		
<b>Diagnosis and Main Criteria for Inclusion:</b> Eighteen years of age or older; evidence of hemorrhage; and tissue hypoxia and cellular hypoperfusion.		

2. SYNOPSIS (Cont'd)

<b>Name of Company:</b> Baxter Healthcare Corporation	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Diaspirin Cross-linked Hemoglobin (DCLHb)		
<b>Name of Active Ingredient:</b> DCLHb		
<b>Test Product, Dose and Mode of Administration, Batch Number:</b> DCLHb administered through an intravenous line. Batch numbers and list of patients receiving study product from specific batches are provided in Appendix 16.1.6.		
<b>Reference Therapy, Dose and Mode of Administration, Batch Number:</b> Normal saline administered through an intravenous line. Batch numbers and list of patients receiving study product from specific batches are provided in Appendix 16.1.6.		
<b>Duration of Treatment:</b> Infusion was to begin no later than 30 minutes after patients met entry criteria, and within 60 minutes of hospital arrival. The entire dosing regimen was to be completed within 60 minutes from start of first infusion.		
<b>Criteria for Evaluation:</b> <u>Efficacy:</u> Survival status at 28 days after infusion.  <u>Safety:</u> Incidence of adverse events; change from baseline analysis of laboratory data; analysis of laboratory data by graded toxicities.		
<b>Statistical Methods:</b> Logrank test (without stratification) was used for the primary analysis for comparison of DCLHb with the normal saline procedure treatment group with respect to 28-day mortality. Kaplan-Meier survival curves were used to describe the survival function in each treatment group. Cox proportional hazards modeling was used to adjust for pretreatment factors and to test the effect of stratification by center. Logistic regression analysis of 28 day mortality adjusted for baseline characteristics, trauma injury score prediction and adjustment (TRISS), probability of survival analysis using "new" models developed by Drs. Champion and Sacco, and analysis of patients with high risk and very high risk factors for mortality were also performed as exploratory analyses.		

2. SYNOPSIS (Cont'd)

<b>Name of Company:</b> Baxter Healthcare Corporation	<b>Individual Study Table Referring to Part of the Dossier</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Diaspirin Cross-linked Hemoglobin (DCLHb)	<b>Volume:</b>	
<b>Name of Active Ingredient:</b> DCLHb	<b>Page:</b>	

**Summary**

**Efficacy Results:** Logrank analysis of 28 day mortality shows that the probability of death is significantly higher for the DCLHb group when compared to the normal saline group (24/52, 46% in the DCLHb group vs. 8/46, 17% in the normal saline group, p-value = 0.003). The Kaplan-Meier estimate of the survival distribution for the two treatment groups shows early separation (by 3 hours after start of infusion) with the survival distribution declining much more rapidly in the DCLHb group than in the normal saline group. Despite an apparent imbalance in baseline injury severity, the difference in mortality rates remain after adjusting for pretreatment factors (Cox proportional hazards model) and significant baseline variables (logistic regression model). These findings remain even after adjustment for predicted probability of death in the two treatment groups (TRISS model). The results of the 48 hour mortality analysis also supports the above findings. Analysis of 24 hour lactate levels shows a significant difference between the DCLHb and normal saline procedure treatment groups when patients who died are included in the analysis (assuming worst rank imputed for death). No conclusive interpretation could be made on the MOD score analysis because of violation of model assumptions.

In a retrospective, independent, blinded analysis of the mortality data in this study by Drs. Champion and Sacco, based on the probability of survival, case control analysis and clinical review of the data, 96% (22/23) of the deaths in the DCLHb group and 88% (7/8) of the deaths in the normal saline group were predicted or not unexpected.

In a further retrospective, but unblinded, analysis, 15 factors were chosen empirically by the lead investigators and endpoint criteria for high risk and very high risk for mortality were defined. Based on these risk variables, 15% (7/46) of the patients in the normal saline group and 29% (15/52) of the patients in the DCLHb group met seven or more of the high risk criteria for mortality at baseline. Of these, 4 patients in the normal saline group and 12 patients in the DCLHb group died. Also, 7% (3/46) of the patients in the normal saline group and 21% (11/52) of the patients in the DCLHb group met four or more of the very high risk criteria for mortality at baseline. Of these, all three patients in the normal saline group and 10 patients in the DCLHb group died. More patients in the DCLHb group met either retrospective criteria of seven or more of the high risk conditions or four or more of the very high risk conditions for mortality when compared to the patients in the normal saline group. Thus, there is an imbalance across treatment groups in the number of patients with high risk and very high risk factors for mortality at baseline, indicating that patients randomized to the DCLHb group had a greater risk of mortality at baseline. These results complicate the interpretation of the mortality rate imbalances between treatment groups.

