The Curious Paradox of Blood

Funny stuff, blood. All that transport of oxygen and nutrients works so well and is perfectly comprehensible — until the blood starts to clot. That's when the problems begin. There is a serious anomaly in the way hemostasis is supposed to work. It was years before I found the answer, and I would never have imagined that, in the fullness of time, my discoveries would be called a “scientific highlight” in the press. Finding the answers to problems that others have not considered has always been a source of fascination. The coagulation paradox fell neatly into this category.

Come with me back to childhood. Like most youngsters, I imagined that blood oozing from a cut dried on the skin, like paint setting in the sun. It was eventually picked off with an eager fingernail, and that's how we recovered from minor traumas. We learned more about blood when I was at The King's School in Peterborough, England. This school was founded by King Henry VIII around 1540, and it had acquired a high standard of scientific education. In the biology classes a different explanation emerged. Blood didn't dry, it coagulated. A cascade of enzymes set in motion the production of fine fibrin fibers, and they trapped the mass of erythrocytes (red blood cells) to make a solid clot. The cells, instead of rushing to the outside world, were held back by the network of fibers and blocked the opening. It was like catching candies in a fish net. Except, the net didn't exist. It couldn't.

Imagine the scene at the microscopical level. You have cut yourself and blood is oozing from tiny damaged blood vessels. The standard teaching says that, in the end, the wound is covered with a network of fibrin within which blood cells are trapped in a jelly-like mass. Yet how could it happen? The stimulus for the fibrin threads to form is when the escaping blood makes contact with the damaged vessel wall. But the precipitation of fibrin starts only as the blood is already escaping — and that is too late. The cut in the wall of a blood vessel will become fringed with fibrin threads, all hanging downstream in the escaping blood, and there's no way that the threads can bridge the gap. They cannot possibly reach across the opening in the blood vessel wall, so the fibrin threads will never be able to stop the blood flow. The standard explanation doesn't work.

The phenomenon soon gave me a novel way of dealing with grazes and minor wounds. If one of my school friends had a small cut, they'd head back home, where mother would wash the wound and smother it with cream. They'd cover it with a dressing. Often the bleeding wouldn't stop, and blood would soak through the plaster. Sometimes the wound became infected, and even when they healed they often left a visible scar. My approach was completely different: If the cut was clean (as it usually was, because mine were most
Typical diagrams of hemostasis reveal the coagulation paradox. This image from the Antiphospholipid Syndrome Support Group claims that fibrin bridges the gap in a capillary with blood still flowing under pressure through the wound. It cannot work like this.

Often caused by a scalpel or a model-making knife, I would simply replace the skin and hold it down tight with a finger. I kept my finger in place for a full five minutes — which, I reasoned, would stop blood escaping and was time enough for the fibrin network to form. At the end of the five minutes, I’d slowly peel the protecting finger away, rolling it off very gently, to find that the skin was back in position and the cut was neatly closed. Of course, it was important not to put stress on that area until the next day, but the cut simply healed, painlessly and invisibly without further attention. I am not going to recommend that everyone should try this method — just in case somebody develops cellulitis or goes down with septicaemia and blames it on this column. But I have always done this since (it works wonderfully for a cut that occurs while shaving), and I still believe that this approach has clinical implications.

The physics of blood coagulation arose again when I had a year with the Medical Research Council (MRC) after leaving school. One of my friends was a medical student named Gareth Edmunds, who took me to the MRC laboratories and recommended me for the post. His young brother was Dave Edmunds, who was training as an apprentice welder. Gareth was destined to become a doctor, while Dave was a keen guitarist. Dave and I played together in a band called the 99ers. Dave’s parents insisted that he should serve his apprenticeship so that he would be confident of earning a decent living as a welder. Instead, he ended up as a chart-topping rock guitarist and eventually became a record producer in Los Angeles, working with Ringo Starr and George Harrison. I don’t think he does much welding.

