Introduction

IOSIFINA FOSKOLOU AND MARTIN JONES

There are many reasons why we proposed the theme of 'Blood' for the 2021 Darwin College Lecture Series. The first reason was quite personal: blood was the connection between one of us (IF) and Darwin. Darwin College funded – through the Evelyn Trust – Iosifina's research on a novel cancer therapy, which uses blood cells to target cancer. Claire Roddie explains in detail how this transformative therapy works in her chapter. From there we moved to explore how blood could connect a plethora of fields and subjects. Although academic merit was one of the most important factors in identifying speakers, we also wanted to give voice to controversial and unfamiliar topics. For example, although it would have been exciting to have a historian talking about blood in wars, battles, or kingdoms of Europe, we instead chose Sara Read, who talked about menstrual blood in early modern England. It is remarkable how little this subject is discussed and how little we know about menstrual health – even in our times – given that half of the Earth's population experiences this monthly cycle. Similarly, when we were thinking about literature, while Bram Stoker's *Dracula* is a predictable choice, we decided to invite Carol Senf, who was one of the first academics to explore feminist themes within that famous text.

Other issues to which we wanted to give voice in this series were social justice/social awareness and climate crisis. Rose George and Marc Quinn seemed the ideal speakers to address social justice and social awareness. Rose George gave voice to heroes and villains of blood. On the one hand, she exposed cruel experiments people used to do in animals until they understood the science behind transfusions, and on the other hand, she reminded us of such heroes as Dame Janet Maria Vaughan, the founder of the UK's blood donation service (NHS Blood and Transplant) as we know

it today. Marc Quinn was chosen not only because of his celebrated work *Self* (shown on the cover of this book) but also for his upcoming exhibition 'Our Blood'. This major public artwork aims to raise awareness of the global refugee crisis. Quinn's work touches upon such social issues as disabilities, social exclusion, and racism. In relation to climate crisis, we couldn't have chosen a better speaker than Stuart Egginton. In his many trips to Antarctica Egginton has confronted at first hand the challenges the Antarctic ecosystem faces due to global warming.

Lastly, we wanted to emphasise the ability of blood to connect us. We chose Walter Bodmer and Tim Pedley for this area. Bodmer was one of the first scientists to suggest the Human Genome Project, subsequently leading the People of the British Isles project. From a different scientific angle, Tim Pedley discussed the ability of blood to connect the different tissues within our body and the physical requirements for making it possible for this fluid to keep us alive.

The organisation of the series began with much excitement. Our speakers quickly accepted our invitations to lecture, and everything was in place by the time the Darwin College Lecture Series of 2020 had reached completion. However, this was also the time of the outbreak of the COVID-19 pandemic. We had no idea how long the pandemic would last. As summer approached, it became increasingly clear that our 2021 series would not be able to take place in its normal format. Instead, the entire lecture series was delivered virtually, with prompt and brilliant support from staff at Darwin College and Cambridge University. That happened, and all of the lectures were successfully delivered. One of our speakers, whose main work was at the frontline of Covid mitigation, had to break off mid-lecture to attend to urgent business. With skilful editing from our Darwin team, our audience remained unaware. Our audience remained loyal, and at the time of writing, the series has received over 14,000 views.

Having outlined above themes in the organisers' minds when assembling the series, we can turn to what we have learnt from the resulting lectures. It is one of the stimulating features of the Darwin College Lecture Series that, although each year it is bound by a single word, additional new themes emerge from what is actually assembled and delivered. A theme that proceeds most directly from the conception of

the 2021 series and IF's own research is that of blood's physiological function, in ourselves and in other animals. The chapters of Pedley, Egginton, and Roddie bring to light the sheer complexity of this most familiar of fluids. Blood is a complex heterogeneous fluid that is routinely required to follow a complicated path around an animal's body, somehow contained within a circulatory system while effecting continuous physical and chemical exchange across that system's boundary walls. Not only is the sheer mechanical task, as explored in Pedley's chapter, considerable; so is the thermoregulatory task, examined in Egginton's chapter. Managing and sustaining this complex attribute of life, especially in our own species, is at the heart of much medical science, a theme developed by Roddie in the context of her work on leukaemia.

Roddie's chapter draws our attention to the prominent role in medicine played by the transfer of blood from one individual to another, a theme enlarged upon and given historical context in George's account of the varied actors in the history of blood transfusion. George expands from a historical treatment of the transfer of blood to probe at the fluid and diffuse boundaries of her theme. She describes how, since the ancient beginnings of medicine, blood has been perceived as a fundamentally mysterious entity, that can either kill us or save us, ideas that turn our attention from medicine to mythology, from the facts of physiological science to the narratives of folklore and fiction. The latter theme of fiction is further developed by Senf in one of the best-known fables about the movement of blood between bodies.