**2. SYNOPSIS (Cont'd)**

<b>Name of Company:</b> Baxter Healthcare Corporation	<b>Individual Study Table Referring to Part of the Dossier</b>  <b>Volume:</b>  <b>Page:</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Diaspirin Cross-linked Hemoglobin (DCLHb)		
<b>Name of Active Ingredient:</b> DCLHb		
<p><b>Safety Results:</b></p> <ul style="list-style-type: none"> <li>• Patients receiving DCLHb in the treatment of severe traumatic shock had a higher death rate (46% versus 17%) and a higher incidence of serious adverse events (48% versus 35%) than patients receiving normal saline.</li> <li>• In both the DCLHb and normal saline groups most deaths (84%) occurred in the first 24 hours following injury.</li> <li>• Retrospective, blinded analysis of mortality data (Appendix 16.4.2) revealed that 96% of the deaths in the DCLHb group and 88% of the deaths in the normal saline group were predicted or not unexpected based on model predicted probabilities, case control analysis, and clinical review.</li> <li>• Retrospective unblinded analysis based on mortality risk variables (Appendix 16.4.3) revealed that more patients in the DCLHb group met the criteria for high or very high risk for mortality at baseline, than did patients in the normal saline group. Thus, there may have been an imbalance across treatment groups in the number of patients at high risk and very high risk for mortality at baseline. The reasons for the apparent failure of adequate randomization are unknown.</li> <li>• In both treatment groups the most frequent causes of death were hemorrhage, cardiac arrest and multisystem organ failure.</li> <li>• More patients receiving DCLHb had cardiovascular and heart rate and rhythm serious adverse events than did patients receiving normal saline procedure (17% vs. 9%, and 15% vs. 9%, respectively). This is not unexpected given the imbalance in mortality.</li> <li>• Seven out of 8 patients having pretreatment cardiac arrests in the field were randomized to the DCLHb group, and all but one of these patients died. This unequal distribution of patients predisposed to a poor outcome may have contributed to the higher incidence of AEs and deaths in the DCLHb group, but the reasons for the imbalance are unclear.</li> <li>• The difference in mortality rates remain after adjusting for pretreatment factors and significant baseline variables.</li> <li>• A transient elevation in serum amylase (peaking at 24 hours post infusion and returning to normal by day 7) occurred in the DCLHb group. Similar results have been reported in previous studies using the same range of DCLHb doses.</li> <li>• In both treatment groups, the death rate for patients who received alpha agonists was substantially higher than the death rate for those who did not receive alpha agonists (80% vs. 15%, in the DCLHb group; 33% vs. 0% in the normal saline group).</li> </ul>		

2. SYNOPSIS (Cont'd)

<b>Name of Company:</b> Baxter Healthcare Corporation	<b>Individual Study Table Referring to Part of the Dossier</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Diaspirin Cross-linked Hemoglobin (DCLHb)	<b>Volume:</b>	
<b>Name of Active Ingredient:</b> DCLHb	<b>Page:</b>	
<p><b>Conclusion:</b> The efficacy and safety analyses revealed a statistically significantly higher mortality rate in patients receiving DCLHb than in patients receiving normal saline. The difference in mortality rates remain after adjusting for pretreatment factors and significant baseline variables. However, retrospective, blinded, analysis of mortality data revealed that 96% of the deaths in the DCLHb group and 88% of the deaths in the normal saline group were predicted based on model predicted probabilities, case control analyses, and clinical review. Furthermore, based on a retrospective unblinded analysis, more patients in the DCLHb group met the criteria for high or very high risk for mortality at baseline, than did patients in the normal saline group. Thus, there is an imbalance across treatment groups in the number of patients at high risk and very high risk for mortality at baseline. Thus, the usefulness of DCLHb in the treatment of severe traumatic hemorrhagic shock could not be demonstrated from these data.</p>		
<p>Date of the Report: November 6, 1998</p>		



# Testing without asking

The most controversial aspect about medical research trials involving a blood substitute was not the higher than expected death rate but the fact that patients never gave their consent.

**By Jeremy Manier**  
TRIBUNE STAFF WRITER

Two years ago, researchers for Deerfield-based Baxter International Inc. began the first advanced trial of an oxygen-carrying blood substitute with great hopes that the product might one day revolutionize emergency medicine by providing a ready treatment for people of all blood types.

That didn't happen. The trial was halted because out of 52 emergency trauma patients around the country who received the blood substitute called HemAssist, 24 died—two more than would have been predicted given the severity of their injuries and far more than the death rate in a group that received only routine treatment.

Though the trial's disappointing results were widely reported last summer, the assessments did not examine its most controversial feature: Consent was never obtained from patients in the study. But recently, some medical experts have called for federal regulators to revisit the policy that permits some experiments on humans to be conducted without the consent of patients or their families.

The absence of consent was allowed under a historic 1996 change in U.S. Food and Drug Administration regulations. Baxter's trial was the first study to take advantage of the new rules, which were designed to facilitate research in emergency medicine that could not happen if doctors had to take the time to get consent.

But in addition to encouraging new discoveries, the regulatory change broke with a 50-year-old doctrine requiring informed consent in virtually all experiments on humans. The failure of the Baxter trial has led some ethicists to question the wisdom behind the rule change.

"People get involved in something to their detriment without any knowledge of it," said George Annas, a professor of health law at the Boston University School of Public Health. "We use people. What's the justification for that?"