Once I had been appointed as a junior research assistant at the MRC, I found that one of the projects involved culturing bacteria on agar plates made with serum. As the most junior member of the team, I was dispatched once a week to the slaughterhouse to collect supplies. I took an enameled bucket with a paper cover and stood by the slaughterman as he killed a cow. The animal would be stunned with a captive bolt gun and then, with its tongue lolling out and its eyes rolling, the cow would be turned over in the massive steel cradle, its head held back and its throat cut with...
a single swipe of a curved knife. A huge spurt of steaming blood spouted from the cavernous wound in the throat, and much of it ended up in my bucket. The paper lid was secured with tape, and I returned to the laboratory carrying a gallon of blood.

By the time I was back, the blood had formed a firm clot. This jelly-like mass floated like a scarlet iceberg surrounded by transparent, straw-colored serum. The blood cells were retained within the fibrinous coagulum, and the serum surrounding it was crystal clear. My mentor was a most able and resourceful man, Prof. Scott Thompson, who explained it all: “The fibrin network traps all the blood cells,” he said. “They are all held together as the clot slowly contracts. We won’t find any blood cells free in the serum. This is how hemostasis works.”

It worked when the blood was lying in the enamel bucket. But how could this be the case when the blood was flowing through a cut in a blood vessel wall? Thompson took me over to the medical school and introduced me to the librarian. He told me to set some spare time aside and consult the papers. “People have been studying this for centuries,” he told me with a smile. “You will find the answer published somewhere, if you take the time to find it.”

A FLUID PHENOMENON

During lunchtimes and sometimes in the evenings after work, I’d read about hemostasis and blood coagulation, and it soon became clear that nobody had perceived the paradoxical nature of the phenomenon. I soon discovered why. Blood coagulation had always been studied as a chemical system, not as a fluid phenomenon. The whole point of coagulation is to cause hemostasis, which means halting the flow of blood. Yet, every time it had been studied, it was blood that was lying still in a test tube or glass dish. Nobody studied live blood. The achievement of hemostasis is a dynamic phenomenon, yet it was always being studied in static systems. As this truth dawned, I closed the bound volumes of those hematology journals and sat for a long time immersed in thought.

Once I was back at the laboratory I set out to model blood coagulation in a bench-top system. Microscopes were everywhere, and so was all the equipment one could desire. We had already constructed a range of plastic circulation systems to study the transmission of solutes across semi-permeable membranes. Frog skin was used, and we used to pith frogs by destroying the brain with a dissecting needle then clamping disks of the still-viable skin between Plexiglas flanges. I tried many ways of adapting this system to study blood flow, but could never make it work. Light microscopy was crucial for this work, and I soon began using darkfield, which showed the tenuous outlines of erythrocytes with exquisite clarity. I was developing techniques that could be used to induce blood flow on the slide — in this way we could observe blood flow and, hopefully, see how it was brought to rest. Two approaches were tried: One was the use of gentle pressure on the coverslip; the other was irrigation by applying absorbent strips to one side of the preparation that would absorb liquid and induce flow.

The most reliable approach was also the simplest. I left a droplet of fresh blood to commence coagulation on the slide, adding a droplet of saline and a coverslip after a few minutes. As I watched, an erythrocyte
would stop moving, even though the fluid around it was still flowing. It stayed in position, with a pointed apex that was oriented upstream. It looked exactly like a child’s balloon. Over the weeks, I adjusted the timing and perfected the judicious use of pressure, so that I could maintain an optimal rate of flow. The image under oil immersion was captivating. As time went by, more and more of the erythrocytes came to rest. The field of view became filled with these curious pointed cells, each of them held invisibly in place as the diluted plasma flowed past. I captured some on movie film, using an army surplus camera fixed to my microscope on the dining room table, and developed the film at home.

