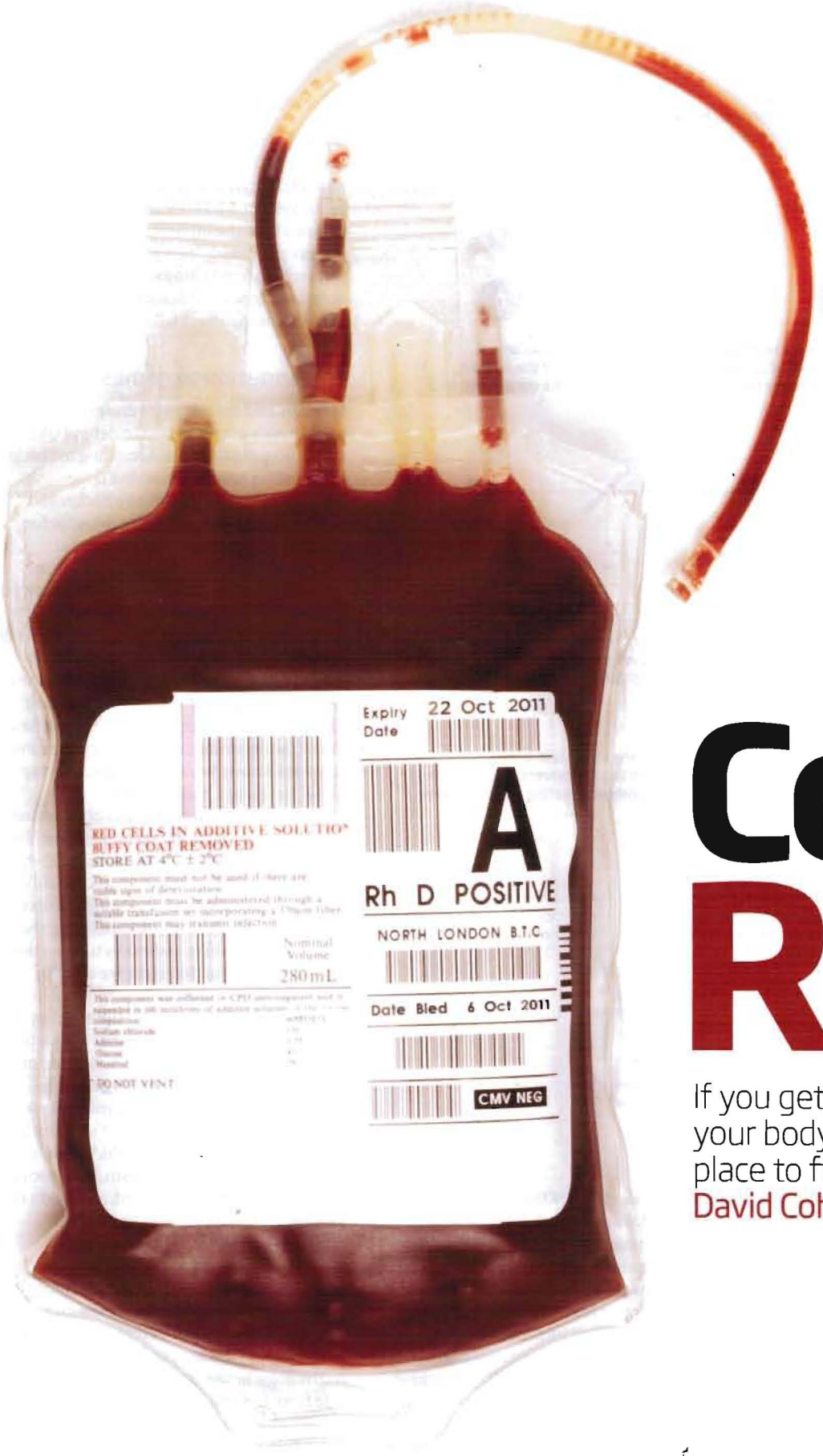


Code RED

If you get hit by a truck, fixing your body should take second place to fixing your blood. David Cohen reports

Your chances of surviving massive blood loss are 50:50

SKIMMING over the London rooftops, the air ambulance takes only minutes to arrive. Its objective: a cyclist who has been hit by a truck. Her pelvis has been crushed and she is haemorrhaging internally from her liver and kidneys. As her blood pressure plummets, the patient goes into medical shock. She is dying.

