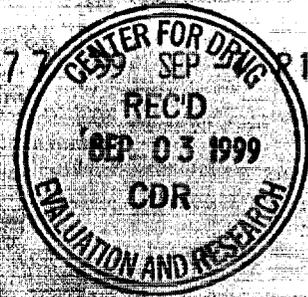


Hemoglobin Therapeutics

2545 Central Avenue  
Suite FD-1  
Boulder, Colorado 80301  
303.440.9988  
Fax: 303.444.3013

**Baxter**

September 2, 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:

The attached information concerning public disclosure following the completion of the clinical investigation of Diaspirin Crosslinked Hemoglobin (DCLHb) involving an exception to informed consent was inadvertently mailed last week to the FDA's Center for Biologics Evaluation and Research (Office of Blood Research and Review) along with our corresponding IND submission. If that document has been forwarded to your offices for Docket 95S-0158, this duplicate submission may be disregarded.

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

958-0158

SUP20

Hemoglobin Therapeutics

2545 Central Avenue  
Suite FD-1  
Boulder, Colorado 80301  
303.440.9988  
Fax: 303.444.3013

**Baxter**

1178 '99 SEP -7 P1:39



**August 26, 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.

Each of the 18 clinical sites involved in the U.S. DCLHb trauma trial which completed pre-study community consultation/public disclosure activities and received investigational product (DCLHb) have completed their post-study disclosure activities.

This submission includes post-study information recently received from Palmetto Richland Memorial Hospital (Columbia, SC), Vanderbilt University Medical Center (Nashville, TN), Lehigh Valley Hospital (Allentown, PA), University of Pittsburgh Medical Center (Pittsburgh, PA), MetroHealth Medical Center (Cleveland, OH), Albert Einstein Medical Center (Philadelphia, PA), Hershey Medical Center (Hershey, PA), University of Maryland Medical Center (Baltimore, MD), Christiana Care Health Services (Newark, DE), St. Anthony Central Hospital (Denver, CO), Washington Hospital Center (Washington, DC), Memorial Medical Center (Savannah, GA), Carolinas Medical Center (Charlotte, NC), and University of Texas Medical Center (Dallas, TX). This submission also includes recent "national" press coverage pertaining to the use of an exception to informed consent in the U.S. DCLHb Trauma Study.

The post-study public disclosure information from Palmetto Richland Memorial Hospital includes an April, 1999 letter, press release, and public notice sent to community members who had been notified of this study during the pre-study community consultation/public disclosure period (Attachment 1). Similar information on the study, including local demographics, was published during May, 1999 in two electronic newsletters, *Notations* and *Focus Stat*, of the Palmetto Richland Memorial Hospital (Attachment 2). The study results were discussed during the monthly Palmetto Richland Trauma Conference in May, 1999 and were scheduled to be released to the press on August 27, 1999 (Attachment 3).

Additional post-study public disclosure information from the Vanderbilt University Medical Center includes a June, 1998 follow-up letter to the Vanderbilt Community Committee summarizing their May, 1998 meeting where this clinical trial was discussed (Attachment 4).

Additional post-study public disclosure information from Lehigh Valley Hospital includes an April, 1998 letter sent via certified mail to all participants in this trial (Attachment 5).

Additional post-study public disclosure information from the University of Pittsburgh Medical Center includes a May, 1999 letter to the City of Pittsburgh Commission on Human Relations which had been consulted during the pre-study community consultation/public disclosure period (Attachment 6). This letter was also copied to the study investigators.

Additional post-study public disclosure information from MetroHealth Medical Center in Cleveland includes a January, 1999 public advertisement translated into Spanish in *Nueves Horizontes* (Attachment 7).

The post-study public disclosure information from Albert Einstein Medical Center includes a public notice published in March, 1999 in the *Philadelphia New Observer* (Attachment 8). The same public notice was also published in March/April, 1999 in the *Olney Times*, *Mt. Airy Times Express*, *Germantown Courier*, and *Northeast Times Newsweekly*. A compilation of documents summarizing the DCLHb U.S. trauma trial was forwarded to Emergency Medicine faculty and residents at the Albert Einstein Medical Center (Attachment 9).

Additional post-study public disclosure activities at Hershey Medical Center included a March, 1999 follow-up letter to personal calls made previously to members of their community group (Attachment 10).

The post-study public disclosure information from the University of Maryland Medical Center includes the minutes from a March, 1999 Community Meeting which included members of the pre-trial community consultation group (Attachment 11), an April, 1999 article in the *Baltimore Times* (Attachment 12), and a copy of a public notice published in May, 1999 in the *Baltimore Sun* (Attachment 13). This public notice was also published during May, 1999 in the *Afro-American*, *Baltimore Times*, and *City Paper*. The trial results were also disseminated at weekly staff meetings at the R Adams Cowley Shock Trauma Center as well as through hospital lectures such as the Nursing Trauma Conference in April, 1998 and the Trauma Fellows Critical Care Lecture in March, 1999.

Additional post-study public disclosure information from Christiana Care Health Services includes an April, 1998 e-mail message to the key study (Attachment 14).

Additional post-study public disclosure information from St. Anthony Central Hospital in Denver includes an article published in the spring, 1999 quarterly hospital publication, *Trauma Rounds* (Attachment 15).

The post-study public disclosure information from the Washington Hospital Center includes a summary of the procedures utilized by WHC during post-study disclosure of DCLHb study termination (Attachment 16). These activities included a meeting with the WHC Community Relations Council (Attachment 17), a DCLHb "Fact Sheet" released to the press in March, 1999 (Attachment 18), and a similar public notice placed during March, 1999 in the *Washington Times*, the *Washington Post*, the *Washington Informer*, and *El Pregonero* (Attachment 19). In addition, this information was published in the April, 1999 Washington Hospital newsletter, *The CenterLine* (Attachment 20).

The post-study public disclosure information from the Memorial Medical Center in Savannah, Ga. includes a May, 1999 public notice published in the *Savannah Morning News/Evening Press* (Attachment 21) and a copy of a recent letter to study participants (Attachment 22).

Additional post-study public disclosure activities at the Carolinas Medical Center in Charlotte, NC included the presentation of DCLHb U.S. trauma study results at a September, 1998 public forum in Charlotte on medical research and drug development issues.

The post-study public disclosure information from the University of Texas Southwestern Medical Center at Dallas includes a May, 1999 public notice printed in the *Dallas Morning News* and translated into Spanish in *El Sol de Texas* (Attachment 23).

Recent national press coverage on the exception to informed consent issue which specifically mention Baxter's DCLHb study includes a March, 1999 article from *Nature Medicine* (Attachment 24) and a March/April 1999 article from the *SAEM Newsletter* (Attachment 25).

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

**LIST OF ATTACHMENTS**

**Palmetto Richland Memorial Hospital (Columbia, SC)**

- Attachment 1: Letter to community members
- Attachment 2: Article printed in hospital newsletters *Notations* and *Focus Stat* (May, 1999)
- Attachment 3: Documentation of in-hospital Trauma Conference; Press release (August, 1999)

**Vanderbilt University Medical Center (Nashville, TN)**

- Attachment 4: Letter to Vanderbilt Community Committee members

**Lehigh Valley Hospital (Allentown, PA)**

- Attachment 5: Letter to trial participants

**University of Pittsburgh Medical Center (Pittsburgh, PA)**

- Attachment 6: Letter to City of Pittsburgh Commission on Human Relations

**MetroHealth Medical Center (Cleveland, OH)**

- Attachment 7: Notice printed in *Nuevos Horizontes Weekly Newspaper* (Jan. 19, 1999)

**Albert Einstein Medical Center (Philadelphia, PA)**

- Attachment 8: Notice printed in local newspapers (*Philadelphia New Observer*, *Olney Times*, *Mt. Airy Times Express*, *Germantown Courier*, and *Northeast Times Newsweekly*) (March/April, 1999)
- Attachment 9: Study summary documents sent to hospital emergency medicine faculty and residents

**Hershey Medical Center (Hershey, PA)**

- Attachment 10: Letter to community members

**LIST OF ATTACHMENTS (Continued)**

**University of Maryland Medical Center (Baltimore, MD)**

- Attachment 11: Minutes from community consultation meeting
- Attachment 12: Article in *The Baltimore Times* (April 9-15, 1999)
- Attachment 13: Notice printed in local newspapers (*Baltimore Times, Baltimore Sun, Afro-American, City Paper*) (May, 1999)

**Christiana Care Health Services (Newark, DE)**

- Attachment 14: E-Mail memo to study personnel

**St. Anthony Central Hospital (Denver, CO)**

- Attachment 15: Article printed in hospital publication *Trauma Rounds* (Spring, 1999)

**Washington Hospital Center (Washington, DC)**

- Attachment 16: Site summary
- Attachment 17: WHC Community Relations Council meeting minutes
- Attachment 18: Information released to press (March, 1999)
- Attachment 19: Notice printed in local newspapers (*Washington Times, Washington Post, Washington Informer, and El Pregonero*) (March, 1999)
- Attachment 20: Notice printed in hospital newsletter *The Centerline* (April, 1999)

**Memorial Medical Center (Savannah, GA)**

- Attachment 21: Notice printed in *Savannah Morning News/Evening Press* (May 15, 1999)
- Attachment 22: Letter to trial participants

**University of Texas Medical Center (Dallas, TX)**

- Attachment 23: Notices printed in *Dallas Morning News* and in Spanish in *El Sol de Texas* (March, 1999)

**National Press Coverage**

- Attachment 24: Article in *Nature Medicine* (March, 1999)
- Attachment 25: Article in *SAEM Newsletter* (March/April, 1999)

[REDACTED]

[REDACTED]

[REDACTED]



April 16, 1999

John Doe  
154 Doe Street  
Columbia, SC 29203

Dear Mr. Doe,

In June 1997, Richland Memorial Hospital sent you a letter notifying you that we were participating in a Federal Drug Administration (FDA) approved efficacy trial of Diaspirin Cross-Linked Hemoglobin (DCHLb) in the treatment of severe traumatic hemorrhagic *shock*.

As a requirement of that study, the FDA requires that once the study is concluded that notification go to the community on the results of that study. In that attached document, we detail the study's national and local results to fulfill that requirement. This information also is being sent to statewide television, radio and print media.

If you have any questions about this information, please contact Palmetto Richland's Public Relations department at 803-434-6891.

Sincerely,

Raymond Bynoe, M.D., F.A.C.S.  
Medical Director, Trauma Services



FOR MORE INFORMATION  
CALL TAMMIE EPPS, 434-4903  
OR JO HALMES, 434-3108  
PUBLIC RELATIONS

FOR IMMEDIATE RELEASE  
April 16, 1999

### Palmetto Richland releases trauma research information

In 1997, Palmetto Richland Memorial Hospital was one of 17 sites nationwide that participated in a research study to determine the effectiveness of a new treatment for trauma victims with severe blood loss due to traumatic injury. The study was canceled in the past year.

In addition to receiving standard care for such cases, participants received Diaspirin Cross-linked Hemoglobin (DCLHb), a blood substitute, or a control saline solution. DCHLb, which contains human red blood cells, was being researched to determine if it could increase blood flow and oxygen to vital organs in patients with traumatic injury.

In January 1998, the trial's sponsoring company, Baxter Healthcare Corporation, ended this trial, following an interim data review by the trial's independent monitoring safety committee. The committee found that patients in the treatment group had an increased mortality compared to those in the control group. Although the data do not indicate that the increased mortality was due to the treatment being tested, Baxter decided to cancel the study out of concern for patient safety. Approximately 100 of 850 expected participants had been enrolled in the study nationwide.

At Palmetto Richland, five adult patients were treated in the research study. Two of those patients received DCHLb—of those who received DCHLb, one patient died as a result of traumatic injuries. Of those that received saline, one patient died as a result of traumatic injuries. There were three African-American patients and two Caucasian patients involved in the study. Three were male and two were female.

"Although this study ended prematurely, this type research continues to lay the groundwork for other research projects that one day will help us save more lives," says Dr. Raymond Byrnoe, Palmetto Richland trauma surgeon and the study's local principal investigator. "I'm encouraged by this type of trauma research."

The research study used the U.S. Food and Drug Administration's guidelines for emergency research, in which patients are unable to give permission to participate due to life-threatening injuries, and they require the immediate medical attention. Those guidelines also require that participating institutions provide public notification of the outcome of these studies.

For more information about this study, contact Palmetto Richland's Public Relations at 803-434-6891.

###

## Public Notice

A 1997 research study involving Palmetto Richland Memorial Hospital and 16 other health-care providers nationwide was cancelled in the past year. The study looked at the effectiveness of a new treatment for trauma victims with severe blood loss due to traumatic injury.

In addition to receiving standard care for such cases, study participants received Diaspirin Cross-linked Hemoglobin (DCLHb), a blood substitute, or a control saline solution. DCLHb, which contains human red blood cells, was being researched to determine if it could increase blood flow and oxygen to vital organs in patients with traumatic injury.

In 1998, the trial's sponsoring company, Baxter Healthcare Corporation, ended this trial, following an interim data review by the trial's independent monitoring safety committee. The committee found that patients in the treatment group had increased mortality compared to those in the control group. Although the data do not indicate that the increased mortality was due to the treatment being tested, Baxter elected to cancel the study out of concern for patient safety. Approximately 100 of 850 expected participants had been enrolled in the study nationwide.

At Palmetto Richland, five adult patients were treated in the research study. Two of those patients received DCLHb. Of those who received DCLHb, one patient died as a result of traumatic injuries. Three African-American and two Caucasian patients were involved in the study. Three were male and two female.

The research study used the U.S. Food and Drug Administration's guidelines for emergency research involving patients needing immediate medical attention but who are unable to give permission to participate due to life-threatening injuries. Those guidelines also require that participating institutions provide public notification of the outcome of these studies.

For more information about this study, contact Jay Hamm, Palmetto Richland Memorial Hospital, at 803-434-6418.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

# Notations

PALMETTO RICHLAND

May 21, 1999

## ***Delinquent Medical Charts Reminder***

The 30-day amnesty period for chart delinquency will expire tomorrow, Saturday, May 22. All delinquent charts should be current by that date. Failure to complete charts will result in enforcement of medical staff by-laws, which will restrict admitting privileges. For more information, call Patsy Hathorn, 434-7863.

## ***Trauma Research Update***

In 1997, Palmetto Richland was one of 17 nationwide sites that participated in a research study to determine the effectiveness of a new treatment for trauma victims with severe blood loss due to traumatic injury. The study was canceled in the past year.

In addition to receiving standard care for such cases, participants received Diaspirin Cross-linked Hemoglobin (DCLHb), a blood substitute, or a control saline solution. DCHLb, which contains human red blood cells, was being researched to determine if it could increase blood flow and oxygen to vital organs in patients with traumatic injury.

In January 1998, the trial's sponsoring company, Baxter Healthcare Corporation, ended the trial following an interim data review by an independent monitoring safety committee when it was found that patients in the treatment group had an increased mortality compared to those in the control group. Although the data do not indicate that the increased mortality was due to the treatment being tested, Baxter decided to cancel the study out of concern for patient safety. Nationwide, approximately 100 of 850 expected participants had been enrolled.

At Palmetto Richland, five adult patients were treated in the research study. Of the two patients who received DCLHb, one died as a result of traumatic injuries. There were three African-American patients and two Caucasian patients involved in the study. Three were male and two were female.

The research study used the U.S. Food and Drug Administration's guidelines for emergency research, in which patients are unable to give permission to participate due to life-threatening injuries, and they require immediate medical attention. Those guidelines also require that participating institutions provide public notification of the outcome of these studies.



## FOCUS STAT

May 20, 1999

### TODAY: DEADLINE TO REQUEST JUNIOR VOLUNTEERS

The Junior Volunteer program will be held June 7-Aug. 6. All departments that would like a junior volunteer in their areas should either complete the form recently sent to all managers or contact Volunteer Services, 6242, by the end of the business day today, May 20. Assignments will be announced June 1.