Senf's reading of Bram Stoker's *Dracula* is not as far removed from 'science' as a subsequent corpus of derivative B-films might lead us to imagine. Indeed, the contrast in Stoker's novel between the blood of the aristocratic past and that of the scientific future seems to allude to the future potential of medical blood transfusion; some of his language suggests Stoker was aware of early attempts at developing an effective procedure. Senf explores the rich variety of meanings that may be attached to the transfer of blood from one body to another, and places *Dracula* at the paradoxical cusp between looking back and looking forward. Prominent within the past are superstition and aristocratic men. Prominent in the future is the New Woman, freeing herself from the shackles of patriarchal Victorian life. Senf is particularly interested in

how Stoker's blood-sucking novel of 1897 looks back upon a disappearing century of stifling gender relations and tentatively forward to a new century ahead, and new possibilities of womanhood.

In various of the volume's chapters, the theme of blood in relation to womanhood recurs.

We learn how intimately blood is entangled in female identity, physiology, and development, and in different cultural perceptions of each of these, and of the powers of good and evil ascribed to them. As Read explains, culturally specific interpretations of the patterns of bleeding at different stages of a woman's life are repeatedly employed to define those stages, and the attendant rites of passage that punctuate the female biography. At the centre of this discourse is menstrual blood, which, as George explains, has a rich cultural history in its own right. The Biblical Isaiah and Pliny the Younger seem to share a horror of the fluid, the latter offering explanations of how a menstruating woman can kill a swarm of bees, and turn iron and brass rusty. In case we imagine such attitudes are lost in the mists of time, George reminds us that, little more than a decade ago, a (male) British Prime Minister seemed unable to utter the word 'tampon' in Parliament, and as recently as 2019, the world's multi-million-dollar advertising industry had great difficulty coming to terms with menstrual blood's true horrific colour.

The associations between blood and womanhood can be viewed through a wide variety of lenses, ranging from the science to imagination and fear. Through the same range of lenses, blood may be viewed in relation to other dimensions of identity, in particular to ancestry, nationhood, and belonging. In the middle ages, that association might also be regarded as 'scientific'. In thirteenth-century England, one meaning of 'blood' or 'blod' was 'person of one's family, race, kindred, offspring', a meaning shared by Latin *sanguis* and Greek *haima*.[1] That sense is also conserved within such modern usages as 'blue-blooded' and 'blood line'. Blood as ancestry is one of the key themes Senf discerns in Dracula, and the words 'blood line' feature in the title of Bodmer's contribution to this volume.

Bodmer discusses and explains modern techniques of genetics that have long displaced mediaeval notions of blood inheritance. Nonetheless, blood

[1] www.etymonline.com/word/blood.

retains a number of roles in his account, most notably in his discussion of pioneering work on blood group genetics, which lies at the foundation of our contemporary understanding of human diversity across the world. This diversity may be resolved in a rich world prehistory that itself can be inferred from that same body of genetic evidence.

It may seem paradoxical that a mediaeval notion of blood ancestry can feature in a cutting-edge account of the genetic science that replaced it, but paradox in itself is a theme to which several authors on the topic of blood return. The manner in which Stoker's text of *Dracula* plays with the paradoxical nature of blood is a recurrent theme of Senf's contribution. 'Blood' can denote the stuff of noble life, while 'bloody' can serve as a curse. The blood of Dracula can allude to strange masculine entities from the past, but also be entangled with the 'New Woman' of a more liberated and egalitarian future. George's chapter also touches on paradox, reminding us that, while blood can save us, it can also kill us. The theme of paradox is especially evident in the conversation with Marc Quinn.

Quinn reflects on the life–death paradox; blood is the essence of life, and it remakes itself, but usually associated with death, violence, and illness. Quinn explores how this theme of paradox moreover applies to the notion of 'self', a notion that has little meaning without acknowledgement of connections that reflect profound interdependence. That collective existence may be captured in the notion of 'blood line', until we acknowledge that the notion of blood line is framed as much around exclusion as around inclusion, returning us once again to the theme of paradox.

So, our exploration of 'blood' emerged by combining a medical research interest in a tangible, vital fluid with concerns of social justice and climate change. Our lecturers picked up those themes and went on to explore themes ranging from blood lines, identity, and womanhood, to the theme of enduring paradox in relation to past and future, to self and community. Such is the intrigue of the Darwin College Lecture Series' tradition of exploring a single word and seeing where it takes us.