**INVISIBLE THREADS**

In time, I had developed a repeatable protocol. I used a nail bed finger prick to obtain a small droplet of blood and transferred it to an inverted microscope slide. I set this to one side for three or four minutes before adding a small drop of physiological saline. The partly coagulated sample was set into radial flow by the capillarity exerted between the coverslip and the slide, and erythrocytes could be seen moving through a partly formed coagulum. We now had a reliable method of watching live blood under the microscope. Channels formed, and within these, one could observe the behavior of the cell population during the development of a fibrin network. It was here that the strange, pointed cells became apparent. They were exactly like balloons — except that we couldn’t resolve the strings. I decided to call them penderocytes, to imply that they were suspended cells.

Inferring that invisible threads were present was possible because of the behavior of the cells. This is similar to the techniques astronomers use to detect the present of a planet in a far-off galaxy, even when the planet itself cannot be resolved. It is the movement of the distant star that indicates the presence of an unseen orbiting planet. Using similar reasoning, I could deduce the presence of an invisible thread. First, the captive erythrocytes were jostled by those moving past. They moved through an arc, subtended by the point of attachment. Secondly, the threads were elastic, and one could demonstrate that by observing what happened when the speed of fluid flow was altered. As the flow increased, the penderocytes moved downstream as the thread stretched and, what’s more, the apex became increasingly acute as they did so.

At a Royal Microscopical Society conference at the University of Oxford in 1962, I eagerly discussed my
findings with several of the great microscopists present. One was John Bunyan, one of the most distinguished presidents of the RMS, who encouraged me to carry out work on wound healing mechanisms. Wound healing was a fascination to me then and has been since. The facilities that Bunyan provided, including the gift of an excellent darkfield condenser, were crucial. I realized that the coordination of cells during the restoration of damaged tissues reveals the autonomy of the cell population, and the report I wrote for Bunyan in September 1962 was my first venture into the microscopy of healing tissues.

DARKFIELD REFINED

During the following two years I refined the work further, and in 1965, I was invited to demonstrate the results at a conference of the British Microcirculatory Society held in London. It was the first time I spoke in the lecture room of the Royal Society in Burlington House, and it was an exciting occasion. There was much interest in these revelations, and in October of that year, I published a paper in the Journal of the Royal Microscopical Society (Vol. 84, p 423). This was all so encouraging that I settled down to refine the darkfield setup and eventually found that one could discern the suspending threads. Calibration of the image showed that the reflectivity of each thread varied — doubtless as a factor of its width — though the breadth of the image of the thread itself did not alter. Although the threads could be observed, they were not being truly resolved. Like particles of smoke in a beam at night, we could catch the reflections, even if the objects from which they were reflected remained theoretically beyond our sight.

The pictures of the penderocytes — complete with their suspending threads — reminded us all, once again, of the transcendental beauty that the microscopic world reveals. Medical News, the British doctors’ journal, was keen to publish the micrographs, and they became a front-page story. It was quickly picked up by the popular press, and the London Evening Standard hailed it as a “sensational discovery.” Their report was syndicated across hundreds of other newspapers, and the pictures were included in the 1966 edition of the McGraw Scientific Encyclopedia, published in New York. The research was international news.

The sight of blood cells, shimmering like galaxies in darkfield under oil-immersion microscopy, is such an entrancing spectacle. Everyone should be familiar with this sight. Occasionally, I observed leukocytes budding off objects that looked exactly like thrombocytes or platelets and once captured the entire sequence on movie film. The micrographs were sent by air mail to several colleagues for comment, and Dr. Walter McCrone wrote from Chicago to express his fascination for the results. He published my paper in The Microscope in July 1968 (Vol. 16, p 277).