First articulated at the Nuremberg tri-  
SEE CONSENT, PAGE 8

Chicago Tribune January 17, 1999

# Consent

CONTINUED FROM PAGE 1

als as a way to prevent hideous experiments such as those performed by Nazi doctors during World War II, informed consent became the guiding principle of research on humans in this country. Violations of the rule normally have met with wide outrage, from the clandestine federal syphilis experiments on African-American Tuskegee airmen to recent allegations that researchers at the National Institutes of Mental Health gave subjects the "date rape drug" ketamine without fully disclosing some psychosis-inducing side effects.

In contrast to the secrecy of those studies, however, the HemAssist trial began under significant public scrutiny as the first under the new FDA regulations. There also was little reason to think the product would have an adverse effect, since initial trials in Europe did not indicate any problem with unexpected deaths.

Although no Chicago-area hospitals participated in the trial, one of its co-leaders was Dr. Max Koenigsberg, director of emergency medical services at Illinois Masonic Medical Center and an overseer of the Chicago EMS system. Koenigsberg said even though the trial's outcome was negative, the procedures used were sound.

"Nuremberg was never intended to withhold needed therapies from patients," Koenigsberg said. "The problem with Nuremberg and Tuskegee was that the medical community and the public were never told."

The new regulations require a level of community notification unheard of for most scientific studies, including extensive community meetings, press releases and post-study follow-up.

Yet it's unlikely that any of the patients who wound up being transfused with the blood substitute in emergency rooms had been reached by the public notification. Even supporters of the FDA rules say such notification cannot replace direct consent from patients or their relatives.

"Public notification means nothing," said Dr. Arthur Caplan, director of the Center for Bioethics at the University of Pennsylvania. "I know people are enamored of it, but it means nothing."

Caplan was lead author of a December article in the *Journal of the American Medical Association* that called for modifications to the FDA informed-consent regulations. His suggestions include requiring researchers do more to prove that a study can only be performed on patients who are so incapacitated by trauma that they cannot give consent themselves.

patients has always been allowed for studies with very minimal risk, in which researchers use only data that would be collected in the normal course of clinical care. In addition, federal regulators made rare exceptions to the informed-consent requirement when experiments involved patients in cardiac arrest or similar conditions when death appears likely.

The 1996 rule allows institutions to waive informed consent for studies of emergency treatment in which available treatments are unproven or inadequate.

Human blood, for example, currently cannot be given while a patient is in the ambulance speeding from the scene, and there can be a delay at the hospital if blood is in short supply. Blood substitutes such as HemAssist would not require refrigeration or cross-

matching for blood type, and so would be immediately available.

The regulations state that informed consent can be waived only if the patient is unconscious or incapacitated, and the family cannot be reached. Risks from the experiment must also be reasonable compared to standard treatment.

Animal studies and preliminary trials on humans suggested HemAssist was relatively safe, although some research suggested it caused an increase in blood pressure. The U.S. Army considered using similar blood products during the Persian Gulf war in 1991 but decided against it because of the blood pressure concern.

Trauma patients in the Baxter study received two to four units of HemAssist within an hour of arriving at the hospital, in addition to regular human blood and a saline solution. Randomly assigned patients in a control group got only human blood and saline. Researchers hoped HemAssist, like human blood, would help supply oxygen to the body's organs in the critical time immediately following severe injury from a car accident or shooting.

That justification met the federal requirement that the product could be shown to fill a need left by human blood, which often is not immediately available. But Boston University's Annas believes such theories are not enough for researchers to bypass informed consent.

"It's presented as if it's better, and we don't know that," Annas said. "That's the definition of research—if we knew it worked, we'd be doing it."

Analysis of the Baxter data has given no conclusive explanation of why the observed death rate for HemAssist was 46.2 percent, compared with the predicted rate of 42.6 percent. In another mysterious finding, mortality for the control group was just 17.4 percent, even less than the rate of 35.5 percent that would have been expected given the severity of that group's injuries. Given such irregularities, Koenigsberg said, it is impossible to show HemAssist caused the excess deaths.

In fact, many experts believe the FDA rules—and even Baxter's study—will be beneficial to patients in the long run.

Dr. Norman Fost, director of the medical ethics program at the University of Wisconsin, said some doctors had resorted to unofficial, unsupervised emergency medicine research before the FDA rules were changed.

"They would do informal studies, with the disadvantage that the data was never collected in a systematic way so you could tell whether the benefits were worth the risks," he said. "Most standard treatment in emergency room settings has never been shown to be safe and effective."

Fost, who lobbied for the FDA's relaxation of informed-consent requirements, said the Baxter study could have the unintended positive effect of deterring unmonitored research.

"This study may have prevented many deaths," Fost said. "Otherwise, the drug may have... been used in an uncontrolled, unstudied way."

The goal, Fost says, is to do what the patient would want if he or she could give consent.

