1964

This is the year that haemophilia treatment was 'revolutionized'. Stanford University scientist Judith Pool ... ... and her colleagues developed cryoprecipitate, a human plasma residue rich in clotting proteins. It came from a single donor or a few donors – not from a plasma pool – and so was **less likely to carry hepatitis or other viruses**. For the first time, haemophiliacs could treat their disease with injections **at home instead of in a hospital.** *(On the trail of tainted blood – haemophiliacs say US cold have prevented their contracting AIDS – Donna Shaw, Inquirer Staff Writer, 16 April 1995)*

ON THE TRAIL OF TAINTED BLOOD -- HEMOPHILIACS SAY U.S. COULD HAVE PREVENTED THEIR CONTRACTING AIDS

Donna Shaw, INQUIRER STAFF WRITER

Philadelphia Inquirer; FINAL Section: EDITORIAL REVIEW & OPINION Page: E01

SUNDAY April 16, 1995

It is one of the little-known stories of World War II. Had more attention been paid to it, hemophiliacs in the United States might not be dying now at the rate of one a day.

It was 1944, five years into the war. At Schick General Hospital in Clinton, Iowa, military doctors were treating a steady stream of wounded men shipped home from overseas. By year's end, Capt. Emanuel M. Rappaport of the U.S. Army Medical Corps had detected a disturbing pattern.

Many of the soldiers were coming down with hepatitis, a viral inflammation of the liver. The men had served in different parts of the world but had one thing in common: Battlefield transfusions. The plasma most received had been drawn from a number of different pools, each made up of donations from dozens of people. The implications soon were clear: Hepatitis was spreading through plasma transfusions. And plasma pools could become tainted if only one of the dozens of donors carried the virus.

In 1945, Rappaport went public with his findings, which by then were apparent to many other doctors. His study, published in July 1945 in the Journal of the American Medical Association, concluded not only that transfusions were to blame but that the "pooling of plasma probably increases considerably the incidence of jaundice (hepatitis) among the recipients."

In a larger study a year later, he proposed more stringent screening of donors and urged immediate research on ways to kill viruses in blood products. "It is likely that this syndrome will be encountered . . . more frequently in the future," he wrote.

Half a century later, that warning is at the heart of scores of lawsuits involving the spread of another virus through blood. This time, the patients are hemophiliacs, and the disease is AIDS.

A key issue in the litigation is why heat-treating techniques that killed hepatitis - techniques first used by Army-financed scientists back in the 1940s - were not

perfected until 1983 for blood-clotting products used by hemophiliacs. By 1983, most of the nation's hemophiliacs had contracted the AIDS virus through blood-clotting medicine made from pooled human plasma.

An estimated 8,000 to 10,000 U.S. hemophiliacs were infected with HIV, the AIDS virus, in the late 1970s and early 1980s. Also infected were thousands of hemophiliacs in Canada, Europe, Japan and elsewhere who used American products - as well as some wives, girlfriends and newborns, who contracted HIV from them. (Hemophilia, caused by too few clotting proteins in the blood, primarily affects men.)

Today, hemophiliacs and their loved ones are demanding to know why the federal government did not require sooner that manufacturers purify the clotting products. The manufacturers say they did all they could to make hemophilia medicines safe, given what was known at the time. They also say that until the early 1980s, they did not know how to kill viruses without destroying plasma's blood-clotting proteins.

The history of how these decisions were made, and of how the government failed to protect the lives of thousands of people adequately, is of more than academic interest, because new viruses - and newly discovered forms of existing ones, including HIV and hepatitis - are appearing all the time. At stake could be the health not only of hemophiliacs but of 40 million other people who receive plasma products each year. At a recent conference in Washington, blood experts from around the world said it was only a matter of when - not if - the next dangerous virus gets into the blood supply.

In early 1940, as it became apparent that the United States might enter the war, the Army's medical department started planning for a serious problem: shock resulting from battlefield blood loss.