But the paramedics do not give fluids to boost blood pressure and reverse the shock as they normally would. Instead, they begin a set of new and controversial last-ditch procedures. The patient is anaesthetised and rushed by helicopter to the Royal London Hospital. Over the radio the crew warn the hospital's waiting trauma team about the patient's state: "Code red."

The new approach has arisen because of recent discoveries about what happens in the chaos of major haemorrhage. Doctors have found that some people can bleed to death even after reaching hospital, because their blood simply fails to clot as it should.

"Every stitch you make bleeds, they start bleeding from the punctures at the site of their infusions, everything you do causes bleeding," says Karim Brohi, a trauma surgeon at the Royal London Hospital. "They bleed from their mouth and nose, and into their lungs, so they start to drown in their own fluids. You're filled with an impending sense of doom. You just know the patient is going to die."

MAIN: JAMIE STOCKMAN/GETTY LEFT: DAVID LEVENE/EYEVINE

"They bleed from their mouth and into their lungs so they start to drown in their own fluids. You just know they are going to die"

It seems that sometimes major injuries trigger a problem with the blood-clotting process, causing blood to leak from the body faster than it can be stemmed. This clotting disorder affects as many as 1 in 4 major trauma victims. So Brohi and others have developed a way of treating people that prioritises fixing their blood over fixing their body. It's a radical departure from standard procedures, and one that is by no means widely accepted, but if they're right it could save thousands of lives every year worldwide, and a whole chapter of trauma care will have to be rewritten.

Key to the switch is a new understanding of coagulation: the mysterious, almost magical, process whereby blood changes from a fluid into a solid to form a clot. Coagulation is regulated by a complex network of blood-born proteins, which ensure that the process is triggered as soon as it is needed and yet only when it is needed; unwanted clots can be lethal in their own right.

Normally, the blood's viscosity is finely poised. If you cut yourself, blood proteins known as clotting factors trigger coagulation. The end result is a plug made of a stringy protein called fibrin, and tiny cell fragments called platelets. Meanwhile, further from the damage, anticoagulants are made that stop the clotting process from spreading too far.

Some people are born with a blood-clotting disorder, or coagulopathy. Blood may fail to clot when it should, such as in people with haemophilia, or it can be too prone to clotting and trigger a stroke. But any one of us who is injured badly enough can experience acute traumatic coagulopathy (ATC), as Brohi discovered 11 years ago.

Clotting switch

Brohi admits he stumbled on ATC almost by accident in 2000 when he decided to study severe trauma patients who had been admitted to hospital. "We were doing an exhaustive search to understand what the data said about patients' clotting ability early after trauma, but we weren't expecting to find anything," he says.

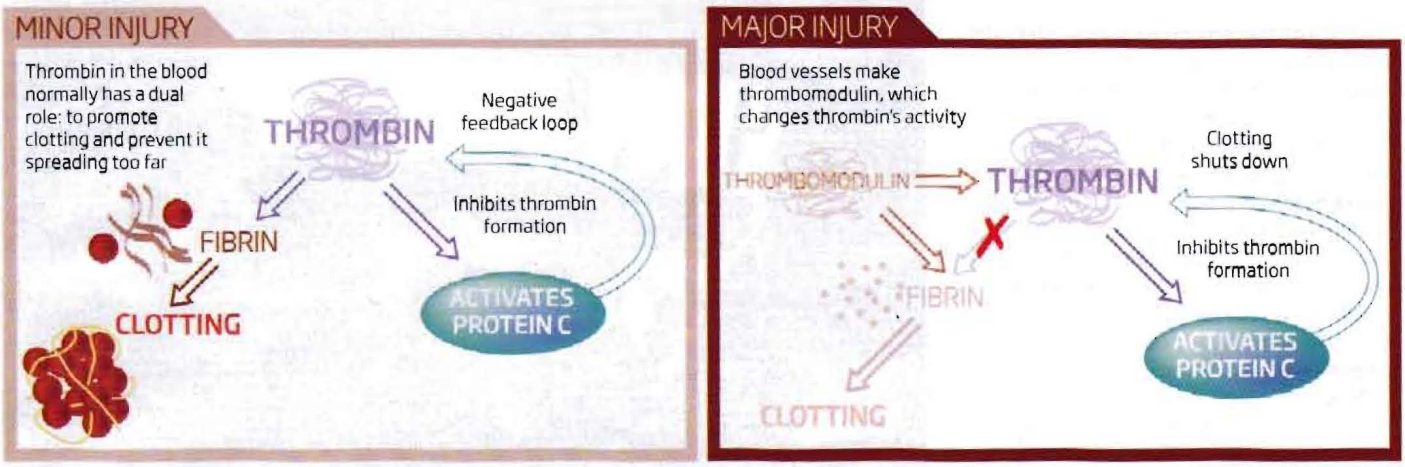
People who bleed heavily were already known to develop some kind of clotting disorder, but it was thought this only became a problem after they had been in hospital for some time, possibly hours after arrival. The problem was thought to result from their deteriorating condition, perhaps exacerbated by the fluids given to raise their blood pressure, which have the unwanted effect of diluting levels of clotting factors.