### FOCUS DISTRIBUTION CHANGES

FOCUS newsletter, which includes PalmettoScope, now will be distributed via hospital mail the first Thursday of each month. The newsletter no longer will be distributed with paystubs. If your department is not receiving FOCUS through in-house mail, please call Tracy McKelvey at 3109.

### PALMETTO RICHLAND RELEASES TRAUMA RESEARCH INFORMATION

In 1997, Palmetto Richland was one of 17 states nationwide to participate in a research study to determine the effectiveness of a new treatment for trauma victims with severe blood loss due to traumatic injury. The study was canceled in the past year. In addition to receiving standard care for such cases, participants received Diaspirin Cross-linked Hemoglobin (DCLHb), a blood substitute, or a control saline solution. DCLHb, which contains human red blood cells, was being researched to determine if it could increase blood flow and oxygen to vital organs in patients with traumatic injury.

At Palmetto Richland, five adult patients were treated in the research study. Two of those patients received DCLHb. Of those who received DCLHb, one patient died as a result of traumatic injuries. Of those who received saline, one patient died as a result of traumatic injuries.

The research study used the USFDA's guidelines for emergency research, in which patients are unable to give permission to participate due to life-threatening injuries, and they require the immediate medical attention. For more information, call 6891.

### JCAHO SURVIVAL: DO EMPLOYEES HAVE RIGHTS?

Do you know that as a Palmetto Richland employee, you have rights when it comes to being assigned to caring for certain patients? The cultural values, ethics or religious beliefs of employees may be considered when assigning an employee to a patient. If there is a direct conflict between the employee's values and beliefs and the patient's care and treatment, Policy 8240-64 outlines how to address this. The policy also says the employee should notify his or her manager in writing.

When the JCAHO surveyors come to Palmetto Richland in January 2000, any employee may be asked a question about employees' and patients' rights. Be prepared. All employees should have the 1999 Palmetto Richland JCAHO Survival Guide. Read the book. If questions, call the Employee Hot Line at 2646.



**Date:** June 8, 1999

**To:** Todd Marshall  
Baxter Hemoglobin Therapeutics

**From:** Jay Hamm, BSN, RN, EMT-P   
Trauma Coordinator

**RE:** DCLHb Disclosure

This is to inform you that the results of the DCLHb study, both locally and nationally, was discussed at our monthly Trauma Conference on May 26, 1999. Dr. Raymond Bynoe discussed the study with the attendees and answered questions. The participants at this conference were from Emergency Medicine, Orthopedics, Surgery, Rehabilitation, Radiology and Nursing. The discussion lasted approximately 30 minutes.

If you have any questions, please call me at 803-434-6418.



FOR MORE INFORMATION  
CALL TAMMIE EPPS, 434-4903  
OR JO HALMES, 434-3108  
PUBLIC RELATIONS

FOR IMMEDIATE RELEASE  
August 27, 1999

### Palmetto Richland releases trauma research information

In 1997, Palmetto Richland Memorial Hospital was one of 17 sites nationwide that participated in a research study to determine the effectiveness of a new treatment for trauma victims with severe blood loss due to traumatic injury. The study was canceled in the past year.

In addition to receiving standard care for such cases, participants received Diaspirin Cross-linked Hemoglobin (DCLHb), a blood substitute, or a control saline solution. DCHLb, which contains human red blood cells, was being researched to determine if it could increase blood flow and oxygen to vital organs in patients with traumatic injury.

In January 1998, the trial's sponsoring company, Baxter Healthcare Corporation, ended this trial, following an interim data review by the trial's independent monitoring safety committee. The committee found that patients in the treatment group had an increased mortality compared to those in the control group. Although the data do not indicate that the increased mortality was due to the treatment being tested, Baxter decided to cancel the study out of concern for patient safety. Approximately 100 of 850 expected participants had been enrolled in the study nationwide.

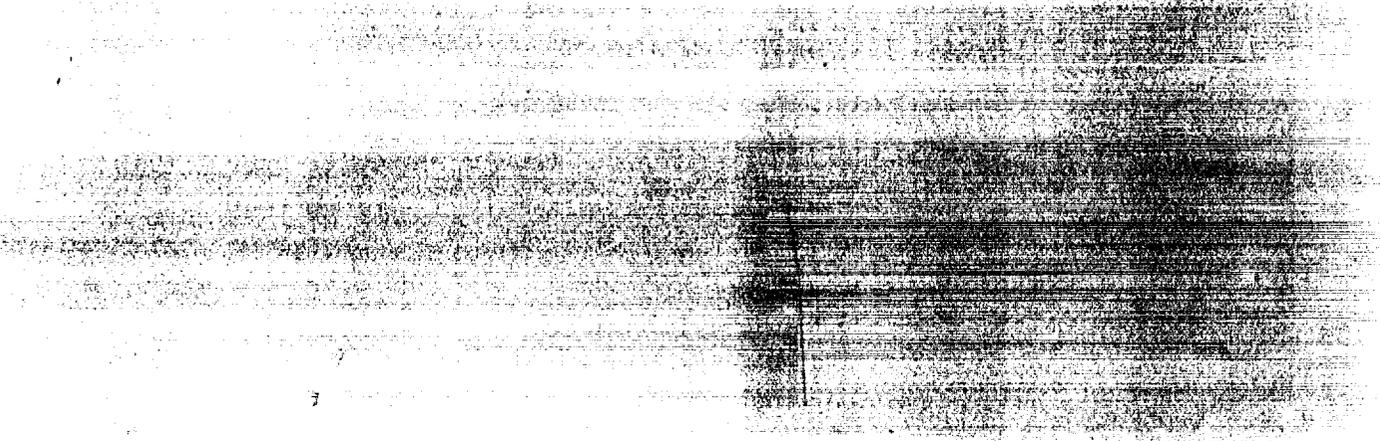
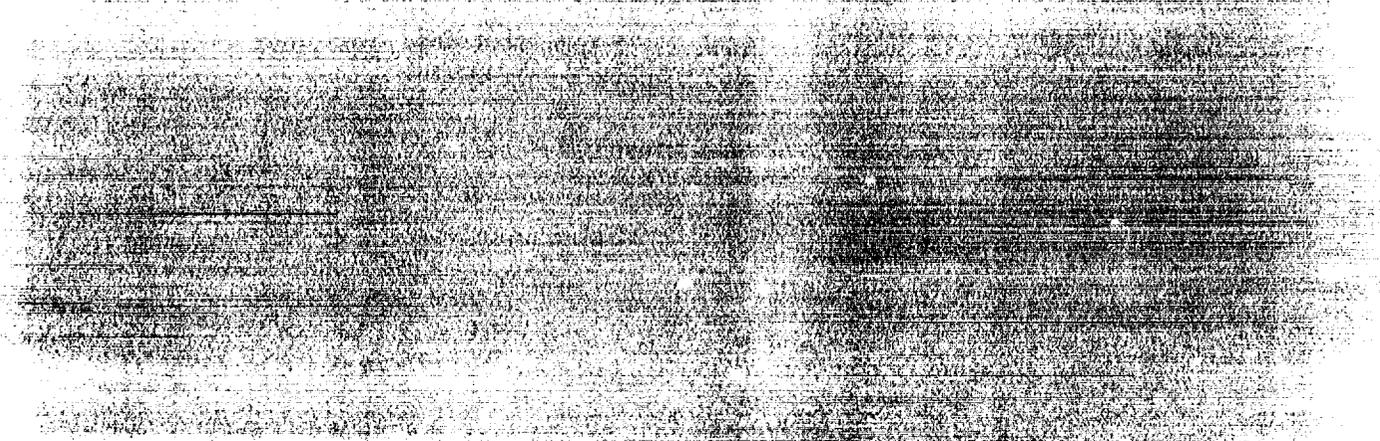
At Palmetto Richland, five adult patients were treated in the research study. Two of those patients received DCHLb—of those who received DCHLb, one patient died as a result of traumatic injuries. Of those that received saline, one patient died as a result of traumatic injuries. There were three African-American patients and two Caucasian patients involved in the study. Three were male and two were female.

"Although this study ended prematurely, this type research continues to lay the groundwork for other research projects that one day will help us save more lives," says Dr. Raymond Bynoe, Palmetto Richland trauma surgeon and the study's local principal investigator. "I'm encouraged by this type of trauma research."

The research study used the U.S. Food and Drug Administration's guidelines for emergency research, in which patients are unable to give permission to participate due to life-threatening injuries, and they require the immediate medical attention. Those guidelines also require that participating institutions provide public notification of the outcome of these studies.

For more information about this study, contact Palmetto Richland's Trauma Services at 803-434-6776.

###



# Vanderbilt University Medical Center

Vice-Chancellor for Health Affairs - Institutional Review Board

CCC-3322 Medical Center North  
Nashville, TN 37232-2103  
(615) 322-2918 Fax: (615) 343-2648  
E-mail: [irb@mcmail.vanderbilt.edu](mailto:irb@mcmail.vanderbilt.edu)

To: All Community Committee Members

From: Institutional Review Board

Date: June 2, 1998

RE: 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)

The Community Committee met on May 29, 1998 to discuss the termination of the above-mentioned study. Dr. John Morris, Jr. and Judy Jenkins, M.S.N., R.N. were present to summarize the course of events of this study and answer questions in accordance with the Emergency Research and Waiver of Consent regulation, 21CFR50.24. The federal regulation requires that the community be informed of the withdrawal or termination of any study meeting the criteria of the emergency research and waiver of consent regulation.

Dr. Morris presented an overview of the study to include a description of the study and a description of the adverse events reported to date. The Baxter Healthcare Corporation Data Monitoring Committee recommended a hold be placed on patient accrual to examine the data collected in January 1998. This hold was based on an apparent imbalance in outcomes in the 2 arms of the study, in which the mortality rates were less favorable in the DCLHb group versus the control group. In March 1998, the Baxter Healthcare Corporation terminated this study based on efficacy and safety analyses, which showed a statistically significantly higher mortality in the subjects who received DCLHb than in the subjects who received normal saline. From analysis of the data, in the interest of patient safety and based on the unlikelihood of being able to achieve the primary efficacy endpoint of reducing the 28-day mortality if the study was continued, the study was stopped. A summary of the study provided by Baxter Healthcare Corporation is enclosed for your information.

For additional information, please feel free to contact the Institutional Review Board office at 322-2918. For specific questions regarding the study, please feel free to contact Judy Jenkins, M.S.N., R.N. at 936-0171.

Enclosures

**Emergency Research and Waiver of Consent  
[FDA 21 Part 50.24, DHHS 45 CFR Part 46.498]**

On October 2, 1996, (Federal Register, Vol. 61, No. 192, pp. 51498-51535), the Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS) issued a new regulation giving Institutional Review Boards the authority to waive informed consent requirements in some acute care clinical investigations. The new regulation applies to a limited class of research activities involving human subjects who are in need of emergency medical intervention, but who are unable to give informed consent and have a life-threatening medical condition and who do not have a legally authorized person to represent them. The intent of the new regulation is to allow research on life-threatening conditions for which available treatments are unproven or unsatisfactory and where it is not possible to obtain informed consent, while establishing additional protections to provide for safe and ethical studies. The new regulation went into effect November 1, 1996.

The FDA and DHHS recognize that subjects with life-threatening conditions who can neither give informed consent nor refuse enrollment are in a vulnerable position and are in need of additional protective measures to ensure their safety and welfare. The new regulation requires additional protective measures be taken by the IRB when reviewing, approving and monitoring research conduct.

The regulation requires that the IRB must find and document the following:

- The research involves a life-threatening situation and available treatment is either unproven or unsatisfactory
- Obtaining consent is not feasible
- The research is of potential direct benefit to the subject
- The research cannot be practically carried out without waiver of consent
- Consultation with representatives from the communities from which the subjects are likely to come
- There must be public disclosure to the community of the risks and of the benefits and purpose of the study prior to initiation
- At completion of the study, there be public disclosure of the demographics of the study population and the results
- Additional reporting and recordkeeping requirements with respect to FDA drug and device applications must be met, and the sponsor must establish an independent data monitoring committee

**What is the status of the DCLHb Trauma trial?**

The Efficacy Trial of DCLHb in the Treatment of Severe Traumatic Hemorrhagic Shock conducted in the U.S. has been stopped by Baxter Healthcare Corporation, the study sponsor. The purpose of the study was to determine if DCLHb could decrease the amount of illness and mortality associated with severe trauma.

**Why was the study stopped?**

There was an observed imbalance in mortality among the treatment group relative to the control group. The imbalance was such that if the study continued it would be highly unlikely to achieve the primary efficacy endpoint of reducing 28-day mortality. For this reason, and to ensure maximal protection of patient safety, Baxter stopped the study.

**How many patients were enrolled in the trial? How many hospitals were involved?**

Approximately 100 patients were enrolled at 17 hospitals in the U.S., with about half receiving DCLHb.

**What were the specific differences in mortality rates? How many patients died in each group?**

The expected mortality rate for this patient population was approximately 40%. There was an observed imbalance in mortality among the treatment group relative to the control group. Complete data will be made available when the study results are fully analyzed and published in the medical literature.  
(results from individual centers may be provided at your IRB's discretion)

**Did DCLHb's use contribute to patients' deaths? Is DCLHb safe?**

The data do not indicate a clear cause and effect between DCLHb infusion and the observed imbalance in mortality. DCLHb has been well tolerated in clinical trials over the past 5 years involving approximately 1000 patients, with approximately 500 receiving the product.

Patients eligible for the study were suffering from severe traumatic hemorrhagic shock-- victims of severe trauma, such as motor vehicle accidents, knife and gun shot wounds-- with a predicted mortality of approximately 40%. Patients involved were among the most injured of all trauma patients, with only about 3% of all trauma patients being eligible for trial inclusion. All individuals enrolled in the study received the best standard emergency care including transfusions of blood, resuscitative fluids, and surgery as required.

**What was wrong with this trial?**

It is certainly not unprecedented for complex clinical trials which study critically ill patients to be stopped. Baxter collaborated with many trauma investigators on this consensus protocol. The information will give us a better understanding of future DCLHb protocols and advances in treatments for trauma patients.

**Where there any notable differences between the treatment and control groups observed?**

Although there are identifiable differences between the two study groups in some variables such as pre-study injury severity and other baseline measures, none were significant enough to allow a conclusion to be drawn

RECEIVED

APR 03 1998

COMMITTEE

as to why the mortality was higher in the treatment group. One cannot assume that the severity of injuries was distributed equally across the treatment groups.

What is the cause for the differences in mortality?

The data do not indicate a clear cause and effect between DCLHb infusion and the observed imbalance in mortality, but as is often the case early (100 of the planned 850 patients) in complex studies of critically ill patients, the answer to "why" may not be one specific factor. Baxter and its clinical investigators are studying the data to better understand why there was a difference.

Although there are identifiable differences between the two study groups in some variables such as pre-study injury severity and baseline physiologic measures, none were significant enough to allow a conclusion to be drawn as to why the mortality was higher in the treatment group. One cannot assume that the severity of injuries was distributed equally across the treatment groups.

What has the FDA said about this trial and this recent development?

The FDA has been notified of all developments

Since this trial was performed under the informed consent waiver, were patients who received DCLHb put at unnecessary risk?

All patients received the best standard emergency care available including the infusion of blood, fluids and surgical intervention if necessary. DCLHb was given as an add-on therapy to all other standard treatments. Nothing was withheld from patients.

Patients eligible for the study were suffering from severe traumatic hemorrhagic shock with an expected mortality rate of 40%. The data monitoring committee and the interim analysis were in place to ensure that patients were not put at unnecessary or avoidable risk. Patient enrollment into the study was halted as soon as a recommendation was received by the committee. The Data Monitoring Committee conducted itself to the highest standards, and it is clear that this approach served the protocol and the patients in the study very well.

In addition, prior to the start of the study, the protocol was reviewed by the FDA and the IRB of each participating center. The IRB consulted with their community and received input from the community as to whether the trial should be conducted.

