HISTORY OF MEDICINE

A Scandalously Short Introduction

SECOND EDITION

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UNIVERSITY OF TORONTO PRESS
Toronto Buffalo London
CHAPTER EIGHT


Blut ist ein ganz besonderer Saft. (Blood is a very special juice)

— J.W. von Goethe, Faust, I, 1 (1808)

Blood as Magic and Mystery

Blood is important. It has always been important, and it has always seemed to be important to everyone. Of the four ancient humours, it alone remains a vital entity, with a status well above that of phlegm or bile of any colour. Most people immediately understand that blood is essential for life. On the other hand, when asked if the spleen, liver, kidneys, or pancreas are essential, they are less certain. People do not think of those organs in the way that they think of blood.

Why has blood always enjoyed a special status? Two reasons. First, it is eminently visible, being the only internal organ that regularly surfaces for perusal; all humans have seen some of their own blood. Every injured person knows that bleeding marks the severity of the wound. Every woman can expect a flow at regular intervals allied to the phases of the moon.

Second, blood is always associated with life. Even children know that when blood is lost in great quantities, death may ensue. In many

*Learning objectives for this chapter are found on p. 453.
languages, it is synonymous with life and health. Some cultures, such as prehistoric peoples of Europe, Africa, and Asia as well as Australian aborigines and the vanished Beothuk of Newfoundland, prepared for burials by colouring bodies or graves with red ochre (containing hematite) to restore the bluish-like colour of life. Scholars have analysed how menstruation influenced perceptions of women at various times and places, noting that myths and traditions cast suspicion on those who could bleed regularly without ill effect. For example, Islam and orthodox Judaism forbid sexual relations with a menstruating woman. In Judaic tradition, a woman is unclean following her menses or delivery of a child, until she has taken the ritual mikveh bath. K. Codell Carter speculates that in the nineteenth century, menstruation may have served as a model for regular bloodletting in men to provide healthful ‘monthly evacuations.’

In ancient Greek mythology, blood was one of the first miracle drugs. Perseus severed the snake-tressed head of the Gorgon monster Medusa and presented the gruesome trophy to the goddess Athena, who placed it on her shield. Athena gave blood from the Gorgon’s head to the healer Asklepios (in Latin, Aesculapius), who used it for amazing cures and to raise the dead. The potent treatment led to his deification as the god of medicine. Asklepios’s staff, around which a snake is entwined, is the medical caduceus, the symbol of medicine for more than 2,000 years.

Christianity has done nothing to diminish the importance of blood in our culture. Blood is central to the mysteries of the sanctuary: not only is it life and health, it also indicates redemption of sin and eternal salvation. The blood of martyrs symbolizes pain and faith; that of children, the worst of the world’s many unjust tragedies. The word ‘blood’ and its derivatives are mentioned no less than 460 times in the Bible; ‘life’ is mentioned only slightly more often (487 times). How often does the word ‘kidney’ appear? Seventeen times. ‘Liver’? Thirteen times. ‘Bile’? Once. And ‘brain,’ ‘pancreas,’ ‘lungs,’ and ‘phlegm’? Never. True, ‘heart’ is mentioned more often than ‘blood’ (817 times). The reason relates to the importance of the religious signifiers: if blood was life, heart was love or soul.

Given its ancient connection with life, blood as therapy is also very old. However, blood-medicine was not always convenient. Wine often served as a proxy, taken as a panacea, a stimulant, a depressant, a restorative, a digestive, a hypnotic, or an escape. Rooted perhaps in their visual similarities, the substitution of red wine for blood was further endorsed by the Christian doctrine of transubstantiation: in the mass, wine becomes the redeeming blood of Christ. Renaissance images showed the body of Christ crushed in the ‘miraculous press’ from which blood trickled into waiting barrels.

The English word ‘blood’ is neither Latin nor Greek in origin, as are so many of the words used in medical terminology. Medicine makes use of the terms ‘hematology’ (derived from Greek) and ‘sanguinous’ (derived from Latin), but words such as these with classical roots are rarely used in regular practice to identify the humour itself. Even the leading journal of the field, published by the American Society of Hematology, is called Blood. The word comes from Old English through Nordic and Saxon roots. Language theory holds that as the French-speaking Norman invaders married the Anglo-Saxon women, Latin-derived French words took over the vocabulary of the external environment of masculine authority; however, words pertaining to the interior, domestic, female environment, and to emotions and feelings, were retained—with these words we have ‘blood.’ The derivation may illustrate blood’s special importance to women’s work rather than its power. For example, the words ‘liver,’ ‘kidney,’ and

More along Linguistic Lines

Anglophones appear to have a special subliminal respect for the word ‘blood.’ Think about the psychic power in its many derivatives: cold blood, blue blood, bad blood, fresh blood, hot-blooded, red-blooded, bloodline, blood red, bloodless, bloodthirsty, blood-curdling, bloody, bloody-minded, bloodshed, bloodshot, bloodstone, blood money, blood poisoning, bloodstain, blood feud, flesh and blood, and lifeblood.

How many similar words can be found for the liver? Liverish, liver spots, and lily-livered—not very impressive words. And for the kidney?
‘heart’ also come from Old English, possibly because these organ-like blood, are edible parts of animal bodies. Body parts with Latinized names—such as aorta, colon, duodenum, rectum, vagina, tendon, and cartilage—have little or no culinary interest.