Observing structures that were too tenuous to be resolved continued to intrigue me, and I published a paper on the nature of visualization in Proceedings of the Royal Microscopical Society (Vol. 3, p 14) in March 1968. That same year, I had a call from the editor of the International Yearbook of Science and Technology. The research had attracted so much attention that they wished to include it in their “scientific highlights” section. The book was an impressive volume, weighing over two pounds, and probably cost as much to send by air mail as the book itself was worth. My copy arrived by special delivery in a bright red Royal Mail van that drove up to my home. My father was staying with us at the time. He was a senior engineer, crisp and unyielding in his manner and was not im-

*A meshwork of fibers is formed as shown in this photograph,*” alleges the caption in Biology for Life by M.B.V. Roberts. This is impossible because the network cannot bridge the gap in a damaged capillary if blood is still escaping.
pressed by my freewheeling lifestyle and bohemian approach to science. He was not a man given to compliments. “Humph,” he said, as I signed for the parcel. “What have you got there?” I opened the wrappers and lifted out the yearbook. There was a “with compliments” slip to mark the relevant pages. “It’s the new science yearbook,” I explained. “They’ve included some of my research.” I passed it over to him, and he turned the pages. There were my penderocytes, proudly printed in the “highlights” section and taking up most of the page. I felt a surge of pride, almost of embarrassment. On the facing page was another highlight — an image sent back from the moon by the lunar lander Surveyor 5. To see my research taking pride of place with such a momentous achievement was hard to grasp.

Father inspected the page and then turned to the index. After a moment or two he closed the book and gave it back to me. “Humph,” he said again. “That’s it, is it? That’s the only thing of yours they have in their book?” I nodded. Father raised his eyebrows in a gesture of disappointment and strutted off to the kitchen for a cup of tea. I turned the pages of the book once more to make sure I hadn’t been imagining it all. Yes, there it was — a highlight of the year. Newspapers were soon reporting the honor, and McCrone proposed to include a lecture on the topic in the program for the annual Inter/Micro conference, which was held at London’s Imperial College in September 1969. This was the first time Walter McCrone and I met in person, and my paper of the presentation appeared in *The Microscope* (Vol. 17, p 271). It was followed by papers on applications of this technique, including one titled “Searching for Ultimate Resolution” for the *British Journal of Photography* in February 1970.

People were following it all with interest, and I began to receive messages, letters, phone calls from cranks in Britain, and particularly from the United States, who believed that my technique for observing blood could be used to diagnose illness and even one’s personality. The study of live blood became a new target of attention, and there were soon hordes of “practitioners” who convinced members of the public that they could identify food allergies, stress levels, weird parasite infestations — just by taking a peek at a droplet of live blood slightly diluted with saline. These people have even featured on television. It is, of course, scandalous.

The interest shown by academia was serious, sane and sound. The medical fraternity was becoming increasingly interested by these discoveries, and my friend Dr. Shang Ng, a hospital consultant, had mentioned it to his colleagues and invited me to discuss it with the surgeons at a cardiac unit at Sully Hospital in South Wales. I had now developed my technique to provide a regular and repeatable test, which might allow one to assess the efficiency of hemostasis by observing the formation of penderocytes. The test wasn’t calibrated, for it was in the early stages, but already it could provide a pointer to the status of coagulation in a given patient, and it was beginning to offer an early warning of post-operative hemorrhage.
THEATER OF OPERATIONS

Sully Hospital was the base for a brilliant, brisk and businesslike cardiac surgeon named Dr. Tom Rosser, who explained that they had a continuing problem with their patients. After open heart surgery, patients sometimes tended to bleed uncontrollably. Worse, they bled into the pericardium, the sac containing the heart. When blood seeps into this space, it produces back pressure on the heart, preventing it from beating efficiently. The phenomenon is known as tamponade, and was a known hazard of open heart surgery. Rosser invited me to come into the operating theater to observe the hospital’s procedures. He gave me pride of place, standing by his left-hand side as he operated. It was an intensive introduction to this remarkable branch of the surgical art, and it taught me so much.