How many patients, if any, gave consent?

Patients eligible for this study were suffering from severe traumatic hemorrhagic shock-- including victims of car accidents, gunshot and stab wounds-- so most could not give consent for themselves. Every institution had informed consent documents approved by their IRBs, for cases when it was feasible to obtain consent from the patient or their legally authorized representative or family member. In addition, every institution had procedures in place to attempt to locate family and obtain consent prior to patient enrollment, if feasible. In addition, procedures were in place to notify the patient's family, legally authorized representative and the patient as soon as feasible after the patient's enrollment to inform them of the patient's inclusion in the study and to obtain consent for further participation.

Two patients were able to give consent themselves. For several others consent was obtained from family members or their legally authorized representative. As was expected in this patient population, in most cases, it was not feasible to obtain consent prior to treatment.

APR 03 1998

COMMITTEE FOR THE PROTECTION  
OF HUMAN SUBJECTS

# VANDERBILT MEDICAL NEWS



Vanderbilt University

OFFICE OF NEWS  
AND PUBLIC AFFAIRS  
MEDICAL CENTER  
CCC-3312  
1161 21st Avenue South  
Nashville, TN 37232-2390  
(615) 322-4747

contact: VUMC Office of News and Public Affairs

phone (615) 322-4747

## VANDERBILT TO TEST SYNTHETIC BLOOD PRODUCT

Vanderbilt University Medical Center's trauma center is gearing up to test a new synthetic blood product on severely injured patients.

The new investigational product will be administered to patients who are in shock due to excessive blood loss. VUMC is one of 35 health care centers across the country testing the new product to determine if it is a viable alternative to saline infusion, the standard treatment.

The upcoming trial falls under recently adopted federal regulations giving research institutions the authority to treat gravely ill patients with investigational drugs or devices in some emergency situations without their consent (see VUMC Reporter, March 14).

The synthetic blood product, called Diaspirin Cross-Linked Hemoglobin (DCLHb), is a purified human hemoglobin solution. Hemoglobin is the protein in red blood cells that carries oxygen. The synthetic blood product, which has already been proven safe in prior studies, is prepared from units of human red blood cells from volunteer donors who have been tested negative for the viruses that cause hepatitis and AIDS. Unlike blood, it does not need to be cross-matched and is easily stored in the emergency department so that it is available as soon as the patient arrives.

The multi-center study will compare the use of the synthetic blood product to saline, the current standard of treatment when blood is not readily available.

"This study is designed to try to identify the very sickest people who can benefit from the administration of a blood substitute when blood is not available," said Dr. John A. Morris Jr., professor of Surgery, and the principal investigator of the Vanderbilt portion of the study. Also participating in the study will be Judy Jenkins, R.N., M.S.N., clinical nurse specialist and case manager in the division of Trauma.

Before blood can be given to a patient, the patient must be cross-matched so that the correct type of blood is given, Morris explained. Giving a patient the wrong type blood can be a "fatal

mistake," Morris said.

Cross-matching can take up to 45 minutes, time that is not available when an injured patient is in shock, he said.

When a patient is in shock the body is unable to deliver enough blood and oxygen to all of the vital organs and tissues, Morris explained. Because of this, the vital organs may no longer be able to function and the patient may die. About 150,000 people die each year due to trauma injuries.

"The ravages of shock are dependent upon two things — the magnitude of the injury and the length of time before the patient gets therapy for that injury," Morris said. "The most important therapy we can give people is the ability to get oxygen to the tissues," Morris said.

A breathing tube can deliver oxygen from the air to the blood, Morris said. But within the blood there has to be a method by which oxygen is carried to the tissues. That is the importance of hemoglobin.

"In a normal situation, the boxcar that delivers oxygen is called hemoglobin," Morris explained. "Hemoglobin is the business end of what a blood transfusion is all about."

But blood transfusions take time to prepare.

"If we had something to give patients in the first 45 minutes that would carry oxygen, i.e. a boxcar, we could shorten the time they are without enough oxygen to the tissues. And that's good," Morris said.

Currently, when it is not feasible to wait for blood to be given, the treatment of choice is the rapid infusion of large volumes of saline to replace fluid loss due to injury, followed by the transfusion of blood to replace the fluid and blood loss.

The nationwide study will involve approximately 850 severely injured patients at the 35 trauma centers. About 20 to 30 patients will be involved at each institution.

Only those at the greatest risk of death can be considered for the study. Patients can be either male or female and must be at least 18. Patients with severe head injuries or whose heart has stopped in the hospital will not be entered into the study.

The study participants will be randomized. Some will receive the new synthetic blood product. Some will receive an equal amount of saline. All will receive standard therapies in addition to the investigational product. The order of assignment will be determined before the patients are entered into the study so neither the patients nor the patients' physician can choose which solution is given. Possible risks associated with the synthetic blood product include a temporary yellowing of the skin, red discoloration of the urine that does not affect kidney function, abdominal cramps and an increase in blood pressure, a desired effect in a patient suffering from shock.

Morris said the implications of the study are important for several reasons.

"It's important to the people of Tennessee for several reasons. This is a rural state and the transport time to definitive care is relatively long. Consequently the risks of shock are relatively

high," he said.

The new synthetic blood product has a shelf life of more than a year, and can be thawed for use after it is frozen.

"All you'd have to do is manufacture it, ship it over on one airplane and thaw it when you need it," Morris said. "If this product is proven to work, it may have tremendous implications for the military not far down the road."

Morris said it is believed that the earlier the synthetic blood product is used the better it may work. If the product is proven effective, it will more than likely be of best use before the patients actually get to the hospital, administered while they are en route, either in a ground or air ambulance.

"The next step will be to get this product into the pre-hospital environment," Morris said.

For now, the question of whether the product works better than saline is all that this project attempts to answer.

"It's not a question of whether this product serves as a boxcar. We know it does. It's not a question of whether it's safe. It has been demonstrated to be safe. The question is can we give it, can we give it early enough and can we give it in volumes sufficient enough to save lives," Morris said.

"We're confident we're not going to make anyone worse. The question is can we make a significant number of people better."

As part of the new regulations giving research institutions the authority to treat gravely ill patients with investigational drugs or devices in some emergency situations without their consent, VUMC is seeking feedback from the community. To respond, please contact Vanderbilt's Institutional Review Board at (615) 322-2918 or fax comments to (615) 343-2648.

VUMC

1

[REDACTED]

2

[REDACTED]

11

[REDACTED]

**LEHIGH VALLEY**  
**HOSPITAL**

April 2, 1998

Mr. [REDACTED]

Dear Mr. [REDACTED]

As a participant in the national HemAssist® (DCLHb™) trauma study sponsored by Baxter Healthcare Corporation, we wanted to inform you that the study has been halted.

Baxter stopped the study after an interim review noted that the survival rate for the group that received the HemAssist® blood product was as expected, compared to a higher-than-expected survival rate in the control group. Baxter felt that to continue this study would not accomplish its goals because of this imbalance.

The data does not indicate a cause and effect between the blood product and patient survival. Baxter and the clinical investigators are assessing the impact of many factors to determine the reason for the imbalance including protocol design, timing of the administration of HemAssist®, other treatments, and severity of patient injuries in the two treatment groups.

Lehigh Valley Hospital was one of 17 sites nationwide to participate in this study investigating the effectiveness of HemAssist® in a trauma application. The blood product in intended to treat the harmful side effects associated with severe blood loss in trauma patients.

You were chosen to participate because of the severe injuries and blood loss you incurred that brought you to the Lehigh Valley Hospital Trauma Center. As part of the study, you were given all the standard emergency care available. Those patients in the control group received saline; those patients in the treatment group received this blood product as add-on therapy only.

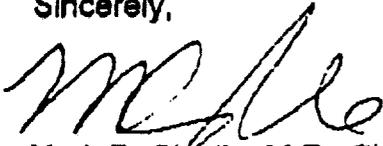
Page Two  
April 2, 1998

Research is responsible for many advances in health care and thus ultimately benefits patients. At Lehigh Valley Hospital, we are committed to providing the best possible care, and being involved in research allows us to do that. HemAssist® has several significant potential benefits including:

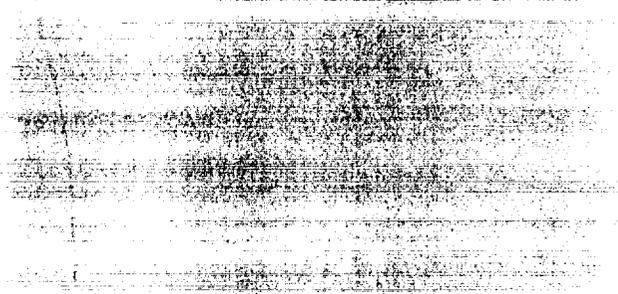
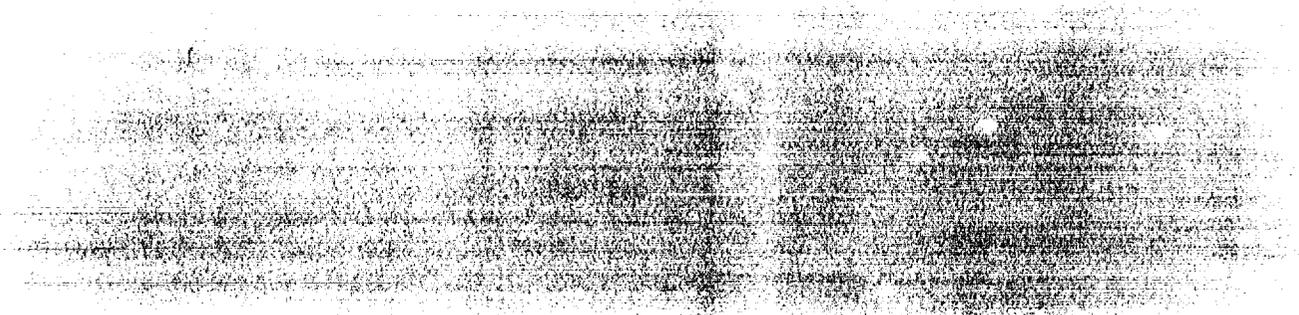
- Increased blood flow to vital organs when a patient is in shock, thus possibly preventing organ failure;
- lower risk of contamination because it is man-made;
- saving critical time in stabilizing a patient because it does not have to be typed or cross-matched;
- and fewer blood supply shortages.

We have attempted to contact you by phone to give you this update. If we have not reached you or you have further questions, please do not hesitate to contact us at (610)402-1286.

Sincerely,



Mark D. Cipolle, M.D., Ph.D., FACS  
Associate Director for Trauma





# UPMC HEALTH SYSTEM

May 19, 1999

200 Lothrop Street  
Pittsburgh, PA 15213-2582

Charles Morrison, Director  
City of Pittsburgh Commission on Human Relations  
Room 908 City-Country Building  
414 Grant Street  
Pittsburgh, PA 15219

RE: The Efficacy Trial of Diaspirin Cross-Linked Hemoglobin (DCLHb™) in the Treatment of Severe Traumatic Hemorrhagic Shock

Dear Mr. Morrison:

The purpose of this letter is to provide a summary of the local results of the study referenced above, which was presented to the Commission in 1997. The Commission was consulted before starting this study, because it was conducted under a new federal regulation which allowed emergency treatment to begin without a subject's consent under certain strictly defined circumstances.

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. Random selection was used to determine which patients received active treatment and which patients received saline solution as a control.

Baxter decided to terminate the study after enrollment of approximately 100 of its expected 850 participants from October 1 to December 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 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 going to be done to determine what factors contributed to the higher mortality rate in the treatment group.

Principal investigator in the study for UPMC Health System was Andrew Peitzman, M.D., professor in the department of surgery. Three patients were enrolled at UPMC Presbyterian during the study period. All three patients were caucasian adults. The first patient, a woman, received the experimental blood substitute and died while in the hospital. The second and third patients, both men, received saline solution and were discharged alive from the hospital.

The Institutional Review Board and the study investigators wish to thank the Commission for their participation as community consultants.

Sincerely yours,

Elizabeth L. Cohn, MPH

c: Marilyn J. Borst, MD  
Anita Courcoulas, MD  
Edward J. Kimball, MD  
Andrew B. Peitzman, MD  
Dennis Swanson, MS  
W. David Watkins, MS, PhD, MD  
Randy J. Woods, MD  
Donald Yealy, MD



**Oportunidades en Ventas de Publicidad**

se a la compañía de publicidad de televisión de más  
lo crecimiento en los estados del Medio-Atlántico, La  
ón Central de Media Partners, el brazo derecho en  
idad de -Adelphia Cable Communications- está bus-  
o unas cuantas personas motivadas y entusiasmadas  
ingresarlas al equipo de ventas. Los candidatos serán  
derados basado en la experiencia, historial de trabajo y  
ividad.

**Gerente Mayor de Cuenta - Erie, PA:** Esta posición  
a cuentas mayores de agencias en -Western  
vania, New York y el Noreste de Ohio. Un diploma  
uela superior o su equivalente, mas al menos cuatro  
de experiencia en venta de publicidad en medios  
nativos es requerido. Un grado de colegio mas experi-  
en cuentas grandes es preferido. Esta posición se  
a al Gerente de Ventas de Erie Pennsylvania y requiere  
individuo orientado en metas que pueda trabajar  
endientemente. Esta posición conlleva un salario,  
iones mensuales, incentivos cuatrimestrales y dietas  
ales por el automóvil.

**Gerente de Cuentas - Erie, PA; Lake County, OH;  
burg, VA; Tazewell, VA.** Un diploma de escuela  
or o su equivalente y dos años o más de experiencia  
ntas de publicitaria en medios informativos es re-  
o. Un grado de colegio con experiencia en ventas es  
do. Conocimiento de mercadeo o publicidad en des-  
e impreso, diseño y producción de radio y televisión.  
posiciones conllevan un salario, comisiones mensu-  
ncentivos cuatrimestrales y dietas mensuales por el  
óvil.

**Asesorador de Ventas de Publicidad - Erie, PA.** Esta  
in provee soporte administrativo, clerical, tráfico y  
ción al departamento de ventas de publicidad. Un



**Termina el Estudio Terapéutico de Hemoglobina en el MetroHealth Medical Center**

El MetroHealth Medical Center ha terminado con el estudio investigativo que fue designado a evaluar un nuevo tratamiento para pacientes seriamente heridos que sufrían de pérdida de sangre severa.

El estudio, llevado a cabo en 17 centros de trauma en la nación, fue detenido por Baxter Healthcare, Inc., desarrolladores del producto de sustituto de sangre patentizado. De acuerdo con los oficiales de Baxter Healthcare, el Comité de Monitoría de Información que estaba sobre mirando el esfuerzo de estudio nacional decidió que el estudio probó el no tener un efecto positivo de beneficio en aumentar la sobrevivencia del paciente.

El estudio terapéutico de la hemoglobina fue el primero en la nación en usar una nueva regulación de la -U. S. Food and Drug Administration- (FDA) que permitía a los pacientes conscientes en peligro de muerte, y para aquellos que no tenían a nadie disponible para dar consentimiento, a recibir un tratamiento experimental si no existía un tratamiento alterno con una buena oportunidad de éxito. La notificación del resultado del estudio es un requerimiento de la FDA.

A la vez que este proyecto en particular no probó que el producto fuera efectivo, los estudiosos en MetroHealth Medical Center creen que la información obtenida por este estudio puede contribuir para otros estudios de trauma.

Baxter Healthcare ha establecido una página en el servicio de la red electrónica <http://dclhb.er.uic.edu> para proveer mayor información acerca del estudio. Usted puede dirigir sus preguntas o comentarios acerca del estudio a:

**DCLHb Study  
c/o MetroHealth Medical Center  
Emergency Medicine  
2500 MetroHealth Dr.  
Cleveland, OH 44100-1000**

[REDACTED]

[REDACTED]

[REDACTED]

neighborhoods.

This may sound like typical political rhetoric, but these candidates insist that they are not just posturing and their individual experiences have placed them in ideal positions to assume the role of a council person.