If the linguistic argument for the special power of blood is unconvincing, a psychological analysis is difficult to refute. Most patients who are referred to a hematology clinic have no symptoms at all; they are sent for abnormalities picked up during routine testing. Even patients with newly diagnosed leukemia may be symptom-free. Nevertheless, people sent to hematologists are apprehensive: a problem with blood is a problem with life.

**Blood as Medical Science**

Medical professionals discount magic and myth, finding them quaint but incredible. As blood has been medicalized and objectified by technology, its mystique with scientists may have waned. But blood and its multiple functions still occupy an exalted state—a position that seeks to reconcile the ancient notions of blood’s great power with our understanding of modern science.

**Blood Therapy: Transfusion**

If blood is life, it is only logical to assume that faltering life might revive with a little extra blood. The first ‘transfusion’ is often said to have been given in 1492 to the dying Giovanni Battista Gibò, who had been elected pope as Innocent VIII in 1484. His Jewish physician, Giacomo di San Genesio, is said to have tried to resuscitate the ailing pontiff by having him drink the blood of three ten-year-old boys whom he had had killed. The evidence for this peculiar treatment is unreliable, and the story is probably an anti-Semitic fabrication, not unlike the rumours of ritualistic child murder that tracked the customs of Passover.

Oral blood had probably been tried many times before, and without the prerequisite of donor death. Moog and Karenberg report on the use of gladiators’ blood for epilepsy in late Roman antiquity. Galen held that blood was elaborated from ingested substances; sure-

In early 1667 the French physician Jean-Baptiste Denis appears to have attempted the first intravenous transfusion between humans when he gave lamb’s blood to a fifteen-year-old boy to calm his nerves.

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**Borrowed Blood**

At dinner on 14 November 1666, Samuel Pepys learned of a successful direct transfusion between dogs, which had taken place in London that day. The potential of such an achievement did not escape the diners. Pepys recorded their mischievous reaction in his famous diary:

This did give occasion to many pretty wishes, as of the blood of a Quaker to be in an Archbishop, and such like. But, as Dr. Croone says, [it] may, if it takes, be of mighty use to man’s health, for the amending of bad blood by borrowing from a better body.

Not to be outdone by the competition from across the channel, Lower performed his own sheep-to-man transfusion later the same year. Back in France, Denis became a transfusion specialist, but the next year a man died following a failed attempt to give him a third transfusion of animal blood. Denis was sued — but the court decided that the patient had been poisoned by his wife, and the doctor was exonerated. However, the sobering publicity dampened enthusiasm, and transfusion activities were curtailed for nearly a century and a half.

Indeed, blood transfusion was (and still is) a potentially life-threatening intervention, never to be undertaken lightly. There problems posed serious hurdles: the reactions that were later known as blood group incompatibility, clotting, and infection.

Transfusion was cautiously revived in the early nineteenth century. The perennial problem of obstetrical bleeding became more obvious to practitioners as childbirth was medicalized (see chapter 11). In the 1820s, James Blundell of Guy’s Hospital in London, England, attempted transfusion for uncontrollable postpartum hemorrhage. Using a syringe, he injected the bleeding mothers with blood taken from the resident housestaff; a few lives appeared to be saved. Patients given this heroic therapy were not expected to live; if death resulted from transfusion, it would have been ascribed to the original hemorrhage.

Another stimulus to transfusion came from the urgent need to save bleeding soldiers. During the Franco-Prussian War of 1870–1, direct transfusions were given on the battlefield, soldier to soldier, by medics in the armies of Austria, Belgium, and Russia. Sterile technique was used, but incompatibility and clotting had yet to be resolved, while storage of blood seemed to be virtually unattainable. These problems found solutions in the twentieth century.

Compatibility

The problem of compatibility began to unravel with the work of the Vienna-born Karl Landsteiner, who in 1901 published a short study based on the twenty-two workers in his laboratory: their blood could be divided into three major groups, A, B, and C (now called O). The following year, two of his pupils discovered the fourth major blood group, AB. Landsteiner’s work was ignored until just before the First World War. He moved to New York to the Rockefeller Institute in 1922 and became an American citizen. His Nobel Prize was awarded in 1930 when the practical application of his discovery had been realized.

In 1937, Landsteiner and his colleague Alexander Wiener also noticed another blood-type system that they called ‘Rhesus’ (Rh), because it appeared in experiments between rhesus monkeys and rabbits and was subsequently found to react to human blood too. Although not exactly identical to the factor that now bears the name, this system helped to explain a strange condition of newborn babies called erythroblastosis fetalis: an Rh-negative mother, sensitized by mixing of blood at the birth of a previous Rh-positive child, develops antibodies that travel across the placenta to attack the blood of the
Now hundreds of blood groups are recognized, the most important still being the ABO and Rhesus systems. The ability to wash, freeze, and thaw blood safely has made it possible to provide a relatively compatible supply for even the rarest types.

**Anticoagulation**

As the researchers discovered, untreated blood will clot within a few minutes. Storage depended on finding a method to inhibit this natural property without harming either the product or the recipient. Testing began on techniques for removing fibrin (the clotting protein) and on anticoagulant drugs. Just prior to the Second World War the Russians took advantage of natural anticoagulation – cadaver blood will not clot because it has already clotted and lysed. Cadaver blood and, for similar reasons, placental blood, were also used for transfusion in India and elsewhere.