1 Battle Blood

CLAIRE RODDIE

The subject of 'Battle Blood' is the treatment of the blood cancer leukaemia. I am a haematologist by training, and treating blood cancer is my daily job. In the present day we are fortunate to have sophisticated methods to diagnose and treat blood cancers, but this was not always the case. The celebrated poet Hilaire Belloc (1907) reflects the experience of haematologists at the beginning of the last century, when they were faced with the prospect of treating leukaemia:

> Physicians of the Utmost Fame
> Were called at once; but when they came
> They answered as they took their Fees,
> There is no Cure for this Disease.

In fact, physicians did not really understand leukaemia, certainly not in 1845 when John Bennett, a Scottish physician, described an unusual case of a 28-year-old slate layer who presented with gross fatigue and a large tumour in the left side of his abdomen (Bennett 1845). This patient developed fevers, bleeding, and abdominal pain, and multiple new tumours appeared in his armpits, groin, and neck, correlating anatomically with the lymph node regions in the human body. The best therapy for this 'condition' in 1845 was a combination of leeches and purging, but unsurprisingly the patient did not respond to these 'treatments' and died from progressive disease a mere few weeks later.

In an attempt to better understand this unusual syndrome, Bennett performed an autopsy and, when he examined the blood, he found it was full of white blood cells, the principal constituent of pus. The function of white blood cells is to protect the body from infection, so naturally Bennett presumed that this patient had died from an overwhelming sepsis. However,

the puzzling aspect was that he could not find a source of infection. He simply concluded that it was a 'suppuration of pus with no clear cause'.

A few years later, Rudolf Virchow, a German researcher, described a 50-year-old lady with an excess of white cells in the blood and a huge spleen, but again no signs of overt infection (Virchow 1856). Virchow concluded that this must be an intrinsic problem with the white blood cells. The word 'leukaemia' is derived from 'leukos', the Greek word for white.

Virchow began to develop systems to classify biological anomalies, including aberrant cell growth. He defined hypertrophy as an increase in cell size, and hyperplasia as an increase in cell number. For Virchow, leukaemia was a pathological, unexplained, abnormal hyperplasia of white blood cells.

In essence, the condition we know today as B-cell acute lymphoblastic leukaemia (B-ALL) is essentially an uncontrolled expansion of immature white blood cells, much as Virchow described it. These immature cells are unable to perform the functions of mature white blood cells, that is, to protect the host from infection. Worse still, the leukaemia cells destroy the normal architecture of the bone marrow and completely disrupt normal blood production. This commonly leads to symptoms such as anaemia, low platelets, and a reduction in normal (functional) white blood cells. Anaemia is the occurrence of low red blood cell levels, and a deficiency in these oxygen-carrying cells can lead to breathlessness and fatigue. The function of platelets is to stop bleeding, and self-evidently, when the platelet count is low, the risk of spontaneous and uncontrollable bleeding is increased. Where the normal white blood cell levels are reduced, severe infection is the likely outcome.

Patients describe myriad other symptoms relating to the rapid growth of leukaemia cells, including fever, weight loss, and bone pains. Indeed, examination of leukaemia patients often reveals enlarged lymph nodes and an enlarged spleen, with associated pallor and bruising.

By the early part of the twentieth century, little progress had been made in the treatment of leukaemia, and the physician's perspective in 1950 wasn't particularly different from the view in the 1840s. William Castle describes acute lymphoblastic leukaemia as follows: 'Its palliation is a daily task, its cure a fervent hope' (Mukherjee 2010).

However, one man helped change the landscape of acute lymphoblastic leukaemia. Sidney Farber worked in Boston as a pathologist at the

Children's' Hospital. He had written a book on the classification of childhood tumours, called *The Post-mortem Examination* (Farber 1937), and developed a scientific interest in what he described as the 'hopeless' condition of childhood leukaemia. At that time there was no national cancer research strategy, and treatment options were limited to radiation and surgery, both of which offer limited value in a blood-borne disease.

Farber reasoned that, to develop better treatments for cancer, research to understand and classify cancer was required. In order to understand cancer, he proposed systems to measure it, and he reasoned that leukaemia was an excellent model system, as white blood cells can easily be measured in the blood. If cancer can be measured, then one can begin to investigate the impact and potency of therapeutic interventions in living patients. If white blood cells grow or die, then that in itself is a measure of the success (or failure) of a proposed therapy.

Farber looked for ideas and inspiration for potential therapies from many sources. He discovered the work of Lucy Wills, an English physician, who in 1928 travelled to Bombay to study the profound anaemia that was observed in factory workers there. Those affected were often malnourished, and, more often than not, the anaemia seemed to specifically affect mothers and their children more than other groups.