A post-study survey at Lehigh Valley Hospital in Allentown, Pa., revealed that most families were satisfied with the treatment even after the trial proved a failure, according to Dr. Mark Cipolle, director of surgical research at the hospital.

"I was a little nervous about

calling the families of patients who died," Cipolle said, "but it wasn't bad at all."

No lawsuits have arisen from the blood trial, a Baxter spokeswoman said.

Still, Baxter's main blood substitute competitor, Evanston-based Northfield Laboratories Inc., said it has no plans to seek waivers for informed consent for studies of its product.

"I honestly am not convinced it's a method we need to use," said Northfield Chairman and CEO Richard DeWoskin. "I think experimental research should be consensual."

Northfield has tried to limit preliminary trials to patients who are less severely injured, or whose families can be reached in time to give their consent.

"We miss some patients, but we still get enough to do the study," DeWoskin said.

In fact, no company besides Baxter has conducted a no-consent experiment under the new rule, and only a few have begun the confidential preliminary process of preparing for one, FDA officials said.

That may indicate that the rules as currently formulated are still too burdensome for drug companies, Fost said.

Yet Bonnie Lee, a senior policy analyst for the FDA, said even the 1996 change was intended to be strict. Still, Lee said, the fact that few companies have plans to use the new rule may be significant.

"If it's not going to accomplish what we wanted it to accomplish, maybe it needs to be changed [again]," Lee said. "In some cases that could mean tightening the regulations or opening up other areas. We would never consider opening it so broadly as to allow just anything to happen."

## Oxygen-carrying blood substitutes

Concentrated efforts to develop blood substitutes were only seriously started after 1986 because of the threat of disease transmission, most notably of HIV and hepatitis C. An increasingly short supply of blood is helping to drive this research.

### Basics about blood

The chief components of blood are red blood cells (RBCs), white blood cells, platelets and plasma. Two drops of blood contain approximately 1 billion RBCs, which give blood its color. Hemoglobin is the active component of red blood cells, carrying oxygen from the lungs to the tissues.

### What is a blood substitute?

The oxygen-carrying hemoglobin in red blood cells is replaced by a natural or synthetic oxygen-carrying substitute. Effective blood substitutes would decrease the need for human hemoglobin in surgeries, traumas and emergencies. They could be used immediately when needed and would not require special storage or matching of human donors.

### Declining blood donations

In the U.S., the number of blood donors continues to fall while the number of elderly, the group that needs blood the most, is growing. Experts project an annual shortfall of 4 million units in the U.S. by 2030.

Sources: Northfield Laboratories, Synthetic Blood International

Chicago Tribune



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## Blood Trials Done Without Consent

CHICAGO (AP) - Twenty-four critically ill patients died after being given a blood substitute without their informed consent, according to federal officials.

Baxter International Inc. (NYSE:[BAX](#) - [news](#)) was able to test the substitute known as HemAssist without consent because of a 1996 change in U.S. Food and Drug Administration regulations.

The change, which broke with a 50-year standard that required informed consent for nearly all experiments on humans, was designed to facilitate research in emergency medicine that could not happen if doctors were forced to take the time to get patient consent.

Baxter officials halted their clinical trial of HemAssist last spring after reviewing data on the first 100 trauma patients enrolled in the nationwide study.

Of the 52 critically ill patients given the substitute, 24 died, representing a 46.2 percent mortality rate. The suburban Deerfield, Ill.-based company had projected 42.6 percent mortality for critically ill patients seeking emergency treatment.

The push to find a blood substitute has been intense because artificial blood could ease the effects of whole-blood shortages. Researchers say it lasts longer than conventional blood, eliminates the time-consuming need to match blood types and wipes out the risk of contamination with such viruses as HIV and hepatitis.

No company other than Baxter has conducted a no-consent experiment under the rule, according to FDA officials.

The new 1996 regulations require a level of community notification that is higher than most scientific studies, including community meetings, press releases and post-study follow-up.

Yet it's unlikely that any of the patients who wound up being transfused with the blood substitute in emergency rooms had been reached by the public notification, the Chicago Tribune reported Sunday.

Some say such notification cannot replace direct consent from patients or their relatives.

"Public notification means nothing," said Dr. Arthur Caplan, director of the Center for Bioethics at the University of Pennsylvania. "I know people are enamored of it, but it means nothing."

The problems with the HemAssist trial are prompting some medical ethicists to question the rule change.

"People get involved in something to their detriment without any knowledge of it," George Annas, a

professor of health law at the Boston University School of Public Health, told the Tribune. "We use people. What's the justification for that?"

A Baxter spokeswoman told the Tribune that no lawsuits have arisen from the blood substitute trial.

"The regulations worked in this instance," Mary Thomas said Sunday. "We voluntarily stopped the trial early on at the first sign of unexpected results to insure patient safety."

Thomas says Baxter is in favor of obtaining patient consent whenever possible. Yet company officials also believe it is important to advance lifesaving medical therapy for patients - something impossible to do without the revised FDA regulations, Thomas said.