Now the preferred anticoagulant is sodium citrate, discovered in 1914. It was systematically applied to battlefield needs of the First World War by an American army doctor, O.H. Robertson, working with a British unit. Using only O-positive donors, Robertson demonstrated that citrate combined with dextrose (to nourish the blood cells) allowed safe storage of blood for up to three weeks – the first blood bank. Work on heparin as an anticoagulant for medicine and surgery was the product of Canadian research by Charles Best, Louis B. Jaques, and D.W. Gordon Murray in the early 1930s.

**Blood Components**

With the problems of compatibility and coagulation under control, hospital blood banking began. By 1927, plasma was usefully extracted from outdated blood by centrifugation. The Mayo Clinic of Rochester, Minnesota (1935), and Cook County Hospital in Chicago (1936) vie for the honour of being the first American hospitals to run blood banks. The controversy arises because individuals had been transfused there and elsewhere for several years, and sometimes the blood had been stored. The Canadian surgeon Norman Bethune helped to establish a mobile unit for plasma transfusion in December 1936.
during the Spanish Civil War. Plasma for shock and clotting factors became the mainstay of emergency treatment in the Second World War. Component therapy, the use of specific parts of blood—red cells, platelets, white cells, factors, and plasma—is now standard practice.

After 1945, blood banking became a regular practice in countries all over the world and could be cited as the beginning of hematology as a distinct professional entity. In the United States, city-, state-, and nationwide services were created with the help of non-physician volunteers. For example, after serving at Pearl Harbor, Bernice Hemp- hill returned to work in a San Francisco blood bank; from 1948 until 1953, she was instrumental in extending the blood-bank cooperation across California, and eventually to the entire country. The National Blood Service of England began in 1946, with separate agencies for Scotland, Wales, and Northern Ireland. In Canada, as in several other countries, the blood transfusion service was run by the national Red Cross from 1947 until 1998. Blood collection, storage, and transfusion was only one of many peacetime services offered by that organization, but its role in Canadian blood banking came to an abrupt end with new controversies over infection (see Krever commission below, on the Red Cross, see chapter 10). Since 1998, the non-profit organization Canadian Blood Services fills this function and oversees a stem cell and marrow registry; HémaQuébec handles the equivalent tasks in Quebec. The Red Cross is still involved in collection as the sole organization or with others in several other countries of Europe, Australia, and the United States.

Infection

Sterile technique for handling blood has been in place for more than a century; however, infection has been a serious problem and is currently the object of public anxiety. Syphilis, several forms of hepatitis, West Nile virus, and AIDS are among the many infections that can be transmitted by blood. Serological testing has reduced the risk. Hepatitis remained the most frequent of the transfusion infections until the early 1990s, when testing finally became available for what is now known as hepatitis C. Vaccination against hepatitis B, which received U.S. Food and Drug approval in late 1981, is an important consideration for medical personnel who can accidentally be exposed to the blood of others. In countries where equipment may not be sterilized properly, donors can transmit infections to each other. And when donors fear infection, supplies falter.

Members of the Christian religious group Jehovah’s Witnesses base their stand against transfusion on an interpretation of biblical passages forbidding consumption of blood. The same passages are cited as an origin of kosher butchery methods in the Judaic tradition. They also illustrate how the story of the Last Supper and the tenets of the Catholic mass, especially transubstantiation, could be seen as a surprising rupture. Concern over infection, added to steady pressure from those who have philosophical objections to transfusion, has stimulated research into blood surrogates such as plasma expanders, hemoglobin, and clotting-factor substitutes.

### Blood Is Life, but You Should Not Eat It

Only you shall not eat flesh with its life, that is, its blood.

— *Genesis 9:4*  

If any man of the house of Israel ... eats any blood, I will set my face against that person who eats blood, and will cut him off from among his people. For the life of the flesh is in the blood.

— *Leviticus 17:10–11*  

Only be sure that you do not eat the blood for the blood is the life, and you shall not eat the life with the flesh.

— *Deuteronomy 12:23*

The shape and image of blood banking and transfusion have been altered. No longer ‘the gift of life,’ blood therapy is mistrusted, especially in the United States, where until the late 1970s donors could be paid. In France, a lengthy inquiry into policies surrounding blood products resulted in the 1992 conviction with a four-year prison sentence for the physicians who had directed the national blood service,
Michel Garetta and Jean-Pierre Allain. France was said to have kept using blood known to be contaminated and delayed AIDS testing with an American product until October 1985 in order to allow the French version to catch up; the investigation continued to the end of the decade. In Canada, a royal commission into the issue of transfusion-related infection, chaired by Justice Horace Krever, began hearings in 1993. It resulted in many changes to the blood system and allegations of wrongdoing by politicians and Red Cross officials. The former national director, Roger Perrault, endured years of RCMP investigation, criminal charges, and a long trial, which he won; his complete exoneration did not occur until 2008, when outstanding charges were dropped.

Entrepreneurial persons have taken advantage of the situation to open private blood banks, where the anxious can stock their own blood for future surgery or a disaster that occurs within convenient reach of the freezer. A similar situation prevails with respect to umbilical cord blood, which since 2000 is banked both publicly and privately in many countries throughout the world, prompted by expectations for stem cell research. Private procedures are a grey area legally and they are inaccessible to many citizens. If tolerated, they will replace the previously imperfect but equitable system with a two-tier system. Donation experts worry that reporting of high-risk behaviours could decline with added pressure for family contributions.