By a surprising turn of events, Wills discovered that the anaemia was cured with Marmite (Wills 1933). And when she investigated this, she found that the active constituent of Marmite is folic acid, a vitamin found in fruit and vegetables that is essential for healthy blood production. Indeed, when we grow and repair tissues in our bodies, cells make copies of themselves and, to do this, they must make copies of their DNA. Adequate folic acid is critical for DNA production. Healthy people make more than 300 billion blood cells every day, so it is incredibly important that folic acid levels are maintained within the normal range.

Applying Lucy Will's findings regarding folic acid to acute leukaemia, Sidney Farber wondered whether folic acid supplementation would improve the low blood counts associated with acute leukaemia. He reasoned that the leukaemia cells were consuming all available folic acid, leading to a state of folic acid deficiency in the residual, 'normal' cells, stopping them from growing properly.

To test this hypothesis, Farber instituted an early clinical trial using synthetic versions of folic acid in paediatric patients with acute leukaemia. Contrary to his expectations, he found that folic acid supplementation seemed only to accelerate leukaemia growth. Whilst this was disappointing, it led him to his second research question: if supplementing folic acid was leading to rapid leukaemia progression, could it be that antagonising or blocking of folic acid would have the opposite effect?

Farber had a close collaborator and friend, Yellapragada Subbarow, a biochemist who was also trained as a physician. Subbarow's biochemistry laboratory was focused on the synthesis of synthetic versions of compounds and chemicals that exist within normal cells, including attempts to create synthetic versions of folic acid. During this process he inadvertently generated a range of folic acid antagonists/blocking molecules, including one called aminopterin (Farber et al. 1948; Mukherjee 2010).

Working with Subbarow, Farber proposed a clinical trial of aminopterin, to block folic acid, for childhood leukaemia. The first patient treated with aminopterin was Robert Sandler, a boy with childhood leukaemia complicated by bone disease and fractures. Following aminopterin, Sandler very quickly achieved a dramatic remission, which was unprecedented in the field of acute leukaemia.

Unfortunately, the remission was short-lived, and he relapsed after several months, but the finding that a single, simple chemotherapy drug could so dramatically control acute leukaemia was a paradigm shift in the field and sparked a new wave of research efforts into many different types of chemotherapy for this condition.

The second huge advance in the field of acute leukaemia was the inception of allogeneic bone marrow transplantation. One of Sidney Farber's protégés, Edward Donnall Thomas, won a Nobel Prize in 1990 for conceiving of this therapeutic approach for the treatment of blood cancers and is known as the father of bone marrow transplantation. Donnall Thomas showed that an obliterative dose of chemotherapy/radiotherapy could eradicate the patient's immune system and that the patient's blood production could be 'rescued' with transplanted bone marrow, taken from a healthy donor (Thomas et al. 1957; 1975).

The first successful allogeneic bone marrow transplant was performed in 1956, in a twin boy with acute leukaemia. He received obliterative

radiotherapy followed by a healthy bone marrow donation from his identical twin and survived. This early success prompted a huge increase in bone marrow transplant research.

Dr George Mathé, a French oncologist and immunologist, was also fascinated by allogeneic bone marrow transplant. He applied this novel approach in six nuclear reactor engineers with severe and debilitating bone marrow aplasia following a nuclear reactor incident. Since they did not have the option of identical twin donors, Mathé gave them bone marrow derived from an unrelated donor. Unexpectedly, all the patients developed an unexplained, debilitating wasting condition following the donor cells, which we now know as graft versus host disease (GvHD) (Mathé et al. 1959). This life-threatening condition arises where the incoming immune cells in the bone marrow donation are not well matched to the patient's own immune system. These mismatched cells can thus recognise the patient as 'non-self' and attack their normal cells and tissues, leading to a devastating immunological treatment complication.

Dr Jean Dausset, a French immunologist, made a critical discovery, identifying the reason for the GvHD phenomenon, for which he won the Nobel Prize in 1980. He described a mismatch in the protein signature on the cell surface of the blood compartment of the patient compared with the donor, referred to as the human leukocyte antigens (HLA) mismatch (Dausset 1958). This mismatch in HLA between donor and patient is the reason both for the immunological rejection of the donor cells by the patient's immune system and for the immunological 'rejection' of the patient's normal cells/tissues by the donor immune system, i.e. GvHD. He reasoned that HLA compatibility is key to the success of allogeneic bone marrow transplant.

With significant further research and development, by the 1980s, doctors were routinely using allogeneic bone marrow transplant for chemotherapy- and radiotherapy-refractory blood cancers.

In the modern day, standard therapy for acute (lymphoblastic) leukaemia is chemotherapy-based. The first step is induction therapy, where newly diagnosed patients receive multiple chemotherapy drugs as an inpatient in hospital over one to two months. This therapy renders the patients aplastic, with no functioning immune system. To protect these vulnerable patients from infection, we isolate them in single rooms in hospital wards.