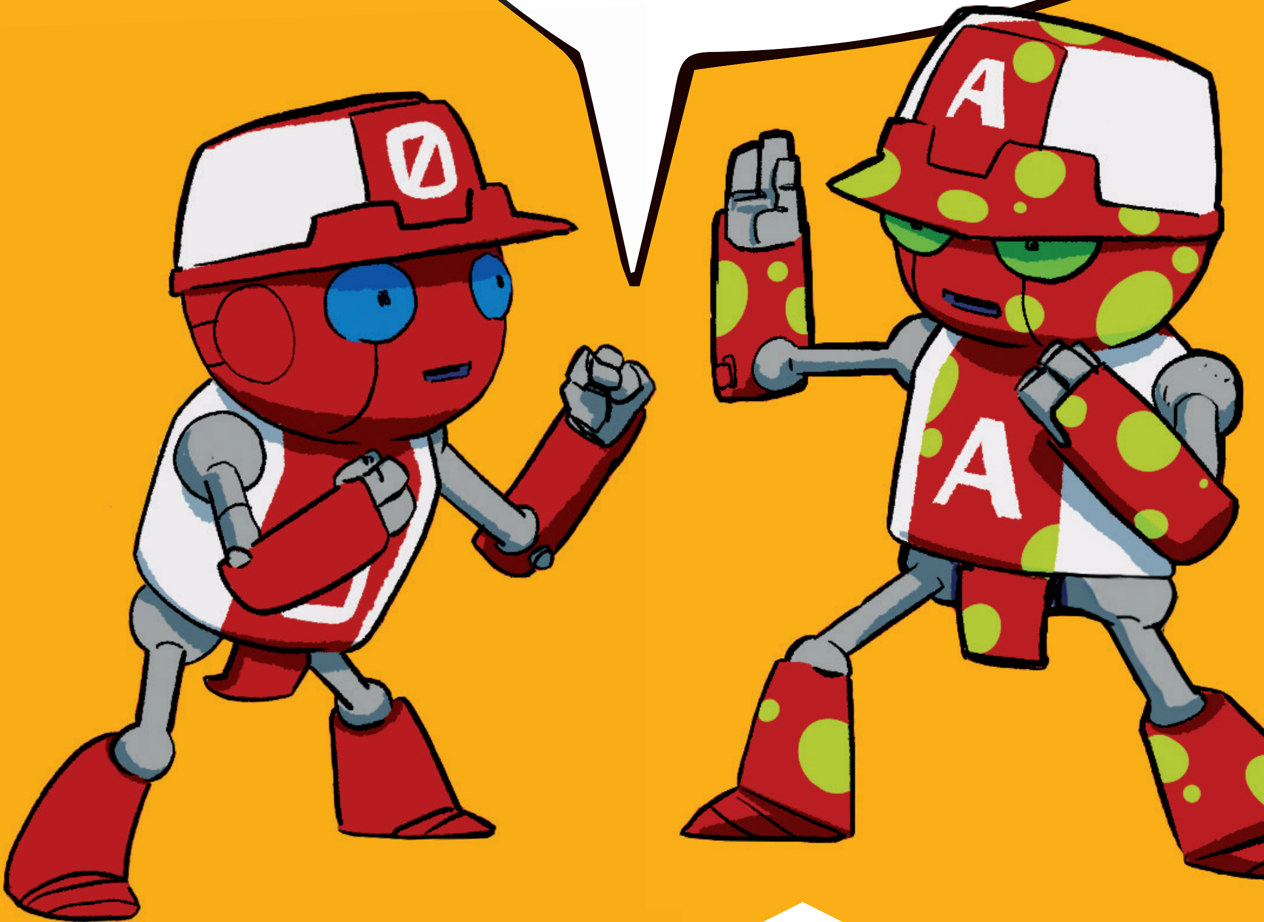
LET'S SCIENCE!

Stefano Fontana

HOW LIFE CIRCULATES

What blood is and why it is important to donate it



IBSA FOUNDATION for scientific research

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IBSA FOUNDATION for scientific research
Repubblica e Cantone Ticino
Dipartimento dell'educazione, della cultura e dello sport

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Graphic project by Ulderico Iorillo and Valentina Pochesci

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PREFACE

How familiar are we with the repercussions of scientific research and medical practice for our daily lives? What are the "passions" and motivations that drive researchers and healthcare professionals? What do we know about their professions?

Society strives to make science and its implications known to ordinary people in many different ways. Just think, for example, of the variety of leaflets promoting the importance of a healthy lifestyle and well-being in general. Of course, school does its part as well, introducing the principles of scientific literacy and raising awareness of a series of issues that help foster scientific thinking among young people.

These considerations are in fact the starting point for the *Let's Science!* project, carried out by the IBSA Foundation for Scientific Research in collaboration with the Department of Education, Culture, and Sport of the Canton of Ticino (DECS). The partnership has made it possible to identify interesting topics that have been addressed by the project, getting scientists working in the canton involved. Two different worlds that are often far apart – scientific research and school – have thus been brought together, promoting dialogue between professionals and students through themed workshops, in order to develop awareness of both the topic itself and how to communicate it.

But what was the range of topics the project would address and what considerations led to certain strategic decisions? Science and research are advancing rapidly, especially in biomedicine and related disciplines, and the continuous expansion of fields of investigation requires a constant effort to stay up to date, in order to both maintain a historical perspective and accommodate the numerous innovations. Access to scientifically accurate information, conveyed in accessible language, opens up the opportunity for children to get to know and become passionate about topics that are generally considered "difficult".

And that's the idea behind the *Let's Science!* series, which aims to broaden the range of scientific topics that can be explored at school. The topics, which are interdisciplinary and directly related to individual health and well-being, are presented in an innovative way: the scientific text is in fact accompanied by a story that draws on the experience of cantonal middle school classes, who, under the guidance of their