Marrow transplantation can be seen as the ultimate form of component transfusion. It was developed during the 1970s in Seattle, Washington, under the direction of E. Donnall Thomas, who used the principles of anticoagulation and intravenous infusion, and the cell-cloning techniques of Canadian researchers J. Till and E.A. McCulloch. Marrow transplant offers hope for chronic anemias and malignancies. As a side effect, the new iatrogenic problem of graft-versus-host disease arose. To help those who did not have suitable donors, autologous (self-) transplantation was developed; however, because the graft-versus-host side effects do not occur with the patient’s own cells, this method is widely used in other situations – for example, to ‘rescue’ a person’s blood-making ability following the ravages of strong treatments for cancers and autoimmune disease. The ultracentrifuge technologies of cell separators allow for the selective collection of stem cells, so that a ‘transplant’ may now involve

more specificity and a smaller volume of cells. E.D. Thomas shared the Nobel Prize in 1990. For their 1960 discovery of hematopoietic stem cells, Till and McCulloch received the Lasker Award in 2005.

**Blood in Diagnosis: What Is Normal Blood?**

Today’s physicians have few opportunities to look at their patients’ blood. Blood is visible in surgery and emergencies, but these settings do not allow for contemplation. Nurses, IV teams, laboratory technologists, blood banks, computerized analysis, and printed reports have distracted the doctor from the physical realities of blood. Not so in the past. From antiquity until the mid-twentieth century, bloodletting was standard treatment, and all doctors regularly examined their patients’ blood for the changes that took place in it upon standing.

Bloodletting seemed to be beneficial in fevers: it lowered the pulse, lessened plethora, and calmed agitation. The let blood soon coagulated and separated into several easily distinguished components, in which could be visualized the four ancient humours: yellow serum above, dark (deoxgenated) blood below, a rim of bright red (oxgenated) blood in the middle, and above it a pinkish-beige layer called the ‘buffy coat’ or ‘web,’ containing white cells and clotting protein. After performing a bloodletting, doctors noted the colour and quantity of each component and were able to link the appearance with diagnosis and prognosis. Dark blood was a poor prognostic sign in pneumonia. A thick buffy layer with a concave configuration (called ‘buffed and cupped’) was a sign of acute inflammation.

**Red Cells: Linking Blood to Air**

**Hemoglobin and oxygen.** With his early microscope, Antonie van Leeuwenhoek observed the tiny ‘particles’ now known as red cells. Their existence, however, was controversial; those who saw them could not explain their function. Around the same time, both the French chemist Nicolas Lemery and Richard Lower of transfusion fame noticed that iron was a constituent of blood. Lower also described the change in colour of venous blood, from dark to bright red, on exposure to air. Some years later, iron became a treatment for anemia after the 1725 observations of the Russian military doctor Alexei Bestouyev-
Rioumine. But neither iron nor the colour change were connected to the little globules, and oxygen had yet to be described.

In 1668 John Mayow demonstrated the life-sustaining properties of some air (see chapter 3), but one hundred years passed before the vital air could be identified. In the 1770s oxygen and ‘laughing gas’ were isolated by Joseph Priestley, an English theologian and chemist, and a sympathizer with the revolutionaries in France. Uncertain of his findings, he explained his discovery to his friend, the French aristocrat Antoine-Laurent Lavoisier, who quickly recognized its importance. With his personal fortune and the help of his wife, Marie-Anne-Pierette Paulze, Lavoisier experimented on respiration, combustion, and oxygen. By 1777 he had formulated a chemical theory of life as a process of oxidation. But the French Revolution put an end to their work: Priestley’s church was sacked, and he fled to the United States; Lavoisier was guillotined.

If life had now become the chemical consumption of oxygen, then oxygen had to be linked to blood, because it too had been equated with life since prehistoric times. This vast scientific project began in the late eighteenth century and extends into our own time. Hemoglobin was identified as the ‘red pigment’ in the globules in 1851 by the German physiologist Otto Funke. His compatriot, Felix Hoppe-Seyler, proved that the pigment could take up and discharge oxygen. Two independent ideas—one ancient, the other relatively new—had been brought together in the red blood cell: blood was life; life was the combustion of oxygen.

A Tragedy Links Blood, Oxygen, and Life

In 1875 the French physiologist Paul Bert sent a hot-air balloon, the Zenith, to 7,900 metres, the highest altitude yet reached by humans. When the balloon descended, two of the three-man crew were dead. Bert concluded that for survival at low pressures, supplemental oxygen was needed to ensure adequate uptake by the blood. His insight laid the ground for the theories of partial pressures in the lung and helped resolve the mystery of the well-known but poorly understood condition called mountain sickness.

An elegant contribution to the characterization of hemoglobin function was the oxygen-transport work of the Danish scientist Christian Bohr, whose son Niels and grandson Aage are both Nobel laureates in physics (1922 and 1975, respectively). Bohr used mathematics to express the relationship of oxygen to hemoglobin. His oxygen dissociation curve describes a remarkable property of blood—its variable affinity for oxygen. The curve is sigmoid; the dips above and below a straight line show how hemoglobin picks up oxygen more readily when it is plentiful (for example, in the healthy lung) and releases it more readily when it is scant (for example, in the healthy tissues). These affinities are ingenious, especially compared with those of a mundane transport protein sporting a banal linear relationship to its object. Moreover, Bohr’s curve shifts right or left, according to the environment in acidosis or alkalosis, to favour the transfer of oxygen to the host. The curve also illustrates the dangerous ‘point of no return’ situation that can occur in severe lung damage, where low concentrations of oxygen ‘on the shoulder of the curve’ can cause hemoglobin to release rather than take up oxygen.