Brohi analysed the records of more than 1000 patients and, to his surprise, found they often had the clotting disorder on arrival at hospital. It seemed to arise within minutes of injury, as a direct consequence of massive tissue damage. What's more, 46 per cent of those who had the disorder on admission died, compared with 11 per cent of those who did not (*Journal of Trauma Injury, Infection and Critical Care*, vol 54, p 1127).

The results flew in the face of conventional wisdom. "We had a lot of difficulty publishing the paper at first," says Brohi. But a few months later, a study of 20,000 patients in a hospital in Miami showed the same thing, and many studies since have confirmed the finding. ›

Blood bath

Major physical injuries can trigger a breakdown of the normal clotting process, causing blood to leak from the body faster than it can be stemmed



Since then Brohi has focused on unpicking the causes of ATC, teaming up with Mitchell Cohen, a surgeon and trauma researcher at the University of California, San Francisco. Normally an enzyme called thrombin is a key driver of fibrin formation. To put the brakes on the coagulation process there is a clever feedback loop: thrombin also activates a compound called protein C, which blocks thrombin formation (see diagram, right).

In someone experiencing ATC, however, cells on the inner surface of blood vessels begin to make a protein called thrombomodulin – not just at the site of injury, but throughout the body. Thrombomodulin switches thrombin from its primary role of forming clots to its other role of activating protein C, leading to a wave of anticoagulant proteins washing through the body. This "thrombin switch" is why people with ATC bleed so profusely.

So what prompts blood vessels to make thrombomodulin? It seems to be severe physical injury combined with the person going into medical shock, which happens when the tissues of the body do not get enough oxygen. "We don't understand why these factors are crucial, but you don't get ATC without both," says Brohi.

It is unclear why big injuries lead to the production of thrombomodulin throughout the body, but from an evolutionary perspective it is not that surprising. Clotting has evolved to deal with small, survivable injuries like cuts and grazes. "Getting hit by a bus is not something we've developed an evolutionary response to," says Brohi. After such an extreme injury, our finely tuned system breaks down.

"Clotting has evolved to deal with small survivable injuries. It can't deal with getting hit by a bus"

The existence of ATC is now widely accepted, but what to do about it is still contentious. As yet there is no drug that specifically reverses the condition, although several groups are trying to develop one. Brohi's team is looking for compounds that inhibit activated protein C, and they have begun testing compounds in mice and rats.

In the meantime, a growing number of doctors are trying to save people by using existing drugs and techniques differently, under a protocol termed damage control resuscitation. It's a switch in priorities: tackling the clotting disorder takes precedence over repairing injuries. "It is a huge change in mindset," says Brohi.

Blood-chilling

Take the cyclist hit by the truck. Previously, paramedics would have immediately given her a large saline infusion to bring up her blood pressure, and so help blood and therefore oxygen return to her tissues.

At the Royal London Hospital, however, the priority is to maintain clotting at all costs for anyone at risk of ATC. So saline is out for several reasons. It would dilute the blood's clotting factors and, as it is stored below body temperature, would chill her blood, which also slows coagulation. What's more, the pushing, pulsing force of blood at higher pressure makes it harder for clots to form, so we want to keep pressure low anyway.

Patients also get different blood products. These days there's no such thing as a plain "blood transfusion"; for many decades, donated blood has been separated into its three constituents – red blood cells, platelets and plasma, the straw-coloured fluid component of blood. It makes storage easier, and giving people different cocktails of these components according to their needs is a better way to husband supplies.