Juan Ramos cites his 29 years of public works that this enhances his appealability. Even a party, his affiliation with the politically influential much an insider, without tainting his ability

was president of the Delaware Valley Voter he increased voter registration in Philadelphia three-year period. It was through advocating that Ramos decided to mount his own campaign year ago as I was in the midst of a voter registration wanted to see new faces, ideas and energy asked me when are you going to run," he

reason for being in the race is to target incumbent councilperson. There has been recent criticism areas relating to the Hispanic community, but is not altogether true. "I want to make it clear everyone is trying to be one of five. You run yourself and this is the focus of my campaign." notion that Ortiz is his focus, he does address with the Ortiz agenda. "There is discontent in performance of Ortiz in the last 14 years. There has could impact the everyday lives of the Hispanic

it and his strongest supporters include former mayoral candidate John F. Street. former city attorney, has been politically chart his course, aligning himself with would enhance his credibility. Nesmith is a work, who co-chairs his campaign with Mayor running for Congress last year, when the first

law to fight for his community.

Nesmith's campaign slogan says that he stands "head and shoulders above the crowd." He says there are four levels of experience that form the basis for this belief: 1) his government experience; 2) his work with community-based organizations; 3) his relationship with the private sector and; 4) his life is a semblance of hope. Nesmith proclaims, "I did not grow up with a silver spoon in my mouth. I struggled. I grew up on welfare and in the projects. I hope to be someone in council that young people can say, 'Steve Nesmith grew up in public housing and on welfare,' and they can say, 'if he can make a better life for himself, then so can I.'"

Blondell Reynolds-Brown believes that her campaign in 1995 has her name fresh in the minds of voters and she's anticipating that this familiarity gives her a significant edge. She said, "The fact that I ran the last time gives me the edge, period. So I know what's required to win and I know that I have to bring everything I

(Continued on page 31)

## PUBLIC NOTICE

The blood substitute clinical trial that involved the administration of blood solution with waiver of informed consent 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 in the study were gravely ill victims of severe trauma, such as motor vehicle accidents, knife and gun wounds, who had high expectancy of mortality.

Approximately 100 patients of the expected 850 participants were enrolled nationwide. 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 while the actual mortality was 46.2 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 was inconclusive. Study results will be submitted to a scientific journal in the near future.

Albert Einstein Medical Center (AEMC) enrolled four participants: a black male, a white male, a black female and a Hispanic female. Three patients received DCLHb, and one was evaluated as a control patient (received placebo, saline.) The three patients who received DCLHb completely recovered with no serious adverse events and were subsequently discharged from AEMC. The control patient (received placebo, saline) recovered with multiple adverse events and was also eventually discharged from AEMC.

All AEMC cases were thoroughly reviewed by William Dalsey, MD, former chairman, Emergency Medicine, AEMC, the Principal Investigator, and the Institutional Review Board. Questions regarding the study can be directed to Mark Kaplan, MD, Department of Surgery, Trauma Program, 456-8258.

Baxter is releasing this clinical information prior to its formal publication to fulfill its responsibilities according to regulations pertaining to the waiver of informed consent.



place to call home.

ices, ECS, needs foster parents for some very medical needs such as diabetes, cerebral palsy, and other conditions. ed programs. ECS. armed people age

All it takes is a big heart and



es Foster Care at 215-351-1419

[REDACTED]

[REDACTED]

ALBERT EINSTEIN MEDICAL CENTER  
DEPARTMENT OF EMERGENCY MEDICINE

Memorandum

TO: Emergency Medicine Faculty & Residents

FM: Pamela Taggart, RN, PhD  
for Dr. Jack Kelly  
Dr. Robert Porter  
Dr. Douglas McGee

*P. Taggart*

DA: 4-5-99

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

---

In November & December of 1997, the Emergency Department participated in the above trial. In January 1998, serious concerns were raised about the safety profile of DCLHb *in this group of patients* (e.g., those suffering severe traumatic hemorrhagic shock) and the trial was placed on hold. An interim safety data review was performed after which the study was voluntarily halted by the sponsor, Baxter Healthcare. It is important to note that other trials using this substance did not demonstrate these safety concerns and have continued.

It has been suggested that we share the final reports with members of our faculty (attached). A summarized version will be appearing in five local papers in the near future (required community notification secondary to use of waiver of consent in this trial). Please keep us informed if you hear any feedback from the community.

**Baxter**

January 4, 1999

Pamela Taggart, R.N., Ph.D.  
Department of Emergency Medicine  
Albert Einstein Medical Center  
5501 Old York Road  
Philadelphia, PA 19141

Dear Dr. Taggart:

Dr. Max Koenigsberg has asked me to forward the following information regarding Baxter's Trauma Clinical Trial to you as follow up to your recent phone conversation.

I enclose:

March 31, 1998 Baxter Press Release  
November 3, 1998 Baxter Letter to PI's  
November 19, 1998 Baxter Letter to PI's with Trauma Study Synopsis

Please do not hesitate to contact Dr. Koenigsberg or myself for any additional information which your site may need to complete its public disclosure activities. Thank you for your continued efforts to complete this important process.

Sincerely,

*Todd Marshall*

Todd Marshall  
Regulatory Affairs Assoc. Dir.  
BAXTER Hemoglobin Therapeutics  
303 541 3320 (Phone)  
303 443 7343 (Fax)

## Baxter Ends U.S. Trauma Study of HemAssist(TM)(DCLHb)

European Trauma and U.S. Surgery Trials Continue on Track

DEERFIELD, Ill., March 31 /PRNewswire/ -- Baxter Healthcare Corporation announced today that it has ended its U.S. Phase III trauma trial investigating the efficacy of its oxygen-carrying solution, HemAssist(R) (DCLHb), for the treatment of severe traumatic hemorrhagic shock. Baxter decided to stop the trial, which had enrolled approximately 100 of its expected 850 participants, following an interim data review by the trial's independent data monitoring committee. The committee found that patients in the treatment group had an increased mortality compared to those in the control group.

Baxter and its clinical investigators are studying the data to better understand why there was a difference in mortality between the patient groups. They are assessing the impact of many factors, including the combined results of the trial's design and protocol, the timing of the administration of HemAssist(R) (DCLHb) and other medical treatments, the wide range of patient injuries and the severity of patient injuries in the two patient groups.

"We are evaluating options for trauma applications in the United States," said Thomas Schmitz, Ph.D., general manager of Baxter's Hemoglobin Therapeutics division. "We are confident that HemAssist(R) (DCLHb) will be of critical importance for both surgeons and emergency-medicine physicians.

"The European trauma trial, where physicians are administering HemAssist(R) (DCLHb) at the trauma site, is continuing on track. Our U.S. Phase III surgery trial moves forward as well."

Baxter continues to expect to bring HemAssist(R) (DCLHb) to market in late 1999 or early 2000.

### Significant Differences in Emergency Care

The ongoing European trauma trial is investigating the product's efficacy in the pre-hospital setting, where doctors administer the product as a first-line therapy at the trauma site. In contrast, U.S. doctors infused HemAssist(R) (DCLHb) in the hospital after patients had been in shock for much longer periods of time. The company noted that in light of the U.S. trauma results the European trauma study has been evaluated by its independent data monitoring committee and that committee has determined that the trial will continue on course.

The patients enrolled in the U.S. trauma trial were gravely ill -- victims of severe trauma, such as motor vehicle accidents, knife and gun shot wounds -- and had a high expected mortality. Patients involved in the HemAssist(R) (DCLHb) trial were among the most severely injured of all trauma victims, with only about 3 percent of all trauma patients eligible for trial inclusion. All individuals enrolled in the study received standard emergency care, including transfusions of blood, resuscitative fluids, and surgical intervention as required.

This U.S. trauma study was conducted under regulations issued by the U.S. Department of Health and Human Services (HHS) and the U.S. Food and Drug Administration (FDA) governing clinical-research practices in emergency medicine. These regulations are designed to protect patients' rights and well-being, while also allowing for an exception to informed consent in narrowly defined life-threatening situations. Several rigorous safety checks and patient protections are required of studies conducted under this ruling, including interim data analysis by an independent data monitoring committee. All institutions involved in the trial worked with their communities to inform them about the potential risks and benefits of the HemAssist(R) (DCLHb) trial. The results of the U.S. trauma study will be made public when the data are fully analyzed.

Baxter's Phase III U.S. surgery trial is investigating the use of HemAssist(R) (DCLHb) as an alternative to blood in patients undergoing elective surgery, such as hip and knee replacements, aortic repair and abdominal pelvic procedures.

Baxter Healthcare Corporation is the principal U.S. operating subsidiary of Baxter International Inc. (NYSE: BAX). Baxter International, through its subsidiaries, is a global leader in the development of products and technologies related to the blood and circulatory system. The company has market-leading positions in four areas: blood therapies, cardiovascular medicine, kidney-disease therapy and medication delivery. Through a combination of technological innovation and global expansion, Baxter is advancing medical care and improving the lives of millions of people worldwide.

This news release contains forward-looking statements that involve risks and uncertainties, including technological advances in the medical field, product approval, demand and market acceptance.

*SOURCE Baxter Healthcare Corporation*

Company News On Call: <http://www.prnewswire.com> or fax,  
800-758-5804, ext. 100340

November 3, 1998

DRAFT

«PI1» «PI2»«Title»  
«SiteAddress»

Dear Dr. «PI2»:

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 your site and sponsored by Baxter Healthcare was terminated during March, 1998. This study was regulated under IND #6859 for Diaspirin Crosslinked Hemoglobin (DCLHb) pursuant to 21 CFR §50.24, exception from informed consent requirements for emergency research.

Regulation 21 CFR §50.24(a) outlines IRB responsibilities for the review, approval, and continuing review of the clinical investigation described by the waiver of informed consent requirements, and §50.24(a)(7)(iii) states the following: Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including demographic characteristics of the research population, and its results. The FDA considers it necessary to provide comprehensive summary data from the completed trial, along with demographic information to the community.

In order to demonstrate to the agency that each investigational site in the study already has or is planning to disclose information to their local communities, Baxter is requesting that you please obtain from your IRB a summary of the plans or actions in the area of exception from informed consent requirements for emergency research and return it directly to our clinical project manager, Jaime Houghton, by November 13, 1998. Baxter needs to provide a compilation of these summaries for a submission to the IND file.

If you have any questions please contact either Jaime Houghton (phone: 847-270-5089; fax: 847-270-5306) or Mark Mannebach (phone: 847-270-2837).

Thank you.

Sincerely,

**Mark A. Mannebach, Ph.D.**  
Associate Director of Regulatory Affairs

**DRAFT**



November 19, 1998

COPY

Dr. William Dalsey  
Department of Emergency  
Albert Einstein Medical Center  
5501 Old York Road  
Philadelphia, Pennsylvania 19141

Dear Dr. Dalsey,

Enclosed is a copy of the synopsis of the final study report for 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 your site and sponsored by Baxter Healthcare. This study was regulated under IND #6859 for Diaspirin Crosslinked Hemoglobin (DCLHb) pursuant to 21 CFR §50.24, exception from informed consent requirements for emergency research.

In addition to the synopsis, the University of Illinois at Chicago (UIC) in collaboration with Baxter has created a web site (<http://dclhb.er.uic.edu/>) to assist in the process of disclosing information to the research community. This web site provides a comprehensive summary of the results of the trial and the site is updated when data becomes available. Also, a publication of the results of the completed investigation is planned.

As per our recent letter dated November 3, 1998, all information disclosed to your local community by your IRB should be summarized and forwarded to Todd Marshall, Regulatory Affairs, at the Boulder address shown below no later than December 18, 1998. Dr. Max Koenigsberg, Mt. Sinai Hospital (phone: 708-848-3988), can provide assistance with completion on the public disclosure process, and he will be directly contacting any site who has not responded to this inquiry by the deadline.



November 19, 1998  
Page Two  
Dr. William Dalsey

COPY

If you have any questions after November 23, 1998, please contact either Michael Saunders, Sr. Director of Clinical Research (303-541-3337) or Todd Marshall, Associate Director of Regulatory Affairs (303-541-3320) as we are moving the Hemoglobin Therapeutics offices from Round Lake, Illinois, to Boulder, Colorado.

Thank you.

Sincerely,

Mark A. Mannebach, Ph.D., R.Ph.  
Associate Director of Regulatory Affairs  
Hemoglobin Therapeutics Division

New Baxter Hemoglobin Therapeutics Office:  
2545 Central Avenue  
Boulder, CO 80301-2857

2. SYNOPSIS

<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>	
<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	
<b>Objectives:</b> <b>Primary Endpoints:</b> 28 day Mortality Reduction. <b>Secondary Endpoints:</b> Morbidity reduction as measured by the multiple organ dysfunction (MOD) scores; 48 hour mortality reduction; and 24 hour lactate level. <b>Pharmaco-economic Endpoints:</b> Blood utilization reduction; ventilator, dialysis, ICU and total hospital day reduction. <b>Safety Endpoints:</b> (a) the incidence and severity of adverse events (AEs); and (b) changes from baseline in clinical laboratory results and summary of graded toxicities.		
<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.		
<b>Investigators, IRBs, and Baxter</b> 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).		
<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>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Diaspirin Cross-linked Hemoglobin (DCLHb)	<b>Volumes:</b>	
<b>Name of Active Ingredient:</b> DCLHb	<b>Page:</b>	
<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> <b>Efficacy:</b> Survival status at 28 days after infusion.  <b>Safety:</b> 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>  <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>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>		
Date of the Report: November 6, 1998		

[REDACTED]

[REDACTED]

March 3, 1999

I am writing to follow-up on our previous telephone conversation to again thank you for your assistance, as a community member, in evaluating a study that we undertook in the Section of Trauma/Critical Care Surgery at the Hershey Medical Center. As you are aware, we were involved in the study which used a blood substance (DCLHb) for resuscitation of trauma victims without, in some instances, obtaining their or their family's prior consent.

This study is now ended, and although we enrolled three patients in the study at HMC, no one received DCLHb here at this center. For reasons that are unclear, there was a higher death rate in the patients that received this drug at other sites around the country (compared to those that received a salt solution) and the sponsoring company stopped the study to examine the issue. It should be noted that all of these patients were severely injured and had a high likelihood of dying, regardless of entry into the study. At this point, however, the reason for the discrepancy is not known. We might speculate that since the investigators were not "blinded", i.e. they knew what solution the patient was receiving, it is possible that they treated the two groups differently (known as investigator bias). We wanted to keep you informed of these findings.

Again, I want to thank you for your participation, and hope that we can count on your support for future studies that require the thoughtful assessment of our community leaders. If you have any questions about the study, please do not hesitate to call me.

Sincerely,

J Stanley Smith, Jr., MD  
Professor of Surgery  
Chief, Section of Trauma/Critical Care Surgery

[Redacted text block]

[Redacted text block]

[Redacted text block]

**MINUTES FROM MARCH 4, 1999 COMMUNITY CONSULTATION FOR BAXTER TRIAL**

On Thursday March 4, 1999, at noon the University of Maryland School of Medicine, IRB held a community notification meeting to inform the community of the outcome of the HemAssist Clinical Trial.

**Community persons:**

Persons from the community invited where: Dr. Doris Hall, president of Poppleton Empowerment Village; Ms. Myrtle McCollough, president of the Farmer Mitchell Board of UMMS; Mrs. Joy Bramble, publisher of the Baltimore Times Newspapers; Clarence Robinson, member of the board of the Poppleton Empowerment Village, and; Rev. Robinson, former president of Poppleton, Director of Agape House and former member of the IRB.

Mrs. McCollough couldn't attend and sent another member of the Farmer Mitchell Board, John Puryear. Mrs. Bramble was unable to attend at the last minute.

**UM attendees**

From the University of Maryland where: Anne Hirshfield, Ph.D, Assistant Dean for Research; Tom Scalea, MD, director of Shock Trauma, Ellen Beth Levitt, director of Public Relations for UMMS and Priscilla Pearson, J.D., senior policy analyst for UMSOM.