Hemoglobin was the first protein to be chemically identified. Using X-ray crystallography, Max Perutz, John Kendrew, and colleagues elucidated the primary, secondary, and tertiary structure of the hemoglobin molecule in 1960. Its genetic basis was so well understood that researchers could define the molecular substitutions, in both protein and DNA, that are responsible for many abnormal hemoglobins. For example, in 1957 Vernon M. Ingram demonstrated that hemoglobin in sickle-cell disease involved the substitution of a single molecule. Variations in hemoglobin structure were related to changes in function. Altered control over the genetic production of hemoglobin explains the common and devastating thalassemias.

This vast restructuring of knowledge into biochemical terminology promises new therapies for abnormal hemoglobins, through reduced-intensity marrow transplants and genetic engineering; but at the time of writing, little change has taken place in the therapy of most afflicted persons. The field is still very messy. Only 10 percent of people with sickle-cell disease are likely to have an unaffected sibling donor. And as several historians have shown, the elegance of molecular discoveries do not soften the hard realities of social construction on the basis of race. For people suffering in sickle-cell crisis, we still
provide the old remedies of analgesics, hydration, oxygen, and transfusion; for thalassemia, transfusion. These treatments generate new iatrogenic problems, which require secondary therapies, including chelation of excess iron following multiple transfusion, social support for addiction to analgesic drugs, and management of infections. It was an industry-sponsored clinical trial to assess a chelating agent in thalassemia that resulted in a famous case of scientific harassment in 1996, when Toronto hematologist Nancy Olivieri dared to warn her patients of side effects (see chapter 5).

**Morphology and a bevy of fathers.** Extending the microscopic observations of van Leeuwenhoek, William Hewson measured the size and shape of blood cells in different animals. He found that the red globule is usually flat, not spherical, and he recognized that coagulation is a process of change in plasma, not red cells. Hewson died in 1777 of an accidental scalpel wound which he sustained while performing an autopsy. For his precise observations and his romantic end, he has been called the father of hematology, especially by the British.

Despite Hewson’s elegant studies, cell theory was not established until late in the nineteenth century. The vista presented by early microscopes was unreliable. Only after the achromatic lens and compound microscope became available in the 1830s did observers begin to trust their eyes and turn their attention to the cellular components of blood. Gabriel Andral and Alfred Donné, both of France, pioneered quantitation in hematology by linking various illnesses with the number, concentration, size, and shape of red cells. These men too have been called fathers of hematology, mostly by the French.

Andral was the first to suggest that anemia could occur if red cells were destroyed (hemolysis), and he described anemia as a decrease in the number of red cells. He associated anemia with pregnancy and with chlorosis. Once called the ‘green sickness of virgins’ for the peculiar cast it gave to the complexion, chlorosis had been described in the sixteenth century by Johannes Lange, who recommended marriage as therapy. It has come to be synonymous with what we would now call iron-deficiency anemia, although it also resembles anorexia nervosa. Andral was the first to observe the small size of red cells in chlorosis. Here was a capital discovery: a diagnosis formerly bound to a patient’s subjective account of vague symptoms and a doctor’s opinion of her complexion could now be reduced to an accessible, objective test: red cell number and size.

Insight concerning red cells sometimes emerged from intensely practical observations. The American George Minot, for example, noticed that fewer than expected red cells were found in patients with the aggressive and uniformly fatal disease pernicious anemia (also known as Biermer’s anemia, for the German physician who described it in 1868). In 1926, Minot reported that red-cell production increased with a diet containing up to half a pound of raw liver daily. Pernicious anemia is now linked to an inability to absorb vitamin B12. At the time of Minot’s celebrated cure, however, the existence of vitamins was still under dispute (see chapter 13). Minot’s diet was yet another example of empirical success, advocated before the definition of the chemical errors in the disease: intrinsic factor was described in 1929 by W.B. Castle; vitamin B12 was isolated in 1948 by E.L. Rickes and K.A. Folkers.

**Red-cell chemistry.** Red cells are unusual. They have no nuclei and no mitochondria. They are tiny, ‘brainless’ packages whose 120-day lifespan is dedicated to the transport of oxygen and carbon dioxide between the lungs and the tissues. Their other functions include buffering, but their physiology is largely devoted to maintaining the integrity of their hemoglobin and cell walls to provide safe, efficient passage of their precious cargo, oxygen or carbon dioxide. Enzymes are the key.

Red cells were known to be consumers of glucose, but how they could use sugar without indulging in oxygen was not understood until the work of three German scientists: Otto Warburg, his student Otto Meyerhof, and Gustav Embden. The three researchers uncovered two enzyme pathways: the hexose-monophosphate shunt, which provides energy to repair damaged hemoglobin; and the glycolytic pathway, which generates energy for the cell itself. Warburg and Meyerhof are both Nobel laureates.

In 1911, during this wave of ‘chemicalizing’ the red cell, H. Günther characterized the porphyrias, hemolytic diseases that result from an absence of enzymes that govern the production of hemo-
globin. Soon after, physicians who are fond of using the ‘retrospec-
toscope’ invoked porphyria to account for strange behaviours of the
past, ranging from the intermittent madness of King George III of
Britain to the werewolf legends of Transylvania.