It also forced me to realize how fortunate we are when we’re under the surgeon’s knife. In each of his operations, Rosser had the patient supported on a bypass pump — the heart-lung machine. The key to its success was the roller pump, in which peristaltic waves are induced outside a flexible tube that propels blood through it with the minimum of trauma. The blood was then passed through a transparent drum, within which were rotating disks. As the blood trickled across the surface of the disks, it was brought into contact with oxygen, and gas exchange could take place. In this way, the perfusion of blood allowed the bypass machine to take over the functions of both heart and lungs. The surgeon was then freed to attend to the heart at will, without having to contend with its functioning as it does in life. He would open the chest with a high-speed bandsaw, as though cutting firewood, and the intoxicating smell of shredded bone remains with me to this day.

On one occasion, Rosser had performed a tricuspid valve replacement on an elderly and obese patient. The heart was mottled with fatty deposits, and the aortic arch was discolored and inflexible. Normally a wave of expansion sweeps along the major arteries with each heartbeat, but this aorta was rigid and didn’t flex as it should. The operation had been a success — until the chest was about to be closed. Suddenly, right before our eyes, the aorta began to rupture. Tiny glimmering beads of blood peeked through the brittle layers and soon began to spurt. The assistants mopped it away with swabs. Rosser called for a surgical needle and a wad of gauze and deftly stitched the fabric over the oozing site. Still, the blood came. He took another small wad of gauze, another, and yet another. Each time he managed to secure it in place with a few meticulous stitches until, at last, the oozing slowed. I could picture the mechanical blockage caused by the gauze, which brought the blood flow to a standstill. Red cells would become entangled in the threads of the gauze and fibrin which was precipitating across the site. The escape of blood was almost stopped as Rosser gave the order to close the patient’s chest.

As the sternum was brought together to be secured with wire, the diseased aorta was still glistening, but Rosser was confident that, once closed, the repair would heal. He was right, and I fully understood the hemostatic mechanisms that underpinned his remarkable technique. Next morning, I accompanied Rosser on his rounds and stopped to talk to the patient, who was propped up in bed, smiling broadly and saying how much better he felt. All I could think of was his battered aorta, its fatal breakdown avoided by the stitching in place of a few wisps of cotton fabric. How fortunate he was, and he would never know what had gone on within him. The patient was a town official and lived on for decades.

At another operation, Rosser suggested the theater nurse should give me the patient’s notes to review. I read them studiously, trying to build up a mental picture of the patient’s condition. This was an elderly patient with congestive heart failure, and his heart had become grossly distended as it vainly tried
to adapt to increasing demand. He had never had cardiac surgery before, and the operation was an attempt to improve his circulatory status. The X-ray films were hanging nearby, and I turned to study those. Nothing made sense. The outline of the heart on the films was of normal dimensions. What’s more, there was the unmistakable image of a previous valve replacement. I looked again at the notes, and the descriptions didn’t agree. Then I noticed the crucial error: The name on the cover of the file was of a Mr. Henderson, but the notes within were all headed with the name of a Mr. Jones.

The operating theater was abuzz with activity, and a visitor is ill-advised to interrupt such a well-lubricated system. I waited for a lull, and then spoke. “Mr. Rosser …” He turned, not pleased at the preparations being abruptly interrupted. “Was there something?” he asked in measured tones. I showed him the file. “I think we, ah, we have the wrong patient on the table,” I ventured. The room fell silent. Rosser perused the pages, and then shot a glance of fearsome intensity from over his gold-rimmed eyeglasses. “This,” he announced to the theater, “is intolerable. Has nobody checked that you have given me the correct notes for the right patient? The procedures are entirely different. The approach is different. The incision is different. Had we begun work on … Mr. Jones, then the entire outcome could have been jeopardized. Nothing like this,” he swept his gaze around the room, making steady eye contact with everyone on his team, “must ever happen again.” He thanked me, and I felt relieved. Furthermore, I didn’t feel as much of an intruder in this private world the next time I attended one of his operations.