**Discussion**

Priscilla Pearson opened the luncheon meeting by welcoming the attendees. All persons introduced themselves. Dr. Pearson stated the persons had been invited with the goal of appraising them that the HemAssist clinical trial had ended and sharing with the community the results, including the demographics of the participants.

Dr. Hirshfield then explained the role of the IRB and gave information on clinical trials. She also invited the community members to nominate someone for the IRB. We informed the invitees that the IRB was seeking a "community representative" and nominations from them would be welcomed. In response to a question Dr. Hirshfield added that there is no requirement that the IRB contain a community member, this is something the UMSOM's IRB does to ensure grassroots involvement.

Dr. Hirshfield then turned it over to Dr. Tom Scalea, director of Shock Trauma, where the HemAssist Clinical Trial was conducted. Dr. Scalea stated shock trauma was an area in which little medical advancement had been made, often because persons came into emergency rooms unable to give informed consent. Without informed consent studies could not take place.

He relayed 2 cases where great advances had been made in shock trauma cases because consent was waived. He elaborated on how Shock Trauma patients were in the greatest need of medical advances, especially patients with penetrating injuries like gunshots. Dr. Scalea stated what the data shows, gunshot victims are usually African American males. They, therefore, stand to gain the most from research advances in this area.

He gave the demographics of the study (see attached). Dr. Scalea volunteered to go and speak to the Poppleton Empowerment Village's board of directors meeting. He stated he would speak to various community forums and invited persons to call him with issues and concerns.

The response from the community representatives was very positive. Dr. Hall and Rev. Robinson said they appreciated our informing them of the results. Dr. Hall said she would look for someone to nominate to the board.

#### Community Recommendations:

In closing we asked the community members where should we go from here?

Persons suggested the following actions:

publish results of the HemAssist clinical trial in the Baltimore Times and the Afro American, two Baltimore newspapers with an African American readership,

\*write letters to the editor,

\*write an article in the Mayor's newsletter

\*write an article in the Housing Commission newsletter

\*write an article in UMMS's publication "Live Where You Work"

#### Follow Up

Pursuant to the community recommendations, Ellen Beth Levitt wrote an article on the outcomes of the HemAssist clinical trial and asked Joy Bramble of the Baltimore Times to publish it. We are starting with that paper since the community members attending the meeting though an African American newspaper should be targeted first.

[Redacted text block]

Attachment 10

[Redacted text block]

# Trauma doctors press for more research to save lives

by Ellen Beth Levin

Every day in the news, we hear about research advances dealing with heart disease, cancer and a variety of other health problems. But it is rare to hear about a new drug or device that can save the lives of people who suffer traumatic injury, because those advances do not occur often.

The reason why is no accident. It is very difficult to include trauma patients in the type of research that routinely leads to improvements in health care.

Most important medical developments result from careful scientific studies that include people with health problems. They hope that by participating, they might benefit by getting well and helping others with the same illness in the future.

Before trying a new, promising therapy, study participants are told of all the potential risks and they give their informed consent. But giving that advanced consent is impossible when a person is rushed unconscious to an emer-

gency room in a life-threatening condition.

"If your loved one was critically injured and the chance of survival was not good, would you want us to try an experimental drug that could save his life?" asks Thomas Scalea, M.D., physician-in-chief of the University of Maryland Shock Trauma Center.

"There have been very few major advances in trauma research in decades because without prior consent, we have been unable to conduct large studies to find out for sure whether certain treatments are better than those we currently have to offer," says Dr. Scalea.

To remedy that problem, the U.S. Department of Health and Human Services and the Food and Drug Administration have issued regulations that are designed to protect patients' rights, while also allowing an exemption to advance consent so that promising studies can get underway. The University of Maryland Shock Trauma Center participated in one of the first nationwide studies last year that

came under the new rules.

The study, called the HemAssist trial, tested a potentially life-saving drug for victims of severe traumatic injury who went into shock from significant blood loss. Like a blood transfusion, the drug carries oxygen to vital organs throughout the body. But drug could be given to anyone — regardless of blood type, saving precious time. It also has a longer shelf life than blood.

Only about 3 percent of trauma patients — the most severely injured — qualified for the study. The expected death rate for that group was about 40 percent.

However, Baxter, the drug-maker, stopped the study early, after 100 patients had been enrolled out of an expected 850 participants. The study's independent data monitoring committee found a much lower death rate — 17 percent — among the people who got a placebo, rather than the real drug. That made the 40 percent death among those receiving the actual drug look much worse.

Among the 15 patients enrolled in the study in Baltimore, there

was no significant difference in mortality between the two groups. Three people died in the placebo group and three died in the drug group. There were 14 men in the study and one woman. Nine were African-American and seven of them had violence-related injuries, mostly gunshots. The rest were injured in car crashes.

Researchers are evaluating the data to find out why there was a difference in mortality between the patient groups. Meanwhile, trauma specialists such as Dr. Scalea say their institutions would be willing to participate in future large studies of new, potentially life-saving therapies.

"We are trying to communicate with people in our local community so that they will understand what we are trying to accomplish. We want to hear their concerns and answer their questions," says Dr. Scalea. People who wish to find out more can call the University of Maryland School of Medicine's Public Affairs Office at 410-706-8519.



**WALKER AVENUE  
COOPERATIVE**

## SENIOR APARTMENTS

**Towson/Govans Area**

**88 One Bedroom Independent Living  
Apartments in a 3 Story Elevator Building**

### Requirements:

**Aged 62 or Older**

**Maximum Income:**

**One Person \$21,100, Two Persons \$24,100**

**Rent:**

**Based On 30% of Each Household's Income**

**Available Fall 1999**

**Developer: Cooperative Services, Inc.**

**National Non-Profit Consumer Cooperative**

**For Information Call**

**410-288-9624**



Beyond Housing Opportunity



### Now Accepting Applications!

The Concord Apartments offer comfortable, cheerful living areas for today's independent seniors. Residents enjoy convenience, companionship and a full range of medical support services and lifestyle amenities right on location. From \$990 a month; federal subsidies may apply.

For more information or an application, call 410-542-4111.

**Concord**  
APARTMENTS

2500 W. Belvidere Ave., Baltimore, MD 21215

An affiliate of the Leinhardt  
Geriatric Center and Hospital



### New Senior Living Community Welcomes Applications for October Move-In!

Introducing a comfortable, convenient new lifestyle choice for today's independent seniors. Comprised of 72 one-bedroom residences with full kitchens, the new Weinberg Woods is linked to the Myerberg Northwest Senior Center. Residents enjoy companionship, support, medical services and a range of lifestyle amenities.

- 24-hour emergency call response system
- Security entry & monitoring
- Recreational, social & education activities
- Social work assistance
- Shuttle transportation for shopping, etc.

Call today for an application: **410-602-8200**



3211 Clarks Lane, Balt., MD 21209



[www.lifebridgehealth.org](http://www.lifebridgehealth.org)



Weinberg Woods is an affiliate of the  
Levinthal Geriatric Center and Hospital.



### Public Notice

#### Hemoglobin Study for Severe Blood Loss Ends at R Adams Cowley Shock Trauma Center

A research study at the R Adams Cowley Shock Trauma Center and centers nationwide to evaluate a new blood substitute on patients with severe blood loss (hemorrhagic shock) due to trauma, has ended.

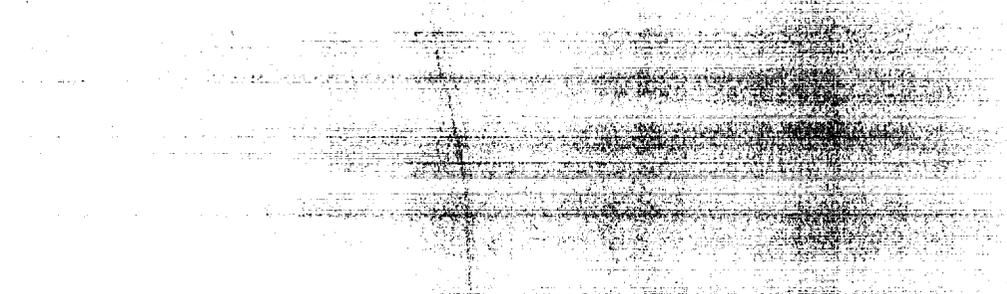
Baxter Healthcare, Inc. (makers of HemAssist/DCLHb) decided to end its US Phase III trauma trial, which had enrolled approximately 100 of its expected 850 patients, following an interim data review by an independent data monitoring committee. The committee found that, nationwide, patients in the treatment group had increased mortality compared to those in the control group. Further analysis of the data is ongoing. However, of the 15 patients enrolled in Baltimore, there was not a significant difference between the two groups.

This study was the first to implement the new US Food and Drug Administration (FDA) set of guidelines for emergency research, in which patients who may benefit from an investigational therapy are unable to give permission to participate due to the life-threatening extent of their injuries, and the immediate need for medical attention. The FDA requires public notification of the outcome of these studies, as well as reasons for study discontinuation.

To communicate with us on this topic, please contact:

David R. Gens  
R Adams Cowley Shock Trauma Center • Program of Trauma  
22 S. Greene Street • Baltimore, MD 21201  
410-328-3055

For further information about rules regulating clinical research, contact the Institutional Review Board (IRB) at 410-706-5037.



-----Original Message-----

From: Tinkoff.G@christianacare.org [SMTP:Tinkoff.G@christianacare.org]  
Wednesday, April 15, 1998 3:38 PM  
Love.K; Katz.C; Townsley.J; Landon.B; Reese.C; Fulda.G; Huss.D@christianacare.org; Jones.L; Ballard.K; Bartley.M; Smick.J;  
Fagraeus.L; Abel.R; Hays.J; Whitney.L; Castellano.J; Bouzoukis.J; O'Connor.R@christianacare.org; Johnson.S; Madden.J;  
Jasani.N; McGraw.P; Rhodes.M@christianacare.org  
Subject: Update

As you may already have been made aware, Baxter Healthcare Corp. has ended its US Phase II trauma trial investigating the efficacy of DCLHb in which we were participating. They decided to stop the trial, which had enrolled approximately 100 of its expected 850 participants, following an interim data review by the trial's independent data monitoring committee. The committee found that in patients in the treatment group had significantly increased mortality to those in the control group. Although the injury severity of the two groups were dissimilar (DCLHb > Control), and a definite cause and effect relationship could not be found between this increased mortality and DCLHb, this finding does make achieving the primary endpoint of reduction in 28 day mortality impossible. Further analysis of the data is ongoing.

We would personally like to thank all of you who participated in this study at our institution. We have reviewed all six of our enrollments and none had any adverse event attributable to DCLHb. We will continue to inform you as more information regarding this study and the other DCLHb trials are made available.

## Findings from DCLHb Hemorrhagic Shock Study

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).

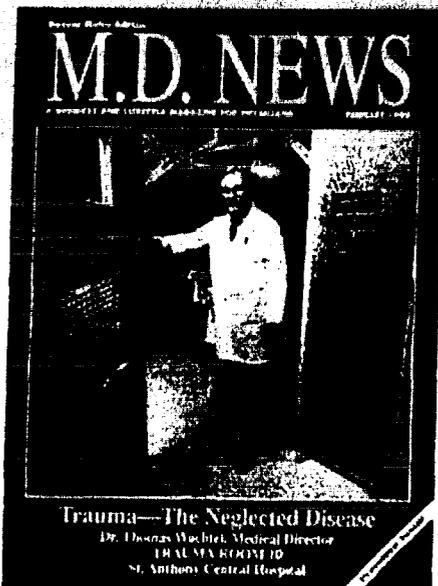
The independent data monitoring committee found that patients in the treatment group had significantly increased mortality compared to those in the control group. As a result, the company decided to stop the study early. The company is continuing to analyze the data from the study and will publish a full report in the future. The hemoglobin therapeutics division of Baxter has relocated to Boulder, Colorado, and is pursuing a new avenue of recombinant hemoglobin for resuscitation of patients with shock.

If you would like additional information about this study, you may contact Thomas L. Wachtel, MD, principal investigator at 303-629-4222 or go to the website (<http://dclhb.er.uic.edu>).

## 23° Obs

The Premier Issue of *M.D. News* was unveiled in February. The lead article for the first issue was "Trauma - The Neglected Disease."

Our very own Dr. Thomas Wachtel, Medical Director of the Trauma Service was featured on the cover and throughout the article. Other "stars" of the article include Dr. Adam Deutchman, members of the nursing staff and Flight For Life. Kudos to everyone who helps make Centura Health a leader in trauma care.



An abstract of the Ski Helmet Program done in conjunction with InterMountain Neurosurgery, Christy Sports, and Winter Park Resort was submitted to the Trauma Nurses Society and was accepted for poster display at the Trauma & Critical Care conference in Las Vegas, Nevada, on March 23. Good work to everyone involved in this project.

The 1999 bike helmet program is underway, and the Injury Prevention Coordinator at St. Anthony Central has been flooded with helmet requests. A total of 1,800 helmets will be donated this season to over 14 separate organizations.

## Just For Laughs

A mother was reading a book about animals to her 3-year-old daughter:  
 Mother: "What does the cow say?"  
 Child: "Moouoo!"  
 Mother: "Great! What does the cat say?"  
 Child: "Meow."  
 Mother: "Oh, you're so smart! What does the frog say?"  
 And this wide-eyed little three-year-old looked up at her mother and replied, "Bud."

## Calendar of Events

Please refer to the following list of conferences, meetings, & presentations in March, April, and May.

### Trauma Research Alliance Committee

Dates:

- 03/18/99 at 0730-0830
- 04/01/99 at 0730-0830
- 04/15/99 at 0730-0830
- 05/06/99 at 0730-0830\*
- 05/20/99 at 0730-0830

Location:

Auditorium A (\* OB Conf Rm)  
 St. Anthony Central

### Trauma M&M

The purpose of M&M is to identify and track issues that may affect patient care in a pro-active, confidential setting. These issues include system issues, pre-hospital events, teaching opportunities, etc.

Please contact the Trauma Service office if you would like to present a patient in this forum.