Later in the century, Canadian Maxwell Wintrobe invented useful
instruments, such as the hematocrit, and made practical observa-
tions about erythrocyte morphology and behaviour in health and disease.
Raised by an Austrian-Jewish family in Halifax, he completed his
MD at Winnipeg and went on to New Orleans, finally settling in Salt
Lake City, Utah. He was the sole author of the first six editions of the
authoritative textbook *Clinical Hematology* (1942–68). Its bibliogra-
phy could serve as a model of thoroughness and historical sensitivity.
Canadians and Americans alike may be understood (if not forgiven)
when they cite him as the father of twentieth-century hematology.

The idea that human illness could derive from modifications in
the biochemistry and survival of red cells came during the Second
World War. Sources of quinine for malaria prevention in the Allied
troops of the Pacific theatre had been stopped and alternative drugs
had to be found. The new antimalarial agents provoked hemolytic
anemia in some soldiers, mostly black males. A similar phenomenon
took place in the Korean War when primaquine was used for malaria
prevention. In the mid-1950s, using volunteers from the Stateville
Penitentiary near Chicago, the American army scientists Alf S. Alving,
Paul Carson, R.J. Dern, and Ernst Beutler demonstrated that the
red cells of hemolysis patients were inordinately sensitive to the drug
because they lacked the X-linked, reducing enzyme glucose-6-phos-
phate dehydrogenase (G-6-PD). Not only did the discovery explain a
new drug problem, but it also provided a scientific basis for favism,
an ancient disease triggered by eating fava beans. Each of the many
red-cell enzymes was discovered when a fortuitous accident of nature
provided a mutant in whom the enzyme was missing.

White Cells

First described in the eighteenth century, white blood cells were
neglected until the nineteenth-century work of the British physician
Thomas Addison and the German pathologist and statesman Rudolf

Virchow. Addison noticed that ‘colourless corpuscles’ passed
through the walls of blood vessels to form pus in inflammation. In
1845 Virchow described leukemia – literally, ‘white blood.’ The thick
buffy layer in these patients was like pus, but without the usual inflam-
mation; he suggested that it was due to an inappropriate production
of abnormal cells at the expense of normal ones (see also chapter 4).

In the late nineteenth century, new staining techniques facilitated
white-cell morphology. This technological change was a by-product
of a search for new treatments. Paul Ehrlich had been seeking dyes
that could act as chemotherapy for infections by bonding with, and
specifically killing, bacteria (see chapter 5). In 1880 he described
white-cell types, inventing names based on their staining properties,
for example, neutrophil, eosinophil, basophil. Ehrlich believed that
white cells played a role in protecting the body from invasion by the
newly discovered bacteria.

Elie Metchnikoff shared Ehrlich’s opinions about the immune
functions of white cells. A Russian working at the Pasteur Institute in
Paris, Metchnikoff discovered the capacity of phagocytosis. To some,
the notion of one kind of cell gobbling up another seemed ridicu-

lous – and belittling the Russian’s strange character. The molecular
biologist André Lwoff recalled Metchnikoff on visits to his childhood
home – lively, but disorderly, with test tubes of blood and other unus-
ual substances poking out of his pockets. But Metchnikoff’s insights
were in concert with the new immunology, and he was awarded the
Nobel Prize in 1908. The ancient idea that ‘bad blood’ brought dis-
ease had been rephrased in a three-dimensional chemical and physi-
cal package that was consonant with contemporary science.

From 1890 to 1910, serotherapy (or serum therapy) – the use of
blood or blood components containing what we would now call spe-
cific antibody – was advocated as treatment for diphtheria, cholera,
tetanus, meningitis, and other infections caused by bacterial agents.
Emil von Behring and his Japanese colleague Shibasaburo Kitasato,
working in Germany, explored the production of antitoxins by expos-
ing animals to specific infections, such as diphtheria, and extracting
the sera they elaborated. Once again, the constitution of these sera
was unknown, but they were effective.

A study of lymphocytes and their manufacture of antibodies led
to a biochemical explanation of immunity and clone theory. Niels Jerne observed a background production of many different antibodies, but when the test animal was exposed to a specific antigen, large amounts of specific antibody would result. Clone theory arose from an extrapolation of the ideas of Virchow and Jerne. The Australian Frank Macfarlane Burnet made two postulates: first, each cell could react to only one antigen; second, in the course of development, millions of potentially reactive cells arose. Clone theory explains normal immune function and provides a model for some hematologic malignancies – multiple myeloma, chronic myelogenous leukemia, polycythemia rubra vera, and essential thrombocytosis. With the advent of the ability to detect gene rearrangement, many more malignancies are shown to have clonal components.

Platelets

After the technical problems of light microscopy had been resolved, the existence of the tiny cells that came to be called platelets was under dispute. In 1868 the Italian anatomist Giulio Bizzozero reported that these tiny blood cells originated in bone marrow and represented a separate cell line. Bizzozero distinguished between thrombus formation and precipitation of clotting factors, and he thought that platelets could trigger the clotting cascade. Knowing of Bizzozero's work, the twenty-four-year-old Canadian William Osler soon joined the debate. He reported that these bodies were 'sometimes' found in normal persons, and he speculated on their relationship with bacteria.