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**Attachment 21**

**ABC-GOOD-MORNING-AMER-08****13:18:05, 20 January 1999**

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**24 Die After Receiving Blood Substitute**

xfdhe ABC-GOOD-MORNING-AMER-08 BLOOD SUBSTITUTE> THIS IS A RUSH TRANSCRIPT. THIS COPY MAY NOT BE IN ITS FINAL FORM AND MAY BE UPDATED.

DIANE SAWYER: Here's a story that surprised us. Did you know if you wound up unconscious in an emergency room, you might be used to test experimental drugs without your consent. It could happen. We learned it from the news that 24 of 52 critically ill people had died over the past year and a half after being given a blood substitute without their consent. Doctors aren't sure the substitute caused the deaths, but the trial was stopped. Joining us now from Chestnut Hill, Pennsylvania, is Dr. Arthur Caplan, director of the Center for Bioethics at the University of Pennsylvania, and from Boston, professor George Annas, a professor of health law at Boston University's School of Public Health.

We thank you both for joining us. Dr. Caplan, first of all, artificial blood, I think it would surprise people it's being used. Has it been tried in humans?

Dr. ARTHUR CAPLAN, University of Pennsylvania: A little bit. Some attempts have been used to test this artificial substitute, this chemical on people. It is basically a thing almost related to paint thinner and it can carry oxygen. The idea is if you can have artificial blood, you don't have to do blood typing, you don't have to worry about blood shortages, which we hear about, you can use it quickly as a substitute for anybody instead of trying to match blood types A, O, B, and that sort of thing we hear about, in an emergency situation where you don't have much time.

DIANE SAWYER: If it is still so experimental, how did it happen that 52 patients, without their consent, were given it?

Dr. ARTHUR CAPLAN: There has been a public policy change. In 1996, the federal government decided in some emergency situations if you didn't have time to get the consent of a subject and there was no family member or anyone else around, in desperate circumstances when you didn't have much in the way of treatment, you could do an experiment on someone without their permission. Pretty controversial decision and this experiment is going to make it more so.

DIANE SAWYER: Professor Annas, is it a good idea? Prof. GEORGE ANNAS, Boston University: I think it's a bad idea. One of the rules we have had since World War II about experiments is that nobody experiments on you, me or any other human being without consent -- consent to the individual if they're competent, consent of the next of kin or someone standing in to act on their behalf if they're not. I think it's a very dangerous precedent to move away from a consent requirement.

DIANE SAWYER: What about the greater good? Learning from science?

Prof. GEORGE ANNAS: The greater good is great if you want to be involved in that, but we've always had the option in America whether we want to contribute to the greater good or not. We used to draft people into the Army, but we never drafted people into being experimental subjects without their consent.

DIANE SAWYER: Dr. Caplan, if you had been in that emergency room and without your consent, would you want to have been given the artificial blood?

Dr. ARTHUR CAPLAN: Probably not in this instance. The argument for emergency research, doing it in situations where you can't get the subject consent, it might make some sense, say you had something where there was no cures, didn't know what to do, people would probably say try anything if that's what you've got. In this case, we do have blood. It's blood versus blood substitute. I'm not sure this is a good paradigm for where experimentation without consent ought to be going. I think George and I would probably agree that while you might be able to come up with situations where experimenting on someone without their permission might make sense, this is not one of those situations.

DIANE SAWYER: Professor Annas, have other drugs been given this way or is blood substitute the only one?

Prof. GEORGE ANNAS: As far as we know this is the only one. A FDA spokesman said this is the only case, but others are under consideration.

DIANE SAWYER: I understand that there are ways that you can stipulate somehow that you can prevent this from happening to you. How would you go about that?

Prof. GEORGE ANNAS: Well, it is a great question, whether you want to put a tattoo across your chest that says no research on me. Theoretically, you can opt out, but in reality, most people have no idea this research is going on. They don't know enough to say no.

Dr. ARTHUR CAPLAN: There is a requirement in this no consent situation where you're supposed to tell the community that you're doing research. It is not clear what that means, you ride around in a sound truck saying, watch out, research being conducted down the street, don't go there. The tough problem is we have to modify our advanced directives and our living-will laws, if we want people to have a right to say no to this, we have to change the law to make that happen.

DIANE SAWYER: Do you think the law will change? Dr. ARTHUR CAPLAN: I think we could see a change. I think this area is going to be hugely controversial. As George points out, we have never had situations where we experiment on people without their permission. I think we can make the case for it, but unless we have that protection and let people opt out, I don't think the public will be too happy with this.

DIANE SAWYER: Thank you both for joining us. Good to have you with us.

And Good Morning America will be back in a moment. (Commercial Break) CHARLES GIBSON: We've been talking about whether the government is paralyzed by the impeachment process and what chances the President has of getting the proposals that he will make tonight in the State of the Union enacted. "USA Today" went back and looked at last year's speech. The President made 27 major proposals, only 10 of them got enacted and even those only in part. We have a scorecard on some of those; He asked for more money to hire teachers, that's the wrong one; He asked for IRS reform, he got that; He asked for campaign finance reform, didn't get that, Republicans filibustered; Tobacco regulations, those ads killed that, and the Senate did, too; Family leave expansion, didn't get it; Child care credits, didn't get it; Hiring more teachers, he got some money for that, but no school construction, didn't get the five-year plan enacted; Juvenile crime, minimum wage increase, Medicare expansion, Patient's Bill of Rights, didn't get them.