I took pinprick samples of blood from patients after extended periods on the bypass machine and compared the extent to which penderocytes formed before and after the operation. It soon emerged that the time spent on bypass correlated with the failure of penderocyte formation. The idea I had was that the rolling of the erythrocytes across the metallic disks within the machine caused a surface trauma that altered the surface properties of the cells and compromised their ability to become attached to the fibrin threads. Only a few tests were made, though I recall testing one patient whose test results were very poor after perfusion. The surgeons were convinced that this operation had gone well, and that there would be no postoperative complications. But my tests led me to predict that she would develop severe tamponade — and, indeed, she did. However, there were far too few results to make a worthy publication and no funding available to launch a major research project. The results were interesting, but not conclusive, and after years of excitement and widespread interest, the subject began to fade from view.

DEBAKEY’S LEGACY

Some people remained intrigued. One of those was the great pioneering heart surgeon Dr. Michael DeBakey. As a young medical student, DeBakey had invented the roller pump which is at the center of the heart-lung machine. I had greatly admired it when researching the effects the perfusion process had on my penderocytes. And here I was at the time, a 23-year-old, the same age this brilliant doctor was decades earlier when he had invented a key component that revolutionized cardiovascular medicine. In 1974, I was invited by the BBC in London to make a two-hour radio show on cardiac medicine, and we con-
tacted DeBakey to feature him in the program. He was delighted and invited me to attend his operating theater in Houston.

I stood by him for hours as he worked, and I watched with astonishment his incredible dexterity. Holding small segments of femoral vein at arm's length, he used minute and exquisite sutures to hold them in place where they could bypass occluded coronary arteries in patients otherwise doomed to an early death. We discussed penderocytes and the traumatic effects of perfusion on blood. It seemed paradoxical that his roller pump reduced cell damage to a minimum, whereas the rotating disks seems to expose the erythrocytes to surface traumas that we could not understand. We remained in contact afterwards and exchanged greetings at Christmas until his passing at the age of 99. Even in his advanced years, DeBakey was in the operating theater, advising younger surgeons on procedures and techniques.

Apart from occasional demonstrations of the technique, little research was done for a decade. Then, in 2005, I had a surprise message from Dr. Neil Ravenhill, editor of the Olympus magazine Illumin8. The request was simple: Could they reproduce some of my micrographs of coagulating blood? I spoke to him by phone. Did he realize that this work was more than 40 years old? He did, of course, but he felt that the work deserved to find a niche in a present-day publication. I wrote an article for Olympus, featuring the original micrographs, and setting them in context with some of the results I had since obtained by observing a smear of my own blood through a Leeuwenhoek microscope made around 1690. It related a rounded story and represented the resonances between Leeuwenhoek’s pioneering work and my own observations. My article appeared in the February 2006 edition of Illumin8.

Olympus liked it, and they presented me with a digital camera as a token of their appreciation. Then I had a message from a medical journal, Clinical Laboratory International. Their editors felt that this work on live blood was potentially important and, with open heart surgery established as a routine procedure, they invited me to submit a full-length paper, which was published later that year in their journal (Clinical Laboratory International, Vol. 30:5, p 12). The project had arisen, disappeared, and been revived several times over the decades, and I presented a summary of the entire saga at Inter/Micro 2007 in Chicago.

The paradox persists to this day in teaching blood coagulation to students, and the answer has still not crept into textbooks. I also have a lingering sense that the use of a single-drop blood test could forewarn doctors of an impending post-operative hemorrhage, and I still reflect on the likelihood that erythrocytes can suffer surface trauma when rolled over the surface of rotating plates in a heart-lung perfusion machine. Once in a while, I hear of a cardiac patient who has spent too long on bypass and then suffers serious tamponade. I think back to John Bunyan’s words of encouragement, Tom Rosser’s interest in the test, Michael DeBakey’s curiosity and Neil Ravenhill’s determination to revive the subject. The International Yearbook for 1968 is still on the bookshelf here, and lurking in a drawer are awards that my micrographs of live blood were granted many decades ago. Blood coagulation is not a subject to which I propose to return with a major research project, but it taught me much and led to some curious adventures.

Above all, it reaffirmed that inevitable conclusion that I made as a teenager: funny stuff, blood.