The Frenchman Georges Hayem devoted much of his career to a series of elegant experiments that linked platelets to hemostasis. Against his own evidence to the contrary, however, he viewed platelets as a by-product of red cells. One historian has speculated that Hayem's error was the result of 'the unimaginative burden thrust on those, who like him, come early to positions of authority' (T.H. Spaet, in M. Winthrope, Blood Pure and Eloquent. New York: McGraw-Hill, 1980, 553). More likely, Hayem's ideas stemmed from preconception – the 'epistemological obstacle' that has allowed many fine researchers to find precisely what they seek. The French look on Hayem, together with Donné and Andral, as yet another father of hematology.

Platelets occupy a huge literature with a high profile in our society, where cerebrovascular and cardiovascular thromboses are the leading causes of death. The genetics and biochemistry of platelet function are used to predict the antiplatelet effects of drugs. Many longitudinal studies of antiplatelet drugs have been conducted over fifty years; by 2000, the old off-patent drug aspirin was finally shown to be effective in primary prevention of cerebrovascular disease. However, because aspirin has many side effects (and costs very little), new (more expensive) antiplatelet drugs have been introduced to become bestsellers (see chapter 5). In the interests of the rising burden of lifestyle disease in developing countries, yet another protocol to review whether or not the benefits of affordable aspirin outweigh its side effects is underway at the Cochrane Collaboration.

Plasma and Coagulation

The tendency to bleed has been recognized since antiquity. Writers of the Talmud seemed to know that male bleeders inherited the problem from their mothers, and they exempted from circumcision the next son of a mother who had already lost two or three boys to hemorrhage (Yebamot, 64b). Well before classical hemophilia had been characterized in chemical terms, it was used as a model by the American geneticist Thomas Hunt Morgan for his Nobel Prize–winning work on sex linkage.

In his immensely popular book of 1968, Nicolas and Alexandra, historian Robert K. Massie suggested that hemophilia helped to fuel the Russian Revolution with the stresses it produced in the family of Tsar Nicholas II. The tsarevitch Alexei suffered from hemophilia, which he had likely inherited from his great-grandmother, Queen Victoria, via his mother, Alexandra. The relationship between a hemophiliac and his mother is poignant: she is doubly tormented, by her child's pain and by the ancient idea that the problem was passed through her blood. Desperate to help her son, Alexandra turned to Rasputin, a self-styled spiritualist healer (in)famous for his excessive appetites in
all things sensual, from cuisine to sex. Rasputin could calm and comfort the boy, and he also appeared to control the bleeding. Against advice, the ‘foreign’ tsarina continued the consultations; detrimental rumours about her relationship with Rasputin further eroded public respect for the throne.

Bleeding problems were defined by measuring the length of time for a clot to form in whole blood or plasma. Hemophilic blood took a long time to clot, if it did so at all. In the late 1930s, when component transfusion was first implemented, it was discovered that the clotting defect in hemophilic plasma could be corrected by mixing it half and-half with normal plasma. Researchers postulated the existence of a vague but essential ‘anti-hemophilic factor’ (AHF) in normal blood. By more mixing experiments, they learned that not all bleeders were the same.

In 1947 an Argentinian team noted the ‘paradoxical fact’ that mixing plasma from two different bleeders sometimes resulted in mutual correction. In her classic paper published at Christmas 1952, Rosemary Biggs presented seven bleeders whose plasma could correct the defect in other hemophiliacs. She reasoned that these patients must have a different disease, which she named Christmas disease, both for the season and for the ‘patronymic’ of her five-year-old Canadian ‘patient no. 1,’ Stephen Christmas, son of the actor Eric Christmas.

Mixing studies continue to be the basis of coagulation screening and the means of identifying new clotting factors. In 1953 the railwayman John Hageman was admitted to a Chicago hospital for elective ulcer surgery. He had no history of bleeding, but his blood clotted poorly on a routine test, and his surgery was cancelled. Hageman’s defect could be corrected in the laboratory by mixing his plasma with either normal or hemophilic plasma. His doctors concluded that the plasma of both normals and hemophiliacs contained something that Hageman did not; it was Factor XII.

Each factor in the seemingly complicated ‘coagulation cascade’ has been found in the same way: someone comes along with a defect that can be corrected by normal plasma and by all other known factor-deficient plasmas. At first, clotting factors were named after the patients who lacked them (e.g., Christmas factor, Hageman factor, Fletcher factor, and Stuart factor). Later, they were numbered to reflect our understanding of their place in the reaction cascade. Mixing studies are basic to coagulation research and service. In the future, new factors will be identified in the same way.

A boon to hemophiliacs, the special clotting properties of cryo-precipitate — a blood component collected by freezing plasma — were recognized and made available in 1964. At that time, researchers still did not know whether the tendency to bleed (the so-called absence of AHF) was caused by a defective molecule, an absent molecule, or the presence of an inhibitor. In 1970–1 classical hemophilia was attributed to a defective Factor VIII molecule. As for the hemoglobinopathies, associated molecular substitutions in DNA have now been defined. In terms of treatment, lyophilized (freeze dried) products were easier to store, use, and carry about, but they were made with pooled plasma, greatly increasing the risk of transmitted infection. The success of blood products in the management of bleeding disorders led to a temporary revolution in pain management and lifestyle, but it soon brought a tragic reminder of the dangers of blood therapy.

Forty years after his diagnosis, a Canadian team published the precise molecular substitution to account for the coagulation problem in Stephen Christmas, but their work could do nothing to prevent his death from AIDS on 20 December 1993. About half of hemophiliacs in developed countries converted to HIV seropositivity before 1985; many have died. In Britain and the United States, the number of seropositive hemophiliacs is estimated at 5,000 and 10,000 respectively. In Canada by 1997, 400 hemophiliacs had died of iatrogenic AIDS, and another 1,000 were infected with HIV and/or hepatitis.