Dates:

- 03/19/99 at 0700-0800
- 03/26/99 at 0700-0800
- 04/02/99 at 0700-0800
- 04/09/99 at 0700-0800
- 04/16/99 at 0700-0800
- 04/23/99 at 0700-0800
- 04/30/99 at 0700-0800
- 05/07/99 at 0700-0800
- 05/14/99 at 0700-0800
- 05/21/99 at 0700-0800
- 05/28/99 at 1700-0800

Location:

ED Conference Room  
 St. Anthony Central

### Trauma Multidisciplinary Committee (Formerly Trauma Surgeon Division Meeting)

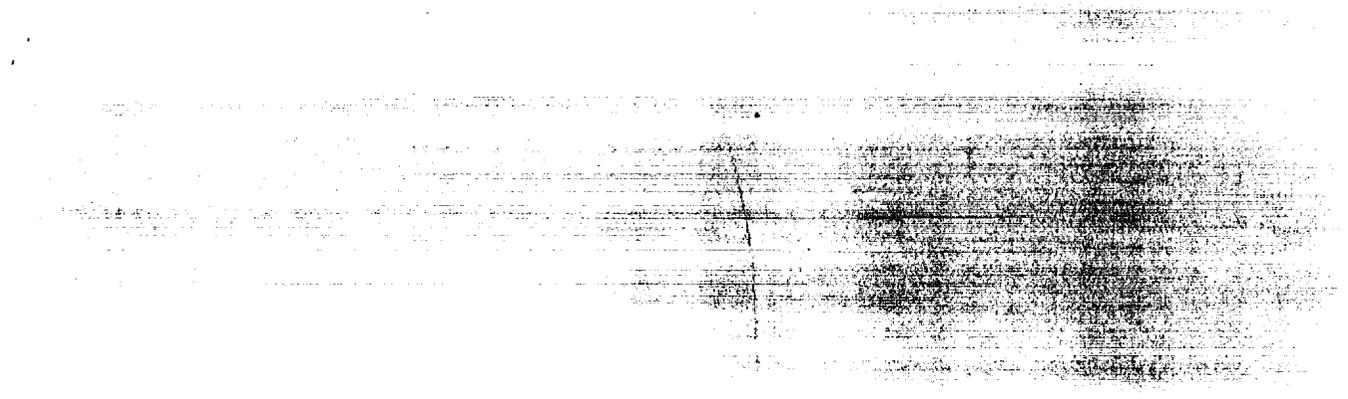
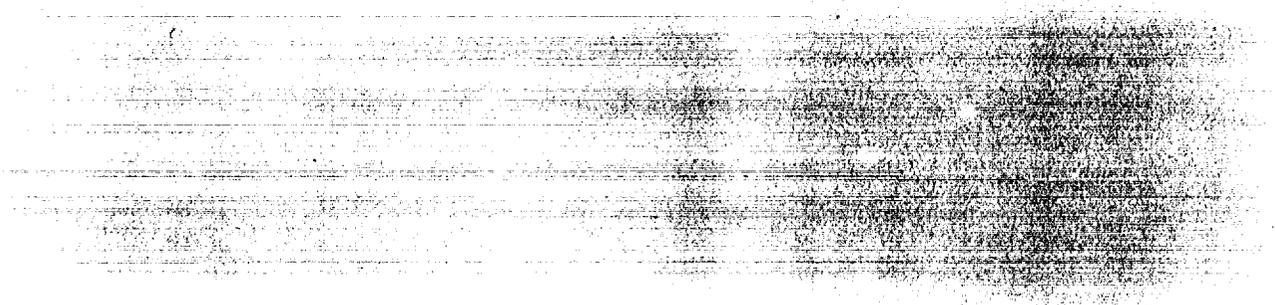
Dates:

- 04/05/99 at 1800-1900
- 05/07/99 at 1800-1900

Location:

Birch Room  
 St. Anthony Central

If you have questions about any of the events listed above, or you would like an event added, please contact the Trauma Service Office at 303-629-4222.



# WASHINGTON

## DCLHB HOSPITAL TERMINATION DISCLOSURE WASHINGTON HOSPITAL CENTER

### **Summary of Procedures from IRB Guidelines:**

*All methods of disclosure were discussed and agreed upon by the IRB.*

#### **Community/ Public:**

Held informal meeting with key members of the study within the hospital: PI, Co PI, IRB members, Study Coordinator.

Held meeting with Community Relations Council

10 members present (see Q&A from meeting) which included a mailing of the results of the trial to be distributed to all members (see letter).

#### **Media/ Media Coverage**

##### ***Public Notices***

Public Notices were sent to the four (4) major newspapers in Washington DC (see the newspaper articles enclosed). Included in the notice was contact information to the PI, IRB chairman, and Medlantic Research Institute President. Also included were national and local results/demographics

Had a dedicated line available in our study office for incoming calls and mailings related to the public notices for a 7 day period.

**Results:** Received one call from a male interested in pursuing the informed consent issue for his thesis. He did not choose to elaborate.

##### ***Press Release with back ground information forwarded to local press:***

In collaboration with our director of marketing sent out a press release to all network and local stations during a week long period

**Results:** No news media picked up the story.

##### ***Utilized minority publications:***

See public notices. 2 of the local newspapers were minority publications. (see enclosed).

**Results:** No feedback calls or mailings from the public.

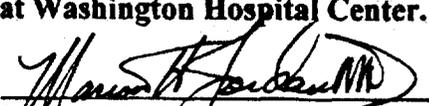
#### **Dissemination of results of the Study Including Demographics to Study Researches.**

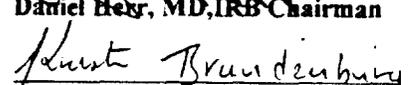
Mailing, informal meetings and direct personal contact via the PI and Study coordinator was completed within the first month following the study closure.

Washington Hospital Newspaper: *The CenterLine* published the results of the study. (see enclosed).

**Post Study Community Disclosure is completed at Washington Hospital Center.**

  
Daniel Herz, MD, IRB Chairman

  
Marion Jordan, MD, PI

  
Kristin Brandenburg, RN, Study Coordinator

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

# WASHINGTON HOSPITAL CENTER

## Community Relations Council Meeting Agenda

Thursday, February 25, 1999  
5:30 p.m.

Cancer Institute Auditorium

I. Call to Order

II. Update on Clinical Trial  
on a New Blood Substitute Product

Dr. Dennis Wang  
Assistant Director, Trauma

*Washington Hospital Center recently conducted a clinical trial on a new blood substitute product that is expected to revolutionize traditional trauma care. Staff will provide an update on the status of the clinical trial.*

III. Discussion of Organization Structure  
for the Community Relations Council

Clarence Brewton  
Ann Chisholm

*Washington Hospital Center's Board of Directors was recently reconstituted and organized after the merger. As a result, the organizational structure of other Hospital Center committees and advisory bodies has been reviewed. Toward this end, it is recommended that Community Relations Council structure be more formalized with board terms to maximize community input in accordance with other advisory groups.*

IV. Update on MedStar Health  
Discussions with Georgetown Hospital

Clarence Brewton

*MedStar Health is currently involved in discussions with Georgetown Hospital regarding a potential partnership.*

V. New Business

VI. Old Business

VII. Adjournment

Dinner will be served.

110 IRVING STREET, NW  
WASHINGTON, DC 20010-2975



## **DCLHb Termination Meeting**

### **WHC Community Relations Council**

**February 25, 1999 at 5:30 PM.**

The meeting with the WHC Community Relations Council was scheduled for February 25, 1999 and was attended by 7 Board members, the trauma research coordinator for the trial, Kristin Brandenburg and the Principle Investigator and IRB Member, Dr. Dennis Wang.

The meeting was opened at 5:30 PM and Dr. Wang and Kristin were introduced by Ann Chisholm, Director of Community Relations.

Kristin Brandenburg, gave out the DCLHb Question and Answer Information Sheet (see enclosed sheet) previously approved by the WHC IRB for distribution. She reiterated the purpose of the DCLHb trial and recapped the meeting and the information exchanged during the initiation phase of the trial.

Dr. Wang summarized the results and conclusion of the trial and introduced the IRB contribution to this trial.

#### **Questions from the Council Included:**

**Q. Why did the FDA approve this study?**

R. The FDA agreed the product could be beneficial to the trauma population who were seriously injured. Also, the non-consent process is approved by the FDA.

**Q. Was the 30 minute window a problem during the Study?**

R. Yes. That was the time allowed by the FDA for family or patient if he/ she was able to consent, and the amount of time DCLHb would be most therapeutic.

**Q. Why is this a non consent study?**

R. The product needed to be given in the first 30 minutes as a potential life saving measure.

**Q. Do you get consent for other emergency procedures?**

R. Most of the other emergency procedures are covered under the non consent clause for emergency procedures in the Washington Hospital center. A majority of those patients were unable to provide informed consent due to their injuries, mental status, or medication administered.

**Q. One of your enrolled patients received product and died but do you feel the patient was at high risk of dying anyway?**

A. Yes. This patient had severe injuries and was at high risk of dying.

Q. **Is the study closed in Europe?**

R. Yes. The study is also closed in Europe.

Q. **Are any other studies with this product going on at present?**

R. No. The product has been discontinued in all countries at all medical sites.

Q. **Why did Baxter terminate studies on this product and are there similar Products in the works?**

R. Baxter Healthcare did not provide a reason for the termination of the product. Speculation is that the failure of this particular study may have decreased its chances for approval by the FDA in the future for other indications. There are three other hemoglobin substitutes in various phases of clinical trial at this point.

The coordinator and PI concluded with an outline of the public disclosure agenda and gratitude for the Council's support.

 4/29/88



# FACT SHEET

## DCLHb Public Disclosure Termination

The Washington Hospital Center MedSTAR Unit was selected to be one of 20 centers, from February, 1997 until January, 1998 to evaluate a product for treating patients with severe blood loss. The product, Diaspirin Cross Linked Hemoglobin (DCLHb), developed by Baxter Healthcare, was used for those patients with severe blood loss. The Federal Food and Drug Administration (FDA) authorized this trial, however as many patients are unable to sign a consent form due to their blood loss, the FDA requested public disclosure at the beginning and end of the trial. The purpose for this notice is to give information to you regarding closure of the trial and to address any questions.

### **Q. What was DCLHb?**

A. DCLHb, made from human red blood cells, filtered, and heated so as to reduce infectious viruses as hepatitis and AIDS, was stored in the MedSTAR unit for easy access and given immediately to patients with life threatening trauma.

### **Q. How many patients were enrolled?**

A. Three patients were enrolled from Washington Hospital Center and a total of 98 patients from the 20 hospitals. The product was administered through an intravenous line to patients who fit entry criteria. The criteria were 18 years or older, evidence of severe bleeding and lack of tissue oxygenation. The product was given within 30 minutes of arriving at the hospital.

### **Q. What were the endpoints of this trial?**

A. Reduce the risk of death and or complications.

### **Q. What were the results of this trial?**

A. The results from collecting the data showed the following:

- a.) 84% of all patients whether they received the product or not died because they were admitted with severe trauma.
- b.) The patients who received DCLHb for their treatment did not do any better. They had a higher death rate and a higher risk of complications than patients who received standard of care.
- c.) In both treatment groups the most frequent causes of death were hemorrhage, cardiac arrest and multi-organ failure.

### **In summary:**

The usefulness of DCLHb in the treatment of severe traumatic hemorrhagic shock could not be demonstrated from this data. A higher mortality (death) rate actually occurred in patients receiving DCLHb; however, 96% of these deaths in the DCLHb group were predicted and not unexpected.

### **Q. How do I obtain more information or where do I direct my questions?**

A. You are encouraged to contact Washington Hospital Trauma Research Team at 110 Irving Street, N. W., Suite 4B39, Washington, D. C. 20010 or phone 202-877-6424; Fax 202-877-3173. You may also contact Medlantic Research Institute, Office of Research Programs, Barbara Howard, Ph.D., President, 108 Irving Street, N. W., Washington, D. C. 20010 or phone 202-877-6536, Fax 202-877-3209.

**IRB APPROVED**  
**DATE: FEB 24 1999**

[REDACTED]

[REDACTED]

[REDACTED]

to get what you want.

Pagans who practice the earth-friendly religion of Wicca call the day Ostara. Many celebrate by planting and by putting out traditional fertility symbols such as eggs and bunnies.

"It's always been a day for people who are tightly bound to the earth," observes Candice Wilson, coordinator of the Arlington Planetarium, where a series of equinox-inspired concerts featuring naturalist and musician Joe Ken-

Photo by Mary P. D'Amico/The Washington Times  
Spring is almost here and Joe Castro (right), 26, and his niece Traci Vasquez, 11, from Texas, enjoy a sunny day in Washington yesterday.

neddy Jr. are planned for today and Sunday.

Miss Wilson says that contrary to popular thought, the equinox does not bring 12 hours of sunlight and 12 hours of darkness.

"The only place that would be true would be at the Tropic of Cancer, where the sun is directly overhead," she says.

Mr. Chester bashes another

equinox myth, saying eggs do not only balance on end on this day.

"Anyone with steady hands can do this at any time of the year," he said.

"There's a lot of hocus-pocus that surrounds this day, which has ancient traditional roots. But it's basically folklore," he notes. "For most people, it's an excuse to put winter behind them."

Wash Times *5/5 March 20* **Public Notice**

The Washington Hospital Center MedSTAR Unit was selected to be one of 20 centers, from February, 1997 until January, 1998 to evaluate a product for treating patients with severe blood loss. The product, Diaspirin Cross Linked Hemoglobin (DCLHb), developed by Baxter Healthcare, was used for those patients with severe blood loss. The Federal Food and Drug Administration (FDA) authorized the trial, however as many patients are unable to sign a consent form due to their blood loss, the FDA requested public disclosure at the beginning and end of the trial. The purpose for this notice is to give information to you regarding closure of the trial and to address any questions.

**Q. What was DCLHb?**

**A.** DCLHb, made from human red blood cells, filtered, and heated so as to reduce infectious viruses as hepatitis and AIDS, was stored in the MedSTAR unit for easy access and given immediately to patients with life threatening trauma.

**Q. How many patients were enrolled?**

**A.** Three patients were enrolled from Washington Hospital Center and a total of 98 patients from the 20 hospitals. The product was administered through an intravenous line to patients who fit entry criteria. The criteria were 18 years or older, evidence of severe bleeding and lack of tissue oxygenation. The product was given within 30 minutes of arriving to the hospital.

**Q. What were the endpoints of this trial?**

**A.** Reduce the risk of death and/or complications.

**Q. What were the results of this trial?**

**A.** The results from collecting the data showed the following:

a.) 84% of all patients whether they received the product or not died because they were admitted with severe trauma.

b.) The patients who received DCLHb for their treatment did not do any better. They had a higher death rate and a higher risk of complications than patients who received standard of care.

c.) In both treatment groups the most frequent causes of death were hemorrhage, cardiac arrest and multi-organ failure.

**In summary:**

The usefulness of DCLHb in the treatment of severe traumatic hemorrhagic shock could not be demonstrated from this data. A higher mortality (death) rate actually occurred in patients receiving DCLHb; however, 96% of these deaths in the DCLHb group were predicted and not unexpected.

**Q. How do I obtain more information or where do I direct my questions?**

**A.** You are encouraged to contact Washington Hospital Trauma Research Team at 110 Irving Street, N.W., Suite 4B39, Washington, D.C. 20010 or phone 202-877-6424; Fax 202-877-3173. You may also contact Medlantic Research Institute, Office of Research Programs, Barbara Howard, Ph.D., President, 108 Irving Street, N.W., Washington, D.C. 20010 or phone 202-877-6536, Fax 202-877-3209.

**Wall**  
**FR**  
1 Yr  
SALE  
\$6.95 sq. yd.  
Big, real \$12.90 sq. yd.  
Available in many finishes  
1 year stain and wear  
warranty

**Experi**  
Starts Beautiful  
Stays Beautiful

**Oriental**  
**Design Rugs**  
8x11 \$89  
6x9 \$59  
4x6 \$39  
2x4 \$19

**VIRGINIA**  
10511 Lee Hwy. (Across from Pizzeria)  
11011 Lee Hwy. (Across from Pizzeria)

[Redacted text block]

[Redacted text block]

[Redacted text block]

## Washington Hospital Center MedSTAR Unit Completes Drug Trial

The Washington Hospital Center MedSTAR Unit was selected to be one of 20 centers, from February 1997 until January 1998 to evaluate a product for treating patients with severe blood loss. The product, Diaspirin Cross Linked Hemoglobin (DCLHb), developed by Baxter Healthcare, was used for those patients with severe blood loss. The Federal Food and Drug Administration (FDA) authorized this trial. Since many patients were unable to sign a consent form due to their blood loss, the FDA requested public disclosure at the beginning and end of the trial. The purpose for this public notice is to give information regarding closure of the trial and to address any questions.

### Q. What was DCLHb?

A. DCLHb is made from human red blood cells that have been filtered and heated so as to reduce infectious viruses as hepatitis and AIDS. DCLHb was stored in the MedSTAR unit for easy access, and given immediately to patients with life-threatening trauma.

### Q. How many patients were enrolled?

A. Three patients were enrolled from Washington Hospital Center and a total of 98 patients from the 20 hospitals. The product was administered through an intravenous line to patients who fit entry criteria. Patients had to be 18 years or older, and have evidence of severe bleeding and lack of tissue oxygenation. The product was given within 30 minutes of arriving at the hospital.

### Q. What were the endpoints of this trial?

A. The goal was to reduce the risk of death and or complications.

### Q. What were the results of this trial?

- A. The results from collecting the data showed the following:
- Eighty-four percent of all patients, whether they received the product or not, died because they were admitted with severe trauma.
  - The patients who received DCLHb for their treatment did not do any better than those who did not receive DCLHb. They had a higher death rate and a higher risk of complications than patients who received standard care.
  - In both treatment groups the most frequent causes of death were hemorrhage, cardiac arrest and multi-organ failure.