Whole blood, the doctors feared, was too fragile to survive the trip to faraway war zones. So in 1941 and 1942, military records show, seven commercial laboratories were hired to freeze-dry plasma, the yellowish, fluid portion of blood.

Among the labs were Cutter and Hyland, two of the four manufacturers that are now defendants in the lawsuits filed by hemophiliacs. Today, Cutter is a subsidiary of Miles Inc. of Pittsburgh, while Hyland is part of Baxter Healthcare Corp. of Deerfield, Ill.

As the war raged and casualties mounted, so did hepatitis cases.

World War II marked the first time that blood products were used widely, and they helped save countless lives. But in Iowa, Capt. Rappaport knew that other doctors, in the United States and in Europe, were observing outbreaks similar to his. The medical literature included several reports on what then was called homologous serum jaundice, or what's now known as hepatitis B.

Rappaport's paper about his patients was published in 1945. In a larger study a year later, he found that "hepatitis following the use of pooled plasma occurred

14 times as frequently as after the therapeutic use of whole blood."

Seventeen years after Rappaport published his study, his conclusions were supported by the Army's Office of the Surgeon General, which reported that "numerous" wartime cases of homologous serum jaundice had resulted from transfusions. By late 1945, "pooled plasma was indicted as the vehicle," reads the 1962 Army report.

The report goes a step further, concluding that the larger the plasma pool, the more likely it was to contain hepatitis. During the war, according to the report, each pool contained plasma from 50 or more donors. And the pools grew progressively larger as the war went on.

"In retrospect, what happened was clear," the report continues. "A single transfusion of blood is likely to cause jaundice in only a small percentage of the recipients. When, however, blood is pooled, as it is when plasma is processed, the chances of contracting jaundice are correspondingly increased."

Attempts, many funded by the military, were made in the 1940s to kill hepatitis in whole plasma while retaining all its therapeutic benefits. The studies were unsuccessful, according to military records, because the ailment's cause was unknown and because no laboratory animals were known to be susceptible to the virus.

Experiments with human volunteers from the military, prisons and state hospitals were abandoned after it became clear that plasma-induced hepatitis "carried a high risk of mortality" and illness, one study said.

Once the conclusions drawn by Rappaport and other researchers became well known, plasma fell out of favor as a substitute for whole blood. By then, the war was winding down and doctors had an alternative product: albumin, a plasma component.

Doctors knew that albumin, because it was heat-treated, was unlikely to cause hepatitis. Heating at 140 degrees Fahrenheit for 10 hours killed the virus but did not kill albumin's therapeutic proteins. Most scientists thought the same temperature would render plasma worthless.

Interest in plasma was revived in 1950 when an Army-funded team led by J. Garrott Allen, then of the University of Chicago, reported that prolonged heating could kill hepatitis. Allen's method, which called for heating liquid plasma at about 90 degrees Fahrenheit for between three and six months, was reaffirmed in followup studies.

The method, though, also killed blood-clotting proteins. Allen was not overly concerned about this because he was seeking primarily to prove that liquid plasma was still useful as a substitute for whole blood.

By the time Allen's study was published, the Korean War had begun. Army doctors were treating the wounded with pooled plasma that had been irradiated

with ultraviolet light in an attempt to kill hepatitis. It didn't work: Nearly 22 percent of the men who received plasma contracted hepatitis.

In 1958, two more studies supported Allen. Some blood banks began using his technique. Many researchers took aim at hemophilia, an inherited condition, usually passed from mothers to sons, in which there are few or no clotting proteins in the blood. The scientists tried to separate the proteins from plasma, with little success.

Then, in 1964, hemophilia treatment was revolutionized. Stanford University scientist Judith Pool - who had studied under Allen - and her colleagues developed cryoprecipitate, a human plasma residue rich in clotting proteins. It came from a single donor or a few donors - not from a plasma pool - and so was less likely to carry hepatitis or other viruses. For the first time, hemophiliacs could treat their disease with injections at home instead of in a hospital.

Two years later came the next major stride: Baxter's Hyland division further refined cryoprecipitate to make the world's first freeze-dried blood-clotting concentrate. It was called Factor VIII, after the most common clotting protein.

The products were made from increasingly larger plasma pools, which made production more economical. While the Army had worried about pools with up to 50 donors, the new clotting drugs were made from pools with thousands - eventually tens of thousands - of donors. Then came a 1968 study by Allan G. Redeker, a University of Southern California physician who asserted that Allen's heating method did not work so well after all. Experts called for renewed caution with plasma.

The National Research Council, which had endorsed Allen's heating technique, changed its mind, saying the Redeker study meant that "serious doubt is cast on the safety of all pooled human-plasma preparations." The council said it saw few good reasons to use whole plasma, especially since albumin was safer. Heat-treated plasma was worthless for blood clotting since it was well known that heat killed those proteins, the council noted.

Allen, who by then had moved on to Stanford, countered that Redeker's work had contained serious flaws. And in an Army-financed study published in 1969, Allen wrote that the National Research Council had not done its homework. He said Redeker had relied on plasma from two commercial operations, Hyland and Courtland Laboratories, in Los Angeles. Those labs, he said, used large pools of plasma from "skid row" donors, who sold their blood for money. The pools, he said, were therefore far more likely to carry disease and had to be heated longer. What's more, Allen said, executives at the two labs admitted to him that neither the council nor government regulators had made any effort to inspect company records. Allen said there was evidence that the labs had not adhered to his standards.

By the time Allen's rebuttal was published, the National Institutes of Health had already approved the first freeze-dried blood-clotting concentrates for sale. They were not heated. And they were made from pools containing the plasma of

thousands of donors, most of them paid.

In 1970, a study by researchers at the National Institutes of Health, published in the Journal of the American Medical Association, warned that just one unit of hepatitis-contaminated plasma could contaminate an entire pool. Diluted 10 million times, it still was infectious.

By the mid-1970s, most American hemophiliacs were taking the new, easy-to-use concentrates, and government-funded hemophilia-treatment centers had been established to offer comprehensive care and training in use of the medicines. Life expectancy and life quality for hemophiliacs had improved considerably.

It wasn't long, though, before hepatitis from blood products had become a leading killer of hemophiliacs. But the government, manufacturers of the blood-clotting concentrates, and some doctors called this an acceptable risk, given the medicine's huge benefits, and federal regulators allowed the medicines to be sold, with labels warning about hepatitis. The drug industry said it needed too much plasma to rely solely on volunteer donors.

No aggressive action was taken or demanded by the government to kill hepatitis in blood products. The companies were ordered to use the best available donor-screening tests for hepatitis B, but the tests were not sensitive enough to detect the virus every time. Some scientists, meanwhile, said the products were dangerous.

In a 1974 letter to federal health officials, Judith Pool, of Stanford, warned against a proposed national blood policy that allowed the continued use of paid donors for hemophilia drugs. By then, studies had found a strong association between paid donors and hepatitis in recipients. Paid donors were more likely to harbor viruses because so many lived in poor areas that were breeding grounds for disease, the studies said. The World Health Organization objected, in particular, to what it called the exploitation of donors in Central and South America, Asia and Africa, where numerous commercial plasma-collection centers had been set up in the 1960s and '70s. The proposed policy, Pool wrote, "in no way requires or even encourages the use of volunteer blood . . . but assumes a continuation of the dangerous, expensive, wasteful and unethical purchase of plasma by pharmaceutical houses. . . ."

By 1975, the World Health Organization was advocating an all-volunteer system of plasma donation. Federal regulators agreed with the industry's argument that the benefits outweighed the risks.

A 1976 government report on the problems of hemophilia therapy recited this U.S. Food and Drug Administration definition of safety for biologic products: "Safety means the relative freedom from harmful effect to persons affected by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time."

At a meeting in 1977, the World Federation of Hemophilia called on the makers of clotting concentrates to kill viruses in their products for the sake of "future

generations of persons with hemophilia." The organization repeated its message in 1979, urging more speed. The federal government stood by its policy.

In July 1982, the U.S. Centers for Disease Control announced the first three AIDS cases in hemophiliacs. There still were no heated clotting medicines sold in the United States. One was available in Germany.

The U.S. firms, which knew of the German drug, were moving quickly to develop their own. A January 1983 internal Cutter memo urged speed in developing a heated product. It cited a projected loss of business should competitors get there more quickly.

The FDA approved the first heated clotting drug in March 1983. Made by Baxter, it was heated at 140 degrees Fahrenheit - as had been done with albumin since the 1940s - for 72 hours. Refinements in the heating process protected the clotting proteins.

In May 1983, another Cutter memo noted the company had been beaten to the marketplace. It called for a temporary solution "that will preserve our market position." In 1985, the FDA approved a solvent-detergent method of purging viruses from plasma that had been developed by Bernard Horowitz and Alfred Prince of the New York Blood Center. Today, that method is considered a world standard. In an interview, Horowitz said that researchers theoretically could have tried sooner to kill viruses in clotting medicines but that they had no way of knowing that AIDS was on the horizon.

"Keep in mind that virus killing isn't new," he said. "The thing was: Can you do it without killing the (clotting) protein? In 1980, it was considered a very difficult problem." As it turned out, he said, "it was less of a problem than predicted." Douglas Bell, a spokesman for the American Blood Resources Association, an industry group, said the task was far from simple. Besides figuring out the proper temperature and time, there were stabilizing compounds to be selected. Researchers also had to determine whether the body's immune system would reject a heated clotting protein as a foreign invader, he said. The testing required for government approval, first on animals and then on humans, was time-consuming. "It took years to do all this work, as required by the FDA," Bell said.

Thomas C. Drees says hepatitis was considered an unfortunate but unavoidable downside of the business. He was the first president of Alpha Therapeutic Corp., a Los Angeles maker of blood-clotting medicines. In an interview, Drees, now a paid consultant for HIV-infected hemophiliacs, said that when he joined the industry in 1972, "it was sort of accepted that all of the workers in our plant were positive for hepatitis B, and so were all the hemophiliacs, and it was accepted that all the hemophiliacs would probably die of hepatitis at some time in their lives."

One published study, performed by federal health researchers from 1968 to 1971 at an unidentified manufacturing company, concluded that hepatitis B was a common occurrence in plasma-industry workers. Similar studies already had

been done at blood banks and hospitals.

The government study found that the most susceptible employees were those who performed "plasma dumping" - opening bottles and slashing open plastic bags of plasma and dumping the contents into larger containers. The unidentified company had a seniority policy that made it more likely that new workers would be assigned to plasma dumping, according to the study.

Drees said the U.S. government and industry reasoned that most hemophiliacs would live longer with the medicine than without it, making the risks worth the dangers.

In the 1970s, he said, heat-treating was not pursued with urgency since earlier experiments had shown that heat destroyed the clotting proteins' potency. "But when AIDS came on the scene . . . then they started heat-treating - and, son of a gun, it got rid of most of the AIDS," Drees said. Had the government demanded heating earlier to kill hepatitis B, he said, "I think that would have saved the game" when AIDS erupted.

But officials at the FDA "tended to drag their feet" - and were too chummy with industry - he added. The FDA declined comment.

Alpha spokesman Ed Colton called Drees a "renegade" who left the company in 1983 when his contract was not renewed. Colton termed Drees' statement about hepatitis-exposed employees "a wild assumption" for which there was no evidence. Even if some workers turned out to have the disease, "it may be unrelated to working" at the plant, Colton said. Citing ongoing litigation, he declined to respond to other questions.

Records from lawsuits filed by hemophiliacs show that Drees was not the only one who thought more could have been done in the 1970s. In a sworn February 1987 statement taken as part of a Kentucky lawsuit, Allen, by then retired as head of surgery at Stanford, spoke about his work with heat-treating. "No medical, economic or social reason could justify ever using . . . unheated, pooled plasma or its clotting products," he said. "Large pools are highly profitable, but they are medically bankrupt."

In a deposition taken later that year for the same case, Allen said he first wrote to the Army about heat-treating plasma in 1940, a year before he started his Chicago study. He also said in the deposition that in about 1971, he urged a top industry official to heat his company's clotting products. In a 1993 deposition taken in a Missouri lawsuit, Charles M. Heldebrant, director of research and development for pharmaceuticals for Alpha, said his company never worked on killing viruses until mid-1982.

The directive to begin research on heat, he said, came from the marketing department, whose job was to keep up with competitors. It took the Alpha scientists only about three or four months to develop a process, Heldebrant said. It involved heating at 140 degrees Fahrenheit for 20 hours. Time and temperature were not the only issues. He said they also had to purify the concentrates further.

As it turned out, he said, the purer product was easier to heat-treat.

During the deposition, a lawyer for an HIV-infected hemophiliac asked Heldebrant what technology he had used that could not have been developed years earlier. "Absolutely nothing," Heldebrant replied. Alpha spokesman Colton, asked to comment on Heldebrant's testimony, said the responses were only one small piece of the proceeding. "It's difficult for me to respond . . . when you are bent at looking at the 1 percent that entices you," he said.

The amount of time it took to develop a heated product proved crucial because heat, scientists were to learn, killed more than hepatitis. It also killed HIV - the virus that causes AIDS. In fact, HIV was even more susceptible to heat than was hepatitis. In 1993, a class-action lawsuit was filed in Chicago on behalf of all U.S. hemophiliacs who contracted the AIDS virus from clotting medicines. The suit's central contention was that drug companies had sold HIV-tainted products even though they had reason to know that there were safe methods by which to cleanse them.

The defendants included the four U.S. companies that made clotting drugs in the late 1970s and early 1980s: Cutter and Hyland, whose labs processed plasma during World War II, and Alpha Therapeutic and Rhone-Poulenc Rorer Inc. of Collegeville, along with its Armour Pharmaceuticals subsidiary.

The fifth defendant was the National Hemophilia Foundation. The plaintiffs said the foundation was too financially dependent on the companies to be an effective advocate for hemophiliacs. The foundation denied that, insisting that it believed the products' benefits had outweighed their risks.

Last month, a federal appeals panel threw out the class certification, saying the lawsuit might bankrupt the U.S. plasma-products industry, which has annual worldwide sales in excess of $2.4 billion. The case is proceeding with fewer plaintiffs and the decertification is being appealed.

The defendants deny any wrongdoing and are vigorously challenging the lawsuits. They say they acted promptly once the risk was known. "We have people here who are really wringing their hands over all of this," said Daniel McIntyre, a Miles Inc. spokesman. "They thought they were doing God's work." William Mutert, vice president of marketing for Baxter's Hyland division, recalled his anguish when, as a camp counselor for children with hemophilia, he learned that some boys had AIDS. "It was really, really hard to see them," he said, "after they were doing so well in the '70s."

The drug companies estimate that they have been named as defendants in 300 lawsuits involving 400 plaintiffs. Of the 13 cases in which verdicts have been returned, 11 have favored the companies. The one case they lost is under appeal. A new trial was recently ordered in the other case.

The companies have prevailed for a variety of reasons. Some plaintiffs have failed to sue within the time allowed by law. Other suits failed because most states, Pennsylvania and Delaware among them, have what is known as blood-

shield laws. (New Jersey does not.) Those laws define blood-clotting drugs as services, not products, so, by definition, there can be no product liability. The companies also have argued successfully that their manufacturing procedures met industry and government standards.

Before the class was decertified, the hemophiliacs rejected a partial settlement from Armour and Baxter, which offered up to $160 million. After all fees had been paid, that would have been about $25,000 per person.

As for government action, at least 17 other nations have set up programs to compensate HIV-infected hemophiliacs. In February, a U.S. representative from Florida introduced a bill in Congress that would pay $125,000 to each U.S. hemophiliac who contracted HIV from clotting medicines. Also eligible would be hemophiliacs' infected spouses and children.

Today's clotting drugs are considered much safer. Donors are screened, and their blood is tested. The products are heated or, more recently, treated with a detergent-solvent method designed to cleanse blood of such viruses as HIV and hepatitis B and C. The newest, purest medicines are genetically engineered - but expensive - and some insurers are reluctant to pay for them.

Few hemophiliacs contracted HIV after the arrival of heated medicines, but the advances have not eliminated the possibility of contamination. Recent reports to doctors from the FDA and other researchers cite various plasma products - hemophilia medicines, albumin, and immune globulins - found to harbor hepatitis A, hepatitis C or parvovirus.

Albumin is used to treat shock, trauma and burns. It is also used during surgery. Immune globulins treat a variety of ailments, including measles, German measles, chicken pox, rabies, tetanus and smallpox.

"Future concern must turn to 'new' infections," Roger Y. Dodd, head of the transmissible-diseases department of the American Red Cross, wrote in a paper presented at an international conference on viruses and blood held last October in Washington.

The conference ended with a panel discussion, during which one of the major topics raised was what the medical community would do when what one panelist dubbed the next "Martian virus" came out of nowhere and entered the blood supply.

Panelist James P. AuBuchon, head of the blood bank at Dartmouth-Hitchcock Medical Center, pointed out that solvent-detergent killed only viruses with a certain type of coating, known as lipid envelopes. "There's nothing to say the next AIDS-like virus . . . will have a lipid envelope," he added.

There also have been reports from government and academic researchers of newly discovered viruses in blood, including a virus dubbed hepatitis G and an HIV strain not easily detected by tests. Hepatitis G has been found in patients

around the globe.

Frank Kung, whose California company Genelabs Technologies Inc. collaborated with the government to identify hepatitis G, says the virus, like other bloodborne hepatitis, appears linked in severe cases to liver cancer and cirrhosis. Is there a hepatitis H? "We really do not know until we find the next one," Kung said.

Even so, the government seems to have learned little from its failure to prevent the tragedy that has decimated the hemophilia community. In December, the FDA's Blood Products Advisory Committee declined to recommend the recall of products containing the plasma of two donors who later died from Creuzfeldt-Jakob disease.

An FDA official said the panel's theory was that the products probably were too thoroughly processed and diluted for any of the abnormal protein that causes the rare, usually fatal, disease to survive.

The panel's recommendation was denounced by the National Hemophilia Foundation and the Committee of Ten Thousand, a Boston-based activist group that spearheaded the class action and takes its name from the number of hemophiliacs infected with HIV.

Last month, the FDA asked the advisory committee to consider whether smaller plasma pools should be used for hemophilia medicines to reduce the risk. The committee recommended against it, primarily because of the higher cost. It voted for broadly worded virus-warning labels on plasma derivatives.

More than three years ago, the FDA asked manufacturers to virally inactivate all plasma products. The agency issued a reminder a year ago. It has yet to be done.

An FDA spokesperson declined to comment for this article.

In 1993 testimony before a House subcommittee, FDA Commissioner David A. Kessler said that he believed his agency had erred in its relationship with the blood industry.

The FDA's reliance upon voluntary compliance was "emblematic of our collegial approach to regulated industry at that time," he said. "Those days are behind us."

Kessler volunteered, though, that when his wife recently underwent surgery, she stored her own blood in advance - just in case.

CAPTION:

PHOTO AND CHART

PHOTO (3)

1. In 1943, an Army medic treated a soldier with plasma as townspeople watched

in Sicily. Many soldiers contracted hepatitis. (The Philadelphia Inquirer)

2. In 1950, J. Garrott Allen, then of the University of Chicago, later of Stanford, reported that heat-treating blood killed hepatitis.

3. Thomas C. Drees, former president of a manufacturer of blood-clotting medicine, says hepatitis was considered an unfortunate but unavoidable side-effect. (Associated Press / DANA FISHER)

CHART (1)

1. Bugs in the Blood (SOURCES: Government, military, industry and university records; The Philadelphia Inquirer)

Webmaster

Home *Methods* *The Liver* *VA News*

TB