With transfusion-related HIV or hepatitis we hear again the term ‘innocent victim’ (see chapter 7). Many drugs, diagnostic procedures, and surgical interventions cause sickness, even death; yet the value-added outrage expressed on behalf of those harmed by ‘tainted’ blood seems to proclaim the primal significance of this fluid in our world.

Blood and Drugs

The hematologic malignancies of lymphoma and leukemia – though
far from being the most prevalent – distinguished themselves early from all other cancers as being responsive to treatment: first by radiation, then by drugs. Almost all these therapies have fascinating histories intimately connected to the scientific discoveries of the late twentieth century. Cures once thought impossible for conditions like Hodgkin’s disease and childhood leukemia are now within the realm of the ordinary, usually with a combination of drugs and radiation. Radiation was accomplished by X-rays and radioactive elements such as radium and cobalt. After 1945, nuclear reactors were built in many places, making it possible to produce radioisotopes for medical uses, such as radiophosphorus (\(^{32}\)P) and radioiodine (\(^{131}\)I).

One of the earliest cancer drugs was nitrogen mustard; its cell-killing (cytotoxic) effect on blood had first been observed in soldiers gassed with mustard in the First World War. In 1950, researchers in England released versions that were relatively safe for medical use, called alkylating agents. These products famously cause hair loss, stomach upset, and bone marrow depression. Around the same time, the hormone of the adrenal cortex (cortisone) was discovered; it produced rapid but short-lived disappearance of lymph masses. When cortisone was combined with the cytotoxic drugs, it produced complete remissions, and even cures. Killing cells in a variety of ways seemed to wipe out tumours so that a small nest of resistant cells could not reanimate the disease; thus the spindle poisons were developed, beginning with the extraction of vinblastine from Madagascar periwinkle in London, Ontario, in 1958. Their application to childhood leukemia resulted in the first cures. Other ‘spindle poisons’ include paclitaxel (Taxol®) derived from the Pacific yew tree. Combination chemotherapy became even more effective with application of the first rational derivatives or designer drugs, which garnered the Nobel Prize in 1988 (see chapter 5). Virtually all these remedies, once proven effective on blood conditions, were applied to other diseases.

A growth factor (or hormone), called erythropoietin is made in the kidney and promotes red cell production in the bone marrow and in the lab. It was purified in 1977, having been hypothesized many years earlier. By the 1980s it was used to treat people with the anemia of kidney failure. In 1989, a synthetic version made by recombinant DNA was patented in the United States, making it possible to manufacture the drug for wider use and to reduce the need for transfusion. For two decades now it has been applied to a host of red blood cell deficiencies that occur naturally or because of chemotherapy; sadly, it has also become one of the drugs abused in high-performance athletics.

Similarly, white blood cell growth is governed in humans by a stimulating factor (or hormone) that has also been synthesized in bacteria using the techniques of recombinant DNA. The drug, called filgrastim (Neupogen®), is widely used to help patients recover from chemotherapy. It costs several thousand dollars for each monthly cycle and is governed by a patent due to expire in 2013; ‘follow-on’ successors are already in trials (see chapter 5).

Most recently, scientists have designed specific drugs in the form of antibodies that attack the molecular markers and pathways produced by defective genes in malignant cells. They result in stunning success rates with relatively few side effects in leukemias, lymphomas, breast cancer, and autoimmune diseases: examples include Rituximab (Rituxan®, launched 1997), trastuzumab (Herceptin®, launched 2000), imatinib (Gleevec® or Glivec®, launched 2001), and the ‘follow-on’ for imatinib, called nilotinib (Tasigna®, launched in 2008). Each singular discovery is greeted with tremendous public fanfare, and patients clamour to be treated. The drugs promise to make chemotherapy ever more effective and better tolerated, but the cost of their development and use is exorbitant. Finding affordable access to these lucrative remedies is already resulting in appeals from developing countries.

**Blood Is Still Special**

The exciting achievements of the last fifty years transformed diseases with gloomy prognoses into curable problems and put blood on the cutting edge. Long considered to be a subdivision of internal medicine or pathology, hematology has grown to become its own specialty with sub-specialties. Specialist examinations in England, Canada, and the United States were implemented in the late 1960s and early 1970s. Soon, oncology arose out of those branches of hematology dealing with malignancy to carry the tools into other organ systems,
and creating moments of rivalry. National and international societies exist, the largest of which is the American Society of Hematology founded in 1958 with 300 delegates; now it boasts 15,000 members and its annual meetings feature more than 500 papers and 2,500 posters and are attended by more than 20,000 delegates.

Despite its lofty stature as a subject of professional and scientific activity, blood is still venerated for its magic and mystery. We may no longer deify great healers like Asklepios, but we do 'canonize' them with the Nobel Prize. Blood research is disproportionately represented among the Nobel laureates even if it is labelled immunology or genetics.

In demystifying blood, new mechanisms are proposed in different, perhaps less magical-sounding words, but the ancient concepts have simply been rephrased; their essential features are unchanged. Galen said that blood exposed to air was charged with the life force. Now, blood is still seen as the equivalent of life, through its links to oxygen and respiration, while its balance, like that of its ancient Greek precursor, is essential for the preservation of health.

Suggestions for Further Reading

At the bibliography website http://histmed.ca.