### In summary:

The usefulness of DCLHb in the treatment of severe, traumatic, hemorrhagic shock could not be demonstrated from this data. A higher mortality (death) rate actually occurred in patients receiving DCLHb; however, 96% of these deaths in the DCLHb group were predicted and not unexpected.

### Q. How do I obtain more information or where do I direct my questions?

A. You are encouraged to contact the Washington Hospital Trauma Research Team at 110 Irving Street, NW, Suite 4B39, Washington, DC 20010; phone (202) 877-6424 or fax (202) 877-3173. You may also contact Mediantic Research Institute, Office of Research Programs, Barbara Howard, PhD, President, 108 Irving Street, NW, Washington, DC 20010; phone (202) 877-6536 or fax (202) 877-3209. □

**DC Mayor Anthony Williams Shares His Vision  
for the District of Columbia**

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

5-15-99

## 015 Miscellaneous Notices

Memorial Medical Center's Participation in the "EFFICACY TRIAL of Diaspirin Cross-Linked Hemoglobin (DCLHb™) in the Treatment of Severe Traumatic Hemorrhagic Shock." (Information regarding public disclosure for "deferred." On Monday, September 1, 1997, the Baxter Pharmaceutical's study listed above, commonly known as "the Diaspirin study," was inaugurated in the Emergency Department of Memorial Medical Center. This Labor Day kick-off had

been preceded by an intensive and unprecedented marketing campaign by Trauma Service professionals, Research Department personnel, and Institutional Review Board members. The great amounts of work presaging this study were mandated because of the special nature of this particular investigative trial.

The first step in enrolling a patient in the usual Clinical Drug Study is to get the patient or the legally responsible next of kin or care giver to sign a comprehensive "Informed Consent". What made Diaspirin special was the fact that due to intensive activity literally counted in seconds which may mean life and death for acutely injured trauma victim, the informed consent for this study was "deferred," that is "put off" until the first appropriate moment AFTER the initial life-saving hour was over. In order to get the most effect from Diaspirin, the infusion of the drug had to start within thirty minutes of the patient "rolling in the door". Deferred Consent was the only method which would allow these critical moments to be best utilized, without seeking family who might not arrive at the ED for hours, family which might be in another state, or penalizing patients who had no information with them concerning responsible parties to notify.

After intensive input which stretched back into the early nineties, the Federal Food and Drug Administration (FDA) agreed to allow this study to be implemented with consent being obtained after surgery or the intensive care admission had been accomplished. However, this did not mean that any slackness of regulation or easing of vigilant administration was allowed in the study. Conversely, more pre-planning and "public disclosure" was required. This public disclosure was comprised of press releases, TV "spots", and preparation for actually meeting with community groups whose members might have been impacted by the study in the area.

Memorial Medical Center screened many, many patients and enrolled five who exactly fitted the entry criteria. One patient was a "control", receiving the normal saline inert comparator, and four received Diaspirin. Four of the patients ultimately expired, and one survived. The data gathered was submitted to Baxter Pharmaceutical, along with the collated information from the other nineteen U.S. study centers where the trial was being implemented.

Baxter's statistical personnel identified patients who were at high risk for mortality at time of entry into the study. They identified fifteen factors which put patients at risk for death from these injuries statistically. If the (individual) patient had four or more of these factors, they died, without exception. Probability of survival by these factors predicted ninety six (96) percent chance of mortality, while eighty eight (88) percent of the control or placebo group were expected to survive. Patients receiving study drug had a higher number of marker factors, putting them in the very high risk mortality group. The patients actually randomly assigned to receive active study drug statistically proved to be more severely injured, not only at MMC but also in all centers nationwide. The most frequent causes of death of these patients were severe hemorrhage, multi-system organ failure and cardiac arrest. Memorial Medical Center results were consistent with national trends. By March of 1998, it was apparent that expected survival outcomes were not being attained amongst the patients receiving study drug. In a voluntary, unilateral measure, Baxter Pharmaceuticals decided to stop the study nationwide.

However, the work on Diaspirin is not yet over. Due to the special requirements for a "deferred consent" study, MMC and the other sites are now requested and required to make a public statement regarding the outcomes of the Diaspirin trial and the reasons for its cessation.

Research goes on at Baxter and other pharmaceutical companies, large and small, for new drugs which will give the severely traumatized patient a better chance of survival. Memorial Medical Center continues to be in the forefront of this and other important research, in its efforts to foster and maintain good medical information to the public... a key to health promotion everywhere.



Dear :

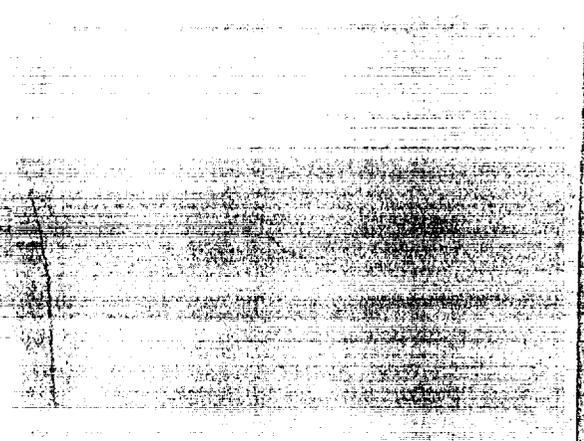
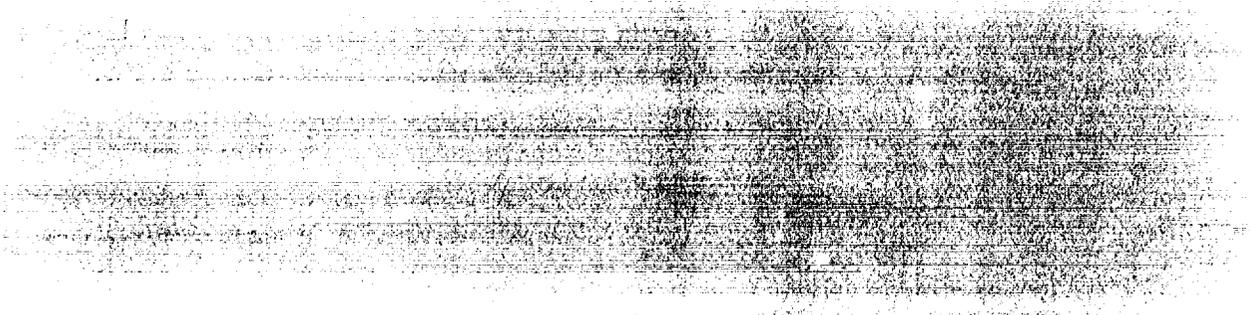
On \_\_\_\_\_, (you or one of your family members) was admitted to Memorial Medical Center Emergency Department in the care of the medical center's Trauma Care Services. Due to the severe type of injuries that (you, your \_\_\_\_\_) came in with, it was necessary to do a great many things in a very short period of time. Because of the severe bleeding, one of the things which we did within the first hour was enter (you, your \_\_\_\_\_) in a special study for patients with large blood loss. We talked to you afterwards and explained why we used the special blood product first and got permission later.

When the study closed at Memorial Medical Center, the company who makes the special blood product, Baxter Pharmaceuticals, asked us to get in touch with all study participants or their families to let them know that the study is no longer going on in the Savannah area and extend their thanks and ours for (you, your \_\_\_\_\_'s) being in the study.

The study drug did not prove to be as effective as the company and Memorial Medical Center had originally hoped. Thank you again for (you, your \_\_\_\_\_'s) participation in this important study, which is the only way that new medications can be approved.

If you have any questions regarding the study, contact Dr. Richard Leighton, Chairman of the Institutional Review Board of Memorial Medical Center, between 8:30 A.M. and 5:00P.M., Monday through Friday, at (912) 350-8707.

Thanks again!



# Drug Trial Testing Stopped at Parkland Trauma Center

In the spring of 1997 Parkland Health & Hospital System's Trauma Department joined several other health care institutions in testing a new drug, DCLHb™, which promised to help save the lives of critically injured trauma patients. DCLHb™, developed by Baxter Healthcare, Inc., is a blood product made from expired human red blood cells suspended in a solution. Because of the emergent conditions under which this product is given, the U.S. Food and Drug Administration permitted its administration without informed consent. Public notices were issued at that time. The study has since been terminated by the sponsor, Baxter Healthcare, Inc. This notice attempts to answer questions about why the drug trial was stopped.

**Q:** How many patients were enrolled in the trial? How many hospitals were involved?

**A:** Approximately 100 patients were enrolled at 17 hospitals in the United States; about half of the participants received DCLHb™. Three patients were enrolled at Parkland; only one patient received the study drug.

**Q:** Why was the study stopped?

**A:** It is not unusual for complex clinical trials that study critically ill patients to be stopped. Baxter collaborated with many trauma investigators on this consensus protocol. When there is even the slightest suspicion that patient safety may be compromised, the prudent and ethical action is to stop the trial.

**Q:** Did DCLHb™'s use contribute to patients' death?

**A:** No. Patients eligible for the study were victims of severe trauma, such as knife and gunshot wounds, motor vehicle accidents, and were suffering from severe shock due to blood loss. Those patients who were involved in the trial were among the most severely injured of all trauma patients. The mortality rate in this injury group is high, approximately 40 percent. Each person who participated in the study received the best standard emergency care, including blood transfusions, resuscitative fluids, and surgery, as was required. The death of one patient who received the study drug at Parkland was not due to the product, but to the devastating injury sustained.

**Q:** Were patients who received DCLHb™ put at unnecessary risk?

**A:** No. All patients received the best standard emergency care available. DCLHb™ was given as an add-on therapy to all other standard treatments. Nothing was withheld from any patient. The data monitoring committee and the interim analysis were in place to ensure that patients were not put at unnecessary or avoidable risk. Patient enrollment into the study was stopped as soon as a recommendation was received by the committee. The Data Monitoring Committee acted with the highest standards, and it is clear that this approach served the patients in the study and the protocol very well. In addition, prior to the start of the study, the protocol was reviewed by the FDA and the Institutional Review Board (IRB) of each participating center. The IRB consulted with their community and received input from the community as to whether the trial should be conducted.

**Q:** How many patients, if any, gave consent?

**A:** Patients eligible for this study were in severe shock from blood loss, and consequently most could not give consent for themselves. Nationwide, only two patients were able to give consent; none of the three patients at Parkland were able to give consent. Nationwide consent was obtained from family members or legally authorized representatives in several instances. As was expected in this patient population, in most cases it was not feasible to obtain consent prior to treatment. Parkland had informed consent documents approved by their IRB for cases when it was possible to obtain consent. In addition, Parkland had procedures in place to attempt to locate family and obtain consent prior to patient enrollment if feasible. Procedures were also in place to notify the patient's family or legal representative and the patient as soon as possible after enrollment to inform them of the patient's inclusion in the study and to obtain consent for further participation. These procedures were followed in all cases at Parkland Health & Hospital System.

To provide comments, or for more information about the study, please call 214 648-9524



Parkland Health & Hospital System  
5201 Harry Hines Boulevard Dallas, Texas 75235

DALLAS Morning News May 20, 1999

20-99  
DMH

# Se Terminan las Pruebas de una Droga en Parkland Trauma Center

En la primavera de 1997 Parkland Health & Hospital's Trauma Department se unió a otras instituciones del cuidado de la salud para hacer pruebas de una droga nueva, DCLHb™, que prometía ayudar a salvar las vidas de los pacientes de trauma críticamente lesionados. DCLHb™ fue desarrollada por Baxter Healthcare, Inc. y es un producto de la sangre hecho de células sanguíneas humanas ya expiradas suspendidas en una solución.

Debido a las condiciones emergentes bajo las cuales se administra este producto, la U.S. Food and Drug Administration permitió su administración sin una autorización informada. Avisos públicos se mandaron en ese tiempo. El estudio a sido terminado por el patrocinador, Baxter Healthcare, Inc. Este aviso intenta contestar las preguntas sobre el porque se dejaron de hacer las pruebas de la droga.

**Q:** ¿Cuántos pacientes se registraron en la prueba?  
¿Cuántos hospitales estuvieron incluidos?

**A:** Aproximadamente se registraron 100 pacientes en 17 hospitales de los Estados Unidos; cerca de la mitad de los participantes recibieron DCLHb™. Tres pacientes estuvieron registrados en Parkland; solamente un paciente recibió la droga del estudio.

**Q:** ¿Porqué se terminó el estudio?

**A:** No es anormal para las pruebas clínicas complejas que estudian pacientes críticamente enfermos que terminen el estudio. Baxter colaboró con muchos investigadores de trauma en este protocolo de consentimiento unánime. Cuando existe la más mínima sospecha que la seguridad del paciente puede estar comprometida, la acción ética y prudente es terminar la prueba.

**Q:** ¿Contribuyó a la muerte de los pacientes el uso de DCLHb™?

**A:** No, los pacientes elegibles para el estudio eran víctima de un trauma severo, como heridas de cuchillo, de armas de fuego, accidentes de vehículos de motor y estaban sufriendo un severo estado de choque debido a la pérdida de sangre. Los pacientes que participaron en las pruebas estaban entre los lesionados más severamente de todos los pacientes de trauma. El índice de mortalidad de este grupo de lesionados es alto, aproximadamente 40%. Cada persona que participó en el estudio recibió el mejor cuidado de emergencia, incluyendo transfusiones de sangre, fluidos de resucitación y cirugía, como fue requerido. La muerte de uno de los pacientes que recibió la droga del estudio en Parkland no se debió al producto, sino a las lesiones devastadoras que recibió.

**Q:** ¿Estuvieron en un riesgo innecesario los pacientes que recibieron DCLHb™?

**A:** No, todos los pacientes recibieron el mejor cuidado de emergencia disponible. DCLHb™ se les dió como una terapia que se agrega a otros tratamientos. No se le negó nada a ningún paciente. El comité de vigilancia de datos y de análisis interino estuvieron en su lugar para asegurar que los pacientes no estuvieran en un riesgo innecesario o que se pudiera evitar. Se detuvo el registro de pacientes para el estudio tan pronto como se recibió la recomendación del comité. El Comité de Vigilancia de Datos actuó con la ética más alta, y esto les sirvió muy bien a los pacientes en el estudio y al protocolo. Además, antes de empezar el estudio, el protocolo fue revisado por el FDA y el Institutional Review Board (IRB) de cada centro participante. El IRB consultó con su comunidad y recibió opiniones de la comunidad si se deberían hacer la pruebas.

**Q:** ¿Cuántos pacientes, si hubo algunos, dieron su autorización?

**A:** Los pacientes elegibles para este estudio estaban en un estado de choque severo por la pérdida de sangre, y por consiguiente la mayoría no podía dar su autorización por ellos mismos. En toda la nación, solamente dos pacientes pudieron dar su autorización; ninguno de los tres pacientes de Parkland pudieron dar su autorización. La autorización en toda la nación fue obtenida de los miembros de la familia o de los representantes legalmente autorizados en varios casos. Como se esperaba en esta clase de pacientes, en la mayoría de los casos no era factible obtener la autorización antes del tratamiento. Parkland tenía documentos de autorización informada aprobada por su IRB para los casos en que fuera posible obtener la autorización. Además, Parkland tenía procedimientos listos con el intento de localizar a la familia y obtener la autorización antes del registro del paciente si hubiera sido posible. Los procedimientos también estuvieron preparados para notificar a la familia del paciente o a su representante legal y al paciente tan pronto como fuera posible después de la registración para informarles de la inclusión del paciente en el estudio y obtener la autorización para una participación futura. Estos procedimientos tuvieron seguimiento en todos los casos en Parkland Health & Hospital System.