People bleeding profusely are normally given mainly red blood cells with small amounts of plasma and platelets, typically in a ratio of 8:1:1. The lack of oxygen-carrying red blood cells is seen as the most immediate threat to life.

But plasma contains the blood's clotting factors and platelets are, after all, a structural component of the clot. "We were giving patients blood without clotting factors in it," says Bryan Cotton, a surgeon at the University of Texas, Houston, who has investigated the best ratios to use.

Under damage control protocols, people get higher doses of plasma and platelets in a 1:1:1 ratio. As fast as possible, they also

NICOLE LEY ADAMS

Road traffic accidents are the biggest cause of death for young people

get extra clotting factors and a drug called tranexamic acid that inhibits clot breakdown. "We send blood products up to the helipad if necessary," says Brohi.

Another crucial element is a switch to what's called damage control surgery, which means doing the minimum work needed to stem the major sources of blood loss, before sending the patient to intensive care where they can be stabilised. Later they can have the more time-consuming reconstructive surgery.

The concept has been around for decades but until now has not been used often. What's new is to routinely use this approach on anyone with possible ATC.

That's what happened with the cyclist. When she reached the operating theatre, the surgeons limited themselves to repairing damaged organs and major blood vessels. Within 25 minutes she was whisked to intensive care to get more blood and extra clotting factors. Only once she was clotting well was her blood pressure returned to normal. Then she was sent back to theatre for further surgery on her pelvis.

At the moment only a handful of hospitals use damage control procedures but the number is growing. Even so, the approach has never been compared with standard practice in a randomised trial – not even in animals. Unlike a new drug or medical device, there is no such requirement for a new surgical technique or a change in the way existing drugs are used.

Individual elements of the approach have come under scrutiny, though. For instance, several studies have supported the idea of giving tranexamic acid, and using less saline than is standard practice.

Clotting like custard

When it comes to blood ratios, however, the evidence is mixed. Some studies have found 1:1:1 is best, and this ratio is now increasingly favoured. But two more recent studies showed no benefit. "I don't think you'll find anyone around the world who thinks this is proven, because it is not," says Thomas Scalea, physician-in-chief at the University of Maryland Medical Center, in Baltimore, who led one of the studies that gave negative results (*Annals of Surgery*, vol 248, p 578).

All the studies so far have been retrospective. In other words, they looked at historical data on what blood products people got and whether they lived or died. There could have been other factors making those who were in better shape more likely to get 1:1:1. What's needed is a prospective trial, where people are randomised to different ratios in advance. A US team that includes Scalea and Cotton is planning just that, but the results won't be out for many years.

Scalea concedes that giving more plasma is probably good, "but at what ratio and in which patients?" It's not nit-picking. The more blood products people are given, the higher the risk of organ failure and infection, so they should only be used if essential.

As it happens, that might not actually be an issue. At Cotton's hospital, which has adopted damage control procedures, doctors have found that giving more plasma early on reduces the need for it during later medical care. "We have decreased the amount of plasma used at the hospital," says Cotton.

There may be a way to work out who needs plasma the most, with a device called a thromboelastometer, currently used to test blood in people with other clotting disorders. It vibrates a needle in small sample of blood, and as the blood begins to clot, resistance to the vibration increases. Normal blood thickens like custard within minutes, but blood from someone with ATC can take much longer. "You can tell within about 5 minutes whether the patient has ATC," says Brohi (*Critical Care Medicine*, in press) Existing tests can take over an hour.

How about comparing hospitals that follow damage control protocols with those that don't? Brohi published a study on this last year, and he says the figures speak for themselves (*British Journal of Surgery*, vol 97, p 109). "If you come to our hospital injured, bleeding and shocked, you are three times more likely to survive than at any other trauma centre in the UK."

But the Royal London is one of the world's top trauma centres, so there may be many factors contributing to those figures. "Certain things may happen on the way to hospital or in intensive care that set the outcome, regardless of the quality of the transfusions," says Scalea.

"In the end we have to prove it at the bedside," he says. "It's important science, but if it doesn't translate into improved outcomes then it's just science. If it translates, then it is revolutionary."

And the cyclist? Her ordeal was by no means over; she needed several further rounds of reconstructive surgery. Two months after the crash, she had to learn how to walk again, and suffers back pain to this day.

But she is alive. ■

David Cohen is a writer based in London