DIANE SAWYER: Very low score of success. Very low score. In fact, we're told that it was the lowest for that year of any two-year presidency since the Eisenhower administration.

CHARLES GIBSON: It shows impeachment having an affect. We'll be back.

(Commercial Break) CHARLES GIBSON: We've been renewed for a second hour. So coming up on Good Morning America, the devastating toll that bullies can take on child and how to stop it before it's too late.

DIANE SAWYER: And finding buried treasure in Death Valley. CHARLES GIBSON: And a woman who gives sex advice for seniors. We'll be back.

(Commercial Break) (Local News) (Commercial Break) (Byline: CHARLES GIBSON / DIANE SAWYER) (Guest: Dr. ARTHUR CAPLAN / Prof. GEORGE ANNAS) (High: EXPERIMENTAL DRUGS CAN BE GIVEN WITHOUT CONSENT) (Spec: MEDICINE / BLOOD / PATIENTS) (Copy: Content and programming copyright (c) 1999 American Broadcasting Companies, Inc. All rights reserved. Transcribed by Federal Document Clearing House, Inc. under license from American Broadcasting Companies, Inc. All rights reserved. No quotes from the materials contained herein may be used in any media without attribution to ABC News. This transcript may not be reproduced in whole or in part without prior written permission. For further information please contact: ABC News's Office of Rights, Clearances and Permission Practices.(212)456-4059)

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● STORY TOP



Attachment 22

IBC's 6th Annual Conference on

# Blood Substitutes and Oxygen Therapeutics

**Advancements Towards Clinical Use**

November 19-20, 1998 • The Ritz-Carlton Pentagon City • Washington, DC

◆ SPECIAL KEYNOTE PRESENTATION ◆

**C. Everett Koop, M.D., Sc.D.**

Public Health Implications and Rationale  
for Innovative Blood Substitutes and Oxygen Therapeutics

**HEAR THE LATEST DEVELOPMENTS FROM:**

- Alliance
- Allos Therapeutics
- Apex Bioscience
- Baxter Healthcare
- Biopure
- EntreMed
- Hemosol
- Northfield
- Synzyme Technologies

**SPECIAL FDA PANEL DISCUSSION**

**Safety and Efficacy Endpoints**

Moderated by  
Harvey G. Klein, M.D., Chief, Department of  
Transfusion Medicine, Warren G. Magnuson  
Clinical Center, National Institutes of Health

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Biopharmaceuticals

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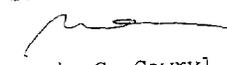
The past year has been marked by major changes and developments in the area of oxygen therapeutics. Basic scientists and clinicians continue to push forward in exploring the true potential and range of applications of oxygen therapeutics. As a result, a number of companies are advancing toward FDA approval of their products.

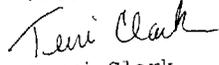
As an industry, we are beginning to progress toward the realization of our efforts. The insight and perspective of our clinical counterparts is thus becoming important to understanding the clinical impact of novel approaches to oxygen delivery and red blood cell replacement.

It is for this reason that our meeting this year will include speakers and participants from the areas of surgery, oncology, anesthesiology and more. These speakers will tie together valuable clinical perspectives and insights into the area of oxygen therapeutics.

As the chairs for the IBC Blood Substitutes conference this year, we would like to invite you to participate in what is sure to be an exciting and informative meeting.

Sincerely,

  
Maria S. Gawryl, Ph.D.  
Vice President, Research and Development

  
Terri Clark  
Director of Biomedical Development

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4:25 Blood and Blood Product Needs in Brazil

Eliete Bouskela, M.D., Ph.D., Professor, Laboratório de Pesquisas em Microcirculação, Universidade do Estado do Rio de Janeiro, Brazil

Mauricio Rocha e Silva, Professor, Faculdade de Medicina, Universidade de São Paulo, Brazil

Rob Shorr, Ph.D., D.I.C., Managing Director, Diamond Investment Group Inc.



The availability of blood and blood products and their safety in the United States, Europe and Japan is such that many have been led to question the need for blood substitutes. This, despite the fact that the availability of such products can simplify the transfusion process by eliminating the need for typing or cross matching, or, in a trauma situation, save additional lives.

In emerging countries where sophisticated networks for blood collection and processing exist, blood and blood product shortages may still occur and unlike the United States be chronic due to a lack of sufficient numbers of suitable donors. In some cases contamination with virus or parasitic infections may be the cause. For these nations the availability of blood substitutes is not a matter of improved transfusion medicine but rather a necessity to meet present and future health care needs. This presentation will explore opportunities for blood substitute development and use for the next millennium.

5:00 Closing Remarks from Conference Co-Chairpersons

5:05 Close of Day One

5:15 Networking Cocktail Reception

All delegates and speakers are cordially invited to enjoy drinks and hors d'oeuvres with colleagues.

Sponsorship Opportunities Available



Friday, November 20, 1998

Exhibit and Poster Viewing, Breakfast Bakeries and Coffee

7:45 Chairperson's Remarks

Maria S. Gawryl, Ph.D.  
Terri Clark

8:00 Recent Development of Hemolink™

George P. Biro, Ph.D., M.D., Vice President, Preclinical Science, Hemosol, Inc.; Professor, Department of Cellular and Molecular Medicine, Faculty of Medicine, University of Ottawa, Canada

F.J. Lou Carmichael, Ph.D., M.D., FRCP(C), Director of Clinical Trials, Hemosol, Inc.; Professor, Departments of Anesthesiology and Pharmacology, Faculty of Medicine, University of Toronto, Canada

Wilfred Lieberthal, M.D., Associate Professor, Boston University School of Medicine and Boston Medical Center

Hemolink™ is highly purified (>99%) human hemoglobin A, cross linked with o-ranifinose. This presentation will review the results of recently concluded safety tests. Multi-dose safety toxicology tests in rats and dogs, given 14 consecutive daily infusions of large volumes of Hemolink™, resulted in no mortality or substantive negative effects, beyond those related to the large loads of protein and iron-porphyrin. There was no evidence of nephrotoxicity in rats given Hemolink™ in 20 and 50% exchange transfusions. A phase II clinical trial in sixteen orthopedic surgical patients, in doses up to 500 ml, has shown no serious treatment-related adverse effects.



9:00 Recent Progress in the Clinical Development of Oxygent™ (Perflubron Emulsion) as a Temporary Oxygen Carrier for Elective Surgery

Peter E. Keepert, Ph.D., Program Director, Oxygen Carriers Development, Alliance Pharmaceutical Corporation

Oxygent™ (60% w/v perflubron-based emulsion) has undergone extensive phase I and phase II clinical testing. To date, > 540 subjects (healthy volunteers, cancer patients, and surgical patients) have been enrolled (> 340 received Oxygent™, 65 received a unit of autologous blood, and 135 were volume-matched controls). Five phase II studies have been



completed recently, including two phase IIb studies in noncardiac surgery (n = 246 orthopedic, urologic, and gynecologic patients), and three phase IIa studies in cardiac surgery (n = 80 CABG patients on CPB). In all studies, Oxygent™ was well tolerated with a very good safety profile. These studies also clearly demonstrated drug activity by enhancing oxygenation status and reversing protocol-defined physiological transfusion triggers. Pivotal phase III studies to demonstrate the clinical benefit of combining Oxygent™ with hemodilution as a means to reduce exposure to allogeneic transfusion in elective surgery patients are expected to begin soon.

Perflubron Emulsion Oxygent™ Delays Blood Transfusion in Orthopedic Surgery: Results of a Multicenter Phase IIb Study

Donat R. Spahn, M.D., Professor of Anesthesiology, University Hospital Zurich, Switzerland

The aim of this multinational, randomized, controlled, single-blind, parallel group study was to compare the efficacy of perflubron emulsion Oxygent™ versus autologous blood (AB) or colloid (COL) infusion in reversing physiologic transfusion triggers. A total of 147 subjects undergoing either unilateral hip replacement surgery or spinal surgery were enrolled. Patients were monitored with radial and pulmonary artery catheters and underwent preoperative hemodilution to a target [Hb] of 9.0 g/dL. Randomization occurred upon reaching one of several predefined transfusion triggers based on tachycardia, hypotension, cardiac output, or mixed venous PO2 levels. Oxygent™ was well tolerated and there were no serious adverse events attributed to the drug. For the 1.8 g/kg Oxygent™ treatment group, both the percentage of trigger reversal (97%) and the duration of reversal (80 min) were significantly different from the AB group (60%, 55 min) and the COL group (76%, 30 min).

9:45 Refreshment Break, Exhibit and Poster Viewing

10:15 Polynitroxyl Hemoglobin (PNH): A Hemoglobin Product with Antioxidant and Anti-inflammatory Activity

Carlton J. C. Hsia, Ph.D., President and Chief Executive Officer, SynZyme Technologies, L.L.C.

A number of hemoglobin-based oxygen carriers are undergoing clinical trials, but while these products may be able to transport oxygen they appear to lack antioxidant capability such as is found in the red cell. Therefore, there may be a risk that these products will promote the formation of reactive oxygen species in patients, with a wide range of potentially adverse clinical results. The vasoconstrictive activities of current, experimental hemoglobin-based products appear to be the most obvious manifestation of this risk. Polynitroxyl technology, utilizing novel molecular mechanisms to control oxygen-derived free radicals in the body, offers a new approach to the problem of oxidative risk in hemoglobin-based products. It is based on a class of compounds called nitroxides (stable nitroxyl radicals), which can act as mimics of the enzyme superoxide dismutase and other antioxidant enzymes. Evidence will be presented to show that the polynitroxylation of hemoglobin to create PNH converts the hemoglobin from a compound with pro-oxidant potential to a compound which can act as an antioxidant enzyme mimic. Three lines of evidence will be discussed. First, unlike current, first-generation hemoglobin-based products, PNH is free of hypertensive (vasoconstrictive) activity. Second, PNH inhibits free radical-mediated inflammation; mechanistic data will be presented. Third, PNH reduces injury in an experimental model of stroke. The antioxidant enzyme activities and the therapeutic potential of PNH as a second-generation hemoglobin product will be discussed.

10:40 Characterization of Hemoglobin Vasoactivity - An Update

Timothy N. Estep, Ph.D., Vice President, Research and Development, Hemoglobin-Therapeutics Division, Baxter Healthcare Corporation

Many hemoglobin formulations currently in preclinical or clinical testing exhibit pharmacologic vasoactive properties which result in physiologic responses different from those expected solely on the basis of oxygen transport and volume expansion. This vasoactivity has been intensively studied as part of the research and development of hemoglobin therapeutics at Baxter Healthcare Corporation and in collaborating laboratories. As part of this effort, both large and small animal model systems have been utilized to evaluate a wide range of modified hemoglobin solutions and interventions to gain insight into the mechanisms and characteristics of hemoglobin-based vasoactivity. In this presentation the results of these studies will be reviewed and compared to the extensive clinical data collected in the evaluation of diaspirin crosslinked hemoglobin.

Clinical Update of the DCLHb Traumatic Hemorrhagic Shock Program

Edward P. Sloan, M.D., M.P.H., Research Development Director, Department of Emergency Medicine, University of Illinois College of Medicine

Diaspirin Cross-linked Hemoglobin (DCLHb) has been tested in two traumatic hemorrhagic shock clinical trials. In the United States, a hospital study utilized a primary mortality endpoint. In Europe, a pre-hospital study examined a primary morbidity endpoint. This presentation will discuss the current status of the study of DCLHb in these traumatic hemorrhagic shock trials. In addition, important study design and informed consent issues will be highlighted, based on the experience gained from these two trials.



11:40 The Application of Recombinant Technology in the Discovery of Novel, Second Generation, Hemoglobin Therapeutics

Richard J. Gorczynski, Ph.D., Senior Vice President, Research and Development, Baxter, Hemoglobin Therapeutic Division

Douglas D. Lemon, Ph.D., Scientist, Baxter, Hemoglobin Therapeutic Division

The potent oxygen delivering capability of hemoglobin-based oxygen carriers (HBOCS) suggests that these agents will have therapeutic potential in the settings of trauma, surgical blood loss, ANH and in radiation and chemotherapy of cancer. It is unlikely, however, that the ideal product profile will be identical for each of these applications. The ideal P50, nitric oxide reactivity, cooperativity, Bohr sensitivity, and half life, for example, are likely different for each clinical use. Recombinant manipulation of hemoglobin structure allows modification of such properties to obtain optimal functionality for a particular use. In addition, through hemoglobin bioengineering, it is possible to reduce or eliminate undesirable pharmacologic effects. For example, using recombinant approaches focused on heme-pocket structure, we have discovered novel hemoglobins which react with nitric oxide much more slowly than wild-type human hemoglobin. Several of these molecules have been shown to be free from vascular and gastrointestinal smooth muscle effects, yet support oxygen consumption normally upon total isovolemic exchange in animals. We have also recombinantly engineered larger hemoglobins with improved properties. Furthermore, the combined application of recombinant structural manipulation with that of chemical polymerization and/or decoration offers an additional approach to second generation drug candidates with improved properties over first generation molecules. We envision that with application of recombinant technology it will be possible to generate an array of second generation hemoglobin-based products that have been tailor-made for specific clinical uses. We will present a summary overview of several of our approaches to discovery of commercially viable second generation hemoglobin therapeutics which possess optimized properties relative to first generation products. In addition, we will describe in detail one promising approach to novel, second generation molecules, namely, manipulation of heme-pocket structure to lower reactivity.



12:30 Lunch on your own

1:45 PolyHeme™: A Large Volume O2-Carrying Blood Replacement — An Update

Richard DeWoskin, Chairman and Chief Executive Officer, Northfield Laboratories, Inc.

Steven A. Gould, M.D., President, Northfield Laboratories, Inc.



2:45 Overview and Current Status of Biopure's Oxygen Therapeutics

W. Richard Light, Ph.D., Director of Protein and Analytical Chemistry, Biopure Corporation

Carl W. Rausch, Chairman and Chief Executive Officer, Biopure Corporation

Virginia T. Rentko, V.M.D., Dipl ACVIM - Director, Veterinary Medicine, Biopure Corporation

Biopure has developed two types of blood substitutes. Oxyglobin® has been approved by the Food and Drug Administration for the treatment of canine anemia. The approval process, as well as the experiences currently being reported from the field, will be shared. An overview of the current market, as well as a market forecast, will



... continued on outside flap

On-line: <http://www.ibtusa.com/conf/bloodsubs>

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