Para ofrecer comentarios o para información sobre el estudio, por favor llame al 214 648-9524



Parkland Health & Hospital System  
5201 Harry Hines Boulevard Dallas, Texas 75235

El Sol de Texas May 26, 1999

## Novo Nordisk invests in academic diabetes research

Britain's National Health Service (NHS) is teaming up with a university and a pharmaceutical company to build a \$16 million center for research and treatment in diabetes and other hormonal and metabolic diseases. The partners hope that by bringing clinicians, academics and patients under one roof, they will ensure that scientists ask the right questions, and that clinicians both influence the research and act promptly on its findings.

The Oxford Centre for Diabetes, Endocrinology and Metabolism, which will open by 2001, brings together six of Oxford University's biomedical and clinical research teams working in diabetes and other hormone-related conditions, such as osteoporosis. The center expects to handle some 15,000 outpatient contacts per year. It will employ around 150 researchers and clinicians, and will offer teaching and specialist training. The diabetes research will focus on areas in which Oxford is already strong, such as the genetics of the disease, the mechanisms of  $\beta$ -cell failure, and large-scale clinical trials of treatments.

The university's diabetes researchers have collaborated with the pharmaceutical company Novo Nordisk, Europe's largest supplier of insulin, for 20 years, and it was they who approached the company to help fund the proposed center. But despite investing 40 percent of the total cost of setting up the center, Novo Nordisk's involvement will be relatively low-profile: it will not have its name on the center, it will have no automatic rights to discoveries that may emerge, and intellectual property rights will remain with the principal investigators.

What Novo Nordisk is getting for its money, says David Matthews, previously director of diabetes and endocrinology at Oxford's Radcliffe Infirmary and now the center's chairman, is a close association with a world-class research effort and the University of Oxford's credentials. There will be collaboration so that each partner can influence the others' ideas, but if the company wants to guarantee specific rights to any discoveries, it will have to commission a project just like any other client.

As Novo Nordisk already has large commercial research bases for identifying ther-

apeutic molecules, it is understandable that its expectations from Oxford are different. However, some observers believe that Novo Nordisk's management may not be unanimous in backing such an open-ended commitment. One commentator suggested that there was "a battle within the organization" between the company's senior, traditionally philanthropic leadership and middle managers that want targets and hard returns on investment. But publicly at least, the company insists it favors the move whole-heartedly and sees no conflict between what it calls "good neighbourliness" and its long-term business strategy.

"We see it as a natural development," says Stig Pramming, senior medical director at Novo Nordisk's Danish headquarters. Oxford's reputation for diabetes research makes it an obvious choice within Europe, he says. "We believe we are the best diabetes company in the world...if we are going to be competitive in the future we need to stay with the best and pick up the best ideas as fast as possible."



John Bell

The biggest financial backer, however, is the NHS itself, which is putting in 42 percent of the cost of the center. Health service managers increasingly need data on the cost-effectiveness of treatments and care regimens, and they will be looking to the center for the kind of research that informs health policy—known in the trade as "outcomes data." Pramming thinks the NHS should be credited with "being visionary and taking an international view" for its

participation in the center.

The mastermind behind the center is Nuffield Professor of Clinical Medicine at Oxford John Bell, who is also chairman of the partnership board. Bell hopes it will stimulate "a renaissance of clinically based, bedside research, fuelled by the molecular revolution." He says the reductionist approach of identifying genes and molecules implicated in human disease has worked "fantastically well," but that it is now time to add translational research to the effort. "It's great to work with a knock-out mouse," he says, "but if you have a human with

exactly that gene defect down the hall, it's interesting to know what the phenotype of that disease is."

Shortly after the initiative was announced, Novo Nordisk's largest shareholder, the Novo Nordisk Foundation, announced separately that it was giving \$16 million to a consortium of Scandinavian researchers to investigate the vascular biology of diabetes complications such as nephropathy and blindness. The Foundation is separate from the company, although the company's board of directors are members of the foundation's governing body.

Ironically, although the Oxford center is emphasizing the importance of putting clinicians and researchers under one roof in the hopes that they will swap ideas over coffee, the Scandinavian consortium is entirely virtual, linked only by e-mail and a generous travel budget. It would be "old-fashioned" to have everyone in one building, says Karl Tryggvason, the consortium's lead investigator, at the Karolinska Institute in Stockholm.

PHYLLIS BROWN, LONDON

## \*No-consent trials raise concern

Data from a trial of a whole blood substitute that was suspended one year ago, has revealed a higher mortality among patients receiving the substitute than those receiving saline. The substitute, HemAssist, made by Baxter Healthcare was administered to subjects admitted to emergency rooms and experiencing severe blood loss, under a controversial 1996 Food and Drug Administration (FDA) protocol that allows testing without the direct consent of patients. Of four studies operated under this rule, two—including the HemAssist trial—have

recently been terminated, renewing concern that individuals are being exposed to risk without informed consent. The dropped trials have also caused anxiety among researchers that corporate sponsors will avoid such studies in the future.

The rule was intended to facilitate research in emergency medicine, in which patients arrive unconscious at hospital and decisions must be made rapidly. Under the system, products can be tested without patients' consent, but only if stringent requirements are met to inform

the community about a trial taking place at their local hospital before, during and after it is done. Such a trial is said to be run under a 'no-consent' protocol.

In drafting the rule, regulators hoped to allow companies to develop products specifically for emergency medicine, a field that often relies on off-label use of an established product. "If a drug or biologic or device becomes FDA approved and has been tested in a controlled setting, that doesn't necessarily mean that you can transfer that information to a trauma setting or the battlefield," explains Susan Fish, research director of Emergency Medicine at Boston City Hospital. The no-consent rule provides a testing ground for emergency room products.

And bioethicists contend that the no-consent rule is ethically inappropriate, regardless of its apparent utility. George Annas, Professor of Health Law at Boston University's School of Public Health, argues that when the rule change was debated, "there was no good rationale for doing [emergency medicine] research without consent. In emergency rooms people use this lunatic thing called implied consent, but you don't imply anything by having a heart attack."

Last month, researchers at Mid-Carolina Cardiology, North Carolina, described difficulties encountered in another no-consent trial—testing a CPR vest developed by

Cardiologic Systems (*Ann. Emerg. Med.* 33, 224-229, 1999). The cost and difficulty of complying with the tough regulations resulted in the trial's termination despite apparently promising early results. Although Baxter overcame these problems, the negative results meant that the company abandoned development of HemAssist and is now focusing on pre-clinical research of a new blood substitute, the market for which is estimated at \$2-4 billion annually.

"I think because of Baxter's experience and the extreme amount of money required to do this type of study ... drug companies are going to shy away from [such] research," says Max Koenigsberg, medical director for the Chicago North EMS system and a leading investigator on the HemAssist trial.

FDA senior policy analyst, Bonnie Lee, says that the agency has an ongoing review of the regulations, but substantial alteration to this rule in the near future is unlikely. "I have heard that the rule is too burdensome. We certainly didn't mean for it to be easy—its purpose is to protect subjects." Different regulations must be applied to emergency situations, explains Lee. "If my child has been in a car accident and is bleeding profusely, you need to intervene as quickly as possible whether I'm there to sign a form or not," she says.

ALAN DOVE, NEW YORK

## Funds bolster Canadian research

As *Nature Medicine* went to press, it was widely anticipated that the Canadian budget announced on February 16th would include provision for a Canadian Institutes of Health Research (CIHR; *Nature Med.* 4, 989, 1998). In a pre-budget speech, Finance Minister Paul Martin told the Canadian parliament that it would also include "hundreds of millions of dollars for research and innovation." This is good news for Canadian biomedical researchers who have suffered cutbacks in federal funding over the last four years.

Alan Bernstein, director of the Samuel Lunenfeld Research Institute of Mount Sinai, a University of Toronto-affiliated biomedical research center, fully expects his Institute to be included in the CIHR network. "We hear about doubling and tripling the NIH budget and because of our proximity to the US, brain drain is a big worry in Canada. But the CIHR, coupled with the new funds being made available is an opportunity for scientists in Canada to dream again," says Bernstein.

Last month, the Lunenfeld was the first biomedical group to receive new funding from an Ontario Challenge Fund established to increase collaboration between the academic and biotechnology sectors, and boost the province's scientific profile.

The Ontario government will give CAN\$12 million (US\$8 million) to the Institute because it has established successful links with three industrial partners—Bristol-Myers Squibb, GlycoDesign and MDS—bringing the Institute's total budget to CAN\$60 million.

The money will support research in proteomics and bioinformatics, directed by Tony Pawson, and functional genomics and animal models of disease, headed by Janet Rossant. An industrial chair in glycobiology and a research training program for 10 post doctoral fellows will also be created.

The Lunenfeld fund was announced only days after the province's Heart and Stroke Foundation donated CAN\$13 million to cardiovascular research at the University of Toronto, where studies will focus on the molecular basis of atherosclerosis and heart failure.

KAREN BIRMINGHAM, NEW YORK

## London college tailors staffing to increase RAE score

Efforts by one of the colleges of the University of London to shift teaching and research resources from civil into biomedical engineering have met with strong resistance from employees over fears that the civil engineering staff are likely to be made redundant.

The reorganization is being justified by Queen Mary and Westfield College both as a reflection of changing patterns in student demand, and as a way of building on the college's research strengths, as measured by its performance in the research assessment exercise (RAE) (*Nature Med.* 4, 990, 1998). Although many higher education establishments are known to rearrange departments to optimize RAE scores, one which government funding is partly based, this is believed to be the first such drastic remodeling undertaken for this purpose.

"Like all universities, we are trying to plan for the next RAE, which is due to be held in 2001, and as part of this we are trying to improve our research profile," says college spokeswoman Delia Ray. According

to her, the college is attempting to build on its existing strengths in biomedical engineering, particularly in areas such as cochlear implants and artificial joints. "There has been a shift in focus, and this appears to be an area in which the government is interested."

The Association of University Teachers (AUT), which represents university lecturers in their negotiations with universities over pay and conditions, is threatening to 'gray-list' the college if it proceeds with this course of action. This would involve warning those seeking employment at, or academic collaboration with, the College that the AUT disapproves of its employment practices. Because of the AUT pressure, the college has agreed to delay the date by which it has asked for volunteers for redundancy until April. It is hoping that the offer will be taken up by those close to the end of their academic career who are considered less 'research productive' than others.

DAVID DE KROM, LONDON



[REDACTED]

[REDACTED]

[REDACTED]

## Emergency Medicine's "Illusion of Efficacy" and the Public Perception of Resuscitation Research

Roger J. Lewis, MD, PhD  
Harbor-UCLA  
SAEM Board of Directors

On January 17, 1999, an article entitled "Testing Without Asking" appeared on the front page of the Chicago Tribune. The article's author implied that a clinical trial completed one year earlier had been conducted in an unethical manner, because most patients could not give informed consent. The trial in question, a randomized controlled study of the use of a hemoglobin-based blood substitute in the resuscitation of critically-injured trauma patients, was the first large, multicenter, pharmaceutically-sponsored trial to be conducted under the 1996 federal regulations allowing a narrow exception to the requirement for prospective informed consent from research subjects (21CFR§50.24). The trial was terminated prior to the first planned interim data analysis, because of an observed increase in mortality among patients receiving the blood substitute, relative to those receiving the saline control. The recommendation to stop the trial was made by an independent Data Safety and Monitoring Committee and was acted on immediately by the study's sponsor, Baxter Healthcare Corporation.

This clinical trial was conducted not under a cloak of secrecy, but instead under the illumination of extensive news coverage both prior to and during its conduct. When patient enrollment was terminated in January 1998, and later when the study was permanently closed, those events were publicized in press releases by the study's sponsor.

While it is obviously unfortunate that this particular blood substitute did not benefit the study subjects who received it, I believe, based on extensive knowledge of the trial, that prior to the study it was reasonable to believe the study participants receiving the blood substitute would benefit. A year later, this clinical trial is being portrayed as an example of unethical and unjustifiable abuse of injured patients and, more importantly, this interpretation is finding fertile ground. Why is the public willing to believe this interpretation of the events? Part of this willingness can be traced to a phenomenon which I will call emergency medicine's "Illusion of Efficacy."

The Illusion of Efficacy is the idea that effective medical therapies currently exist for virtually all life-threatening emergencies. The lay public has a tremendous need to believe that if they suffer a medical emergency or a traumatic injury, the emergency medical system (defined in the broadest sense)

will come to their aid quickly and they will receive effective therapy. Perhaps because of our own human need to feel efficacious, we have made relatively little effort to ensure the public understands the relatively primitive nature and unknown effectiveness of much of emergency medical therapy. In addition, the television media has been phenomenally successful in raising public awareness of our specialty and, unfortunately, portrays emergency medical therapies as highly effective, even in the most dire of circumstances.

Now consider the public reaction to the clinical trial mentioned above—specifically, to the enrollment of patients in a randomized trial without their consent. Because we live in a free society, we all expect that our personal autonomy, and our related right to make decisions about our own medical care will be preserved and respected. When we are incapacitated by injury or illness and that autonomy is lost, however, our societal custom is to expect standard medical therapy will be given to us. The 1996 federal regulations only allow a deviation from this custom if such a deviation holds the prospect of direct benefit to the patient, i.e., when the standard therapy is unproven and it is reasonable to believe the experimental therapy may be better. Under a waiver of consent in a randomized trial, an incapacitated patient is given either the standard therapy or an experimental therapy according to random assignment. This is a radical change from our societal norm of automatically giving only standard therapies which, according to the Illusion of Efficacy, are so effective. Such a radical change in medical behavior, in such dire circumstances, can only be understood by the lay public if that same public understands the lack of evidence supporting the standard therapies. In other words, if they understand the true nature of the Illusion of Efficacy.

How unsure are we about the effect of common emergency therapies? As an example, consider a recent study whose results suggested that multiple doses of epinephrine, when used in ACLS to treat patients in ventricular fibrillation, may actually reduce the chance of a good neurologic outcome, independent of the duration of CPH.<sup>1</sup> Also consider the controversies surrounding the effect of the use of "lights and sirens" during EMS response to medical emergencies, or a study presented at last year's SAEM Annual Meeting whose results demonstrated that prehospital intubation of pediatric

patients does not improve outcome.<sup>2</sup> In each case, therapies and procedures that are commonly used and publicly viewed as beneficial are found, upon close scientific scrutiny, to be of unclear effectiveness or safety.

What can be done to eliminate the Illusion of Efficacy? As academic emergency physicians, we should be open and honest about the fact that we both use and teach therapies with limited scientific support. We should explain, when discussing treatment options with patients we see, which of the therapies we are recommending are known to be effective and which ones are customarily used but of unproven efficacy. When we interact with non-physicians (e.g., medical scientists, public officials, members of the lay public, etc.), we should be careful not to sell emergency medical therapies as uniformly effective but, instead, communicate the message that many emergency medical therapies are unproven.

Greater public understanding of the limitations of current emergency medical therapies will result in a better understanding of the need for research on the effectiveness of experimental therapies, even if that research requires giving up our custom of automatically giving only standard, non-experimental therapies to incapacitated patients. Without such research, future patients will be condemned to receive therapies as unproven as the ones in use today (even if they are not the same unproven therapies). Ironically, the future patients condemned to receive unproven therapies will be those with conditions that make them unable to object. The current federal regulations, allowing a narrow exception to the requirement for informed consent represent a major step forward for our specialty and for our future patients. It is up to us, however, to ensure that the public sees the Illusion of Efficacy for what it is, understands the need for research on therapies for incapacitated patients, and understands that the federal regulations are a step forward, not a step towards Tuskegee.

### References

1. Behringer W, Kittler H, Starz F, et al. Cumulative Epinephrine Dose during Cardiopulmonary Resuscitation and Neurologic Outcome. *Annals of Internal Medicine* 1998;129:450-456.
2. Gausche M, Lewis RJ, Stratton SJ, Haynes B, Gunter CR, Goodrich S, Poore PD, McCollough MD, Henderson DP, Pratt F, Seidel JS. A Prospective Randomized Study of the Effect of Prehospital Pediatric Intubation on Patient Outcome. *Academic Emergency Medicine* 1998;5:428.