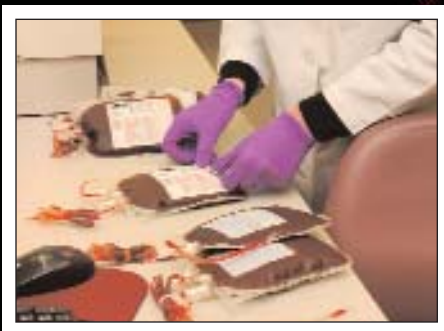


By Laura Stephenson Carter

BLOOD PRESSURE



The inset images above show several steps in the testing, typing, and labeling of donated blood. The background image is of magnified red blood cells.

Blood makes the headlines almost every day: There's not enough of it. And what there is may be contaminated. Some hospitals plead for donors. Others postpone elective surgery. Two patients in Florida contract HIV from a transfusion. West Nile virus is found in some samples of donated blood. Bacteria-infected batches of blood are destroyed. White particles are discovered floating in bags of blood in Georgia. Are they infectious agents? Pieces of the plastic bags, disintegrating from the inside out? Or just clumps of blood cells?

Sure, blood is tested for HIV, hepatitis, and other diseases. And some components can be treated to inactivate pathogens. Still, there's concern that other fatal, infectious agents—like mad cow disease, for which there is no blood test and no cure—might slip undetected into the blood supply.

All of this means that blood banks around the world are scrambling—to collect enough blood to meet ever-increasing needs as the population ages, and to keep up with constant technological advances to ensure the safety of what they do collect. Leading the charge is Dartmouth's James AuBuchon, M.D., whose name seems to pop up whenever there's a story about blood—such as in a February 27 article in the *Wall Street Journal* about mis-transfusions. (See the "Media Mentions" section on pages 16 and 17 in this issue.)

AuBuchon keeps plenty busy as the chair of DMS's Department of Pathology, as the medical director of DHMC's blood bank and transfusion service, and as a professor of pathology teaching medical students and residents. In addition, as an official spokesperson for the American Association of Blood Bankers (AABB), he is regularly asked to comment on blood supply and safety issues.

While the news about blood seems to be dominated by horror stories about the latest infectious agent that's managed to seep into the blood supply, AuBuchon says such fears are misplaced. The number-one danger is the risk of getting a transfusion of the wrong blood type. Although it concerned donated organs rather than blood, the recent death of a teenager who received a transplanted heart and lungs of the wrong blood type is an example of this sort of error.

"When patients are going to get a unit of blood, they're scared to death that they're going to get AIDS. They never think, 'Is that the right unit for me?' It just never crosses their mind," says AuBuchon, speaking before the recent organ mix-up,

Ensuring a sufficient and safe supply of donated blood is a growing challenge for medicine.

A member of the Dartmouth faculty is a national leader in the field of blood-banking.

While doing the research for this article, Laura Carter, the associate editor of DARTMOUTH MEDICINE magazine, was inspired to become a regular donor in DHMC's blood donor room.

RED CELLS: STEVE ALLEN / ALL OTHER IMAGES: FLYING SQUIRREL GRAPHICS



Blood-typing, pictured here, is a key link in the blood-supply chain.

Someone receives the wrong kind of blood about once in every 12,000 transfusions.

A FEW SIGNIFICANT FACTS ABOUT BLOOD

10

Pints of blood in the body of an average adult

1 billion

Number of red blood cells in two or three drops of blood

120

Number of days a red blood cell lives in the circulatory system

4.5 million

Number of American lives saved each year by blood transfusions

3

Number of lives saved by each pint of donated blood

32,000

Pints of donated blood used every day in the United States

120/20

Number of platelet and red-cell donations, respectively, used by one bone marrow transplant patient

53/47

Percentage of transfusions that go, respectively, to women and men

14

Number of tests (11 of them for infectious diseases) performed on each pint of donated blood

42/5

Number of days in the shelf life of donated red blood cells and platelets, respectively

1

Number of years in the shelf life of frozen plasma

60

Percentage of the U.S. population that is eligible to donate blood

5

Percentage of the U.S. population that does donate blood

603/650-6416

Phone number to schedule an appointment in DHMC's blood donor room
(or e-mail dhmc.blood.program@hitchcock.org)

which did raise public consciousness about the problem. In fact, someone receives the wrong kind of blood about once in every 12,000 transfusions—which makes the risk of dying from such a mistake about 2 per million, or a couple dozen people a year in the United States. By comparison, the risk of contracting HIV, the virus that causes AIDS, via a transfusion is only 0.5 per million.

The blood supply is safer now than it was 20 years ago, when blood-banking practices did indeed result in AIDS being transmitted through blood transfusions, especially to hemophiliacs who received clotting factors extracted from blood pooled from thousands of donors. But nowadays, donated blood undergoes such sophisticated testing and treatment before it's transfused that most infectious agents are likely to be detected, so any infected units can be destroyed.

But the testing has introduced another concern. "I have been struck by the very poor cost-effectiveness of some of the things we are doing now in transfusion medicine," AuBuchon reflects. "For example, the latest addition to HIV-testing . . . did make the blood supply safer, but the cost effectiveness [is] calculated at about \$2 million per year of life extended. By comparison, most medical and surgical interventions have a cost effectiveness of less than \$50,000 per year of life extended."

A former member of the AABB board (he had to rotate off after serving two terms), as well as the current chair of the AABB's clinical transfusion medicine committee and a recognized expert in decision-analysis regarding blood safety, AuBuchon has been implementing cost-effective measures to protect DHMC's blood supply since his arrival at the Medical Center in 1990. Under his leadership, DHMC was one of the first hospitals in the nation to test platelets for bacterial contamination and to institute an inexpensive system to prevent mistransfusions. DHMC is also conducting research and clinical trials aimed at resolving some of the thorniest blood-supply and -safety problems.

As busy as he is, AuBuchon finds the time to do what he wishes more people would do: donate blood. In fact, DARTMOUTH MEDICINE interviewed him as he was hooked up to an apheresis machine, donating platelets and red cells. He keeps himself occupied during the 90-minute donation period by working on his laptop computer, talking on the telephone, and being interviewed. He hardly seems to notice the needle in his arm, as his blood courses through plastic tubing into the apheresis machine. There, a centrifuge separates the blood into its components—platelets, red cells, and plasma—and keeps the platelets and red cells



PRACTICING WHAT HE PREACHES: Pictured here in DHMC's blood donor room, James AuBuchon, DMS's chair of pathology and a national authority on blood-banking, regularly donates blood.

Under AuBuchon's leadership, DHMC was one of the first hospitals in the nation to test platelets for bacterial contamination and to institute an inexpensive system to prevent mistransfusions.

while returning the rest to AuBuchon's arm. He squeezes a little rubber ball every few seconds to keep the blood flowing.

"When I came to Hitchcock in 1990, we did not collect any of our blood," says AuBuchon. "We counted on the Red Cross to supply all of it. We had an adequate supply . . . and the cost wasn't free, but it wasn't unreasonable."

Although donors give their blood for free, it costs money to collect, process, and test it and deliver it to hospitals. There is no set price for blood. The cost varies from center to center and from region to region. Whole blood is usually separated into three or four components: red blood cells, which deliver oxygen; platelets, the clot-forming cells; plasma, the liquid portion of blood; and sometimes cryoprecipitate, which is a part of the plasma concentrated in some clotting factors, including Factor VIII, the antihemophilic factor. Red cells are the most expensive component, while type O blood, the universal donor, is more expensive than types A, B, or AB.

In the 1990s, DHMC had to stop relying on the Red Cross as its sole supplier of blood and set up its own collection system—for platelets in 1996, for



A shipment of red cells is logged in using computerized bar-coding.

DHMC gets its blood from three different sources, including its own blood-donor room.

platelets and plasma in 1998, and for whole blood in 2000. The decision to collect platelets came soon after the Red Cross closed its platelet donor center in Lebanon, N.H., and moved its blood-testing laboratory from Burlington, Vt., to Dedham, Mass. “Those two changes, which happened at about the same time, meant that we were getting our platelet units delivered a day later in their shelf life,” AuBuchon explains. “Platelets can only be stored for five days. So losing a full day off the shelf life meant an immediate jump in our out-date rate.” It meant increased costs, too.

DHMC began collecting plasma a couple of years later amid growing concern that the only plasma available for purchase underwent a disinfecting process considered by many blood-bankers to be unsafe. Several thousand units of plasma were pooled and then chemically disinfected to inactivate viruses like HIV and hepatitis C and B.

“That sounds great,” AuBuchon says. “The only problem is that this technique . . . did not inactivate all viruses, just some viruses—those that had a lipid envelope. Because of the pooling process, it was possible that a donor might have a non-envelope virus that would not be inactivated by the process and now would be transfused not to just one patient but to several thousand patients.”

To address that problem, DHMC collected, tested, froze, and stored its own plasma, and then retested the donors 112 days later—and used the stored plasma only once the retest results came back. The tests available then weren’t sensitive enough to pick up viruses like HIV or hepatitis C and B in donors who might have been infected just before donating. But such a person would test positive after 112 days. “We thought it provided an extra degree of safety,” AuBuchon explains. DHMC no longer needs to use this donor-retesting process, because more sensitive tests are available now.

By the late 1990s, health-care institutions nationwide were experiencing problems getting enough red blood cells: the demand was climbing; the collection rate was falling; and the American Red Cross, the main supplier, had jacked up its prices. Hospitals across the country began seeking alternatives: contracting with other providers; establishing their own donor centers; and forming collection associations with other hospitals.

One of the reasons for the price increase was that the Red Cross began providing only leukoreduced red cells—ones from which the leukocytes, the white blood cells, had been filtered out—and filtered products are always more expensive than unfiltered products. The Red Cross began the practice in 1998, soon after an advisory committee recommended that the Food and Drug Administration

(FDA) mandate leukoreduction in all blood centers. When white blood cells are transfused in whole blood, they can cause fevers and chills in some patients. But members of the blood-banking community, including AuBuchon, argued that there wasn’t enough evidence to prove that leukoreduction was beneficial for everyone.

“There still is an ongoing discussion in blood banking about the importance of white cells in units of red cells,” says AuBuchon. “The Red Cross took the attitude that they knew what was better for our patients than we did. [They] decided that they were going to filter out white cells from every unit of red cells and, of course, charge us for that. That, plus a move on their part to recapture more cost, caused our cost-per-unit of red cells to double between December of 2000 and July of 2001,” from \$92 to \$186 per unit. All these changes “added a million dollars to our laboratory budget overnight, all within one fiscal year,” says AuBuchon.

He acknowledges that some patients do indeed benefit from leukoreduced blood. About a third of transfusions go to patients who need to avoid white cells—patients who get regular transfusions, bone marrow-transplant patients, and chemotherapy patients. But, he adds, “as far as we could see, the average patient who comes in after an automobile accident, or needs a couple of units of blood after surgery, wasn’t going to get any benefit.” Recently, in response to published data showing no benefit from universal leukoreduction, “the FDA has backed off and indicated that they are not likely to require it,” says AuBuchon. But it’s too soon to tell if the Red Cross will change its practices.

Blood transfusions were performed with limited success as far back as the 1600s—from dogs to dogs and from animals to humans. In 1665, English physician Richard Lower resuscitated a dog by transfusing blood into its jugular vein from the neck artery of another dog. In 1667, French physician Jean-Baptiste Denis successfully transfused lamb’s blood into several patients, but one of his patients died after being transfused twice with calf’s blood. It’s surprising that these early attempts worked at all. In fact, blood transfusions were subsequently outlawed.

They were tried again in the 1800s—this time with human blood. In 1818, British obstetrician James Blundell performed the first successful recorded transfusion of human blood. But no one understood why many transfused patients did well, while a third of them had serious problems or died.

Then, in 1901, an Austrian physician, Karl Landsteiner, discovered blood groups. “If you look at . . . the mix of ABOs, about two-thirds of the

time just by luck you will give an ABO-compatible transfusion,” explains AuBuchon. “About one-third of the time it would be—guess what, that’s where the bad reaction was coming from.”

In 1917, the first blood “depot” was established when a U.S. Army doctor collected and stored type O blood, using a citrate-glucose solution, to prepare for the arrival of casualties during a World War I battle. In the 1930s, what came to be called blood-banking took off. Transfusions were used regularly during World War II to save the lives of soldiers on the battlefield. In 1943, pathologist Elizabeth French, M.D., the first woman member of the Hitchcock Clinic, opened a blood and plasma bank at Mary Hitchcock Memorial Hospital.

After the war, the Red Cross couldn’t keep up with the nation’s demand for blood products, and for-profit collection centers sprang up and started paying for blood. Paid donors were more likely to be poor and infected with viruses transmissible via blood. So in the 1970s, the FDA began requiring that blood be labeled as to its source, and payment of donors stopped almost overnight—though FDA regulations don’t prohibit payment.

The management of the plasma supply is still a for-profit operation, however. Since WWII, pharmaceutical companies have separated plasma into therapeutic components called fractions—like Factor VIII, the clotting factor that hemophiliacs need. Commercial plasma centers still pay donors, but plasma derivatives can be virally inactivated so infection in donors is not an issue.

The FDA now sets standards that all blood centers must follow. Potential donors are told who can and can’t give blood and are asked questions ranging from whether they’ve ever had certain diseases to whether they’ve lived in the United Kingdom or Europe since 1980 (to determine if there’s a risk of their introducing the human version of mad cow disease, an incurable neurodegenerative disease, into the transfusable blood supply).

Today, DHMC gets its blood from three different sources—its own blood-donor room, which is run by a company called Coral Therapeutics; a Midwestern organization called United Blood Services; and the American Red Cross. Dartmouth-Hitchcock was one of the earlier places to diversify its blood supply by establishing multiple sources. This makes it easier to adapt to fluctuations in availability or price from any one source.

In DHMC’s blood donor room, each donor’s blood is collected in a plastic bag and labeled with a code; a sample is sent to a blood-testing facility in Florida, while the bag is delivered to the blood bank in the pathology department. The samples are tested to determine the donor’s blood type; to screen for



ONLY PERFECTIONISTS NEED APPLY: Linda Cooper, the supervisor of DHMC’s blood bank, performs repeat testing to confirm that the type of blood in each bag matches what’s indicated on the label.

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infectious diseases such as HIV, syphilis, and hepatitis B and C; and to check for unexpected antibodies that might cause a transfusion reaction.

The blood is stored in a walk-in refrigerator in the pathology department but isn’t transfused until after the test results—available within 24 hours on a password-protected Web site—confirm that the blood is safe.

The blood bank stores and distributes all blood used throughout DHMC—about 10,000 units of red cells, 3,000 units of plasma, and 1,000 platelet units a year. No matter where the blood comes from, blood-banking staff use a computerized automated system and electronic cross-matching to check and double-check that each unit has been labeled properly as to blood type.

“A lot of testing is checking, checking, checking,” says blood bank supervisor Linda Cooper, who has worked in blood-banking for 25 years—12 of them at DHMC. The job “requires a great deal of attention to detail,” she adds, noting that people drawn to the field tend to be “perfectionists.”

The blood components are stored—red cells in the walk-in refrigerator, plasma in special freezers, and platelets at room temperature—until they are



The Bloodloc system is used by only 40 or 50 hospitals nationwide.

The Bloodloc resembles a giant decoder ring and is affixed to each unit of blood.

needed. The operating room (OR) uses an electronic ordering system to notify the blood bank in advance of how much and what types of blood will be needed for scheduled surgeries. Orders for blood also come in from the OR for emergency surgeries, from the emergency room, and from other departments as well.

A plastic loop called a Bloodloc, resembling a giant decoder ring, is affixed to each unit of blood before it's put into a pneumatic tube system to be whisked off to a patient. DHMC started using this simple safety system right after the Medical Center moved from Hanover to Lebanon in 1991. At the old site, pretransfusion samples were collected by blood-bank technicians. But at the Lebanon location, pretransfusion samples are collected by phlebotomists instead. "The blood-bank techs know what happens if something goes wrong," says AuBuchon. "We had more confidence that they were going to be labeling everything correctly."

But the change that worried him most was that blood would no longer be delivered by humans to the operating suites and other departments, but would be traveling through the Medical Center via pneumatic tube. Each bag of blood would be labeled with the name and identifying information about the recipient. Then, says AuBuchon, they "put the unit of blood into a tube and watch it go 'schhhhp' into the wall."

Luckily, the Bloodloc system came on the market in the nick of time. A unit of blood can't be transfused until it's unlocked with the right code—a random, unique, three-letter code that's been imprinted on a label attached to each patient's hospital wristband as well as transcribed on the pretransfusion blood sample. A blood-bank staffer issues the blood components for a patient, sets the Bloodloc with the patient's code, and attaches it to the bag, then sends it on its way through the pneumatic tube. When the unit gets to the patient, the transfusionist dials in the code on the patient's wristband to open the lock.

"There's only 40 to 50 hospitals using this technique," says AuBuchon. "Many began using it only after there was a fatality." DHMC has never had a fatality from mistransfused blood, but the system has prevented a few near misses.

If getting the wrong blood is the number-one transfusion-related cause of death, the number-two cause is bacterial contamination. Almost one in 4,000 transfusions results in a severe reaction due to bacterial contamination, and as many as one in 17,000 can lead to death.

DHMC was the first medical center in the United States to culture platelets for bacteria. Platelets

are more likely to grow bacteria because they're stored at room temperature—an ideal growing condition for bacteria like salmonella and staphylococcus. Some types of bacteria can grow in refrigerated blood, too.

Bacteria can get into platelets in a couple of ways: from the donor's blood if the person has a low-level, chronic infection; from the donor's blood if it is taken during one of the brief periods in a day when there are bacteria in one's bloodstream (after brushing one's teeth or defecating, for example); or from the donor's skin if the needle pushes through a subcutaneous location where bacteria weren't killed by disinfection of the skin.

The trick is to identify infected units so they won't be transfused, but usually there aren't enough bacteria initially to be measurable. About one in a thousand units of platelets contain bacteria, according to AuBuchon. Culturing is a way to find those units.

The culturing process begins the morning of the second day after collection, and the results are available in 12 hours—so if there are no bacteria present the platelets are ready to transfuse by day three. Under current FDA regulations, platelets must be used within five days, even though they can live for seven days. AuBuchon hopes that the FDA will one day allow blood banks that use bacterial testing to extend the storage of platelets to seven days.

Another safety measure that AuBuchon has instituted is hiring a transfusion safety officer to focus on safety issues outside the walls of the blood bank. DHMC and most other hospitals already have compliance officers, as well as multidisciplinary transfusion committees made up of doctors and nurses. Blood banks in other countries have transfusion safety officers, but DHMC is the first place in the U.S. to establish such a position. "We have come to recognize that although we can certainly make errors in the laboratory, there are significant problems that can occur outside the laboratory—for example, all the problems related to mistransfusion," AuBuchon explains. "To my knowledge, we are the first American hospital to have not only a compliance officer that looks internally at the laboratory but a transfusion safety officer that performs the same kinds of functions, but whose view is meant to be external—that is, to look at the clinical transfusion process."

Blood centers everywhere are concerned not just with safety but also with the challenge of keeping the blood flowing—of finding enough people willing to donate blood. AuBuchon hopes that the DHMC blood donor room will increasingly attract donors who don't mind giving blood but might not

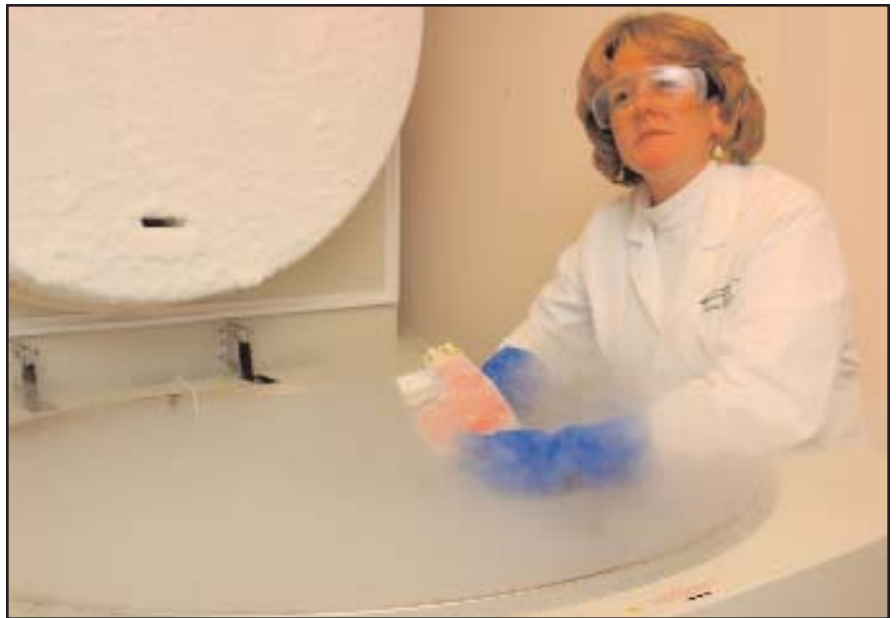
have found it convenient to participate in community blood drives in the past. The blood donor room, he explains, is open every weekday year-round, while community drives are one-day events, held just a few times a year.

Other means of increasing the blood supply and reducing the amount of blood needed are being explored, too. Some blood banks are trying double red-cell donations, whereby donors meeting certain criteria would be allowed to give twice as much blood—two units (or pints)—at a time. In addition, 38 blood centers have gotten FDA approval to use blood from donors with a hereditary condition called hemochromatosis, in which unhealthy levels of iron are stored in the body. People with this condition must have their blood drawn regularly to get rid of the excess iron, and most of that blood has been discarded. Being able to use it could boost the nation's blood supply by several hundred thousand pints a year. In February, AuBuchon was quoted in the *Kansas City Star* as saying, "As blood centers feel they can take this on, I think it will be an important addition to the supply of blood." But he has no plans for DHMC to collect, buy, or transfuse such blood, because "too few of these people would qualify as donors" so he feels it would be economically unfeasible.

DHMC is, however, using a new technique to salvage red blood cells during surgery and return them to the same patient. AuBuchon estimates that DHMC's battery-operated, mobile blood-salvage system, which accompanies the patient from the operating room to the hospital room, saves about 120 units of blood a year.

While AuBuchon is working to ensure the safety of the blood supply at DHMC and throughout the nation, Dartmouth pathologists and microbiologists are conducting research on blood, too. Ongoing projects include an international study to determine the appropriate dose of platelets; a comparison of different methods of collecting and storing blood; a test of a process to enzymatically convert all donated blood to type O (the universal donor); and studies of stem-cell and bone-marrow transplant procedures. In 2000, AuBuchon reported results of the first human trial demonstrating that red cells virally inactivated with an experimental compound could be stored and safely transfused. Other DHMC departments are doing blood research, too, such as a study which showed that administering recombinant human erythropoietin to critically ill patients stimulates the production of red blood cells and may reduce the number of transfusions needed.

AuBuchon has also been collaborating with a



A GOOD CLIMATE FOR RESEARCH, TOO: Susan Webber, a technical specialist who heads DHMC's bone marrow transplant lab, retrieves stem cells stored in a freezer that stays at -140° Celsius.

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Boston-area company to enzymatically convert A, B, and AB blood to O. "All is going well so far," he says. "However, this is not going to be an approved technology, let alone widely used, for at least two to three years." While converting all blood to type O, which can be transfused to anyone, would help with the supply problem somewhat, it wouldn't eliminate overall shortages in the blood supply.

Dartmouth researchers are also conducting clinical trials as well as basic research with stem cells. Susan Webber, a technical specialist who heads the bone marrow transplant lab, oversees the processing of stem cells, whether they are for clinical use or for research. Stem cells are harvested from patients via the apheresis machines in the blood donor room, and the process can take from one to several days.

Scientists around the world are engaged in research seeking to find substitutes for blood. Cow blood products have been considered, although the fear of mad cow disease makes them an unlikely prospect.

Most blood substitutes are chemically modified hemoglobin solutions extracted from human blood

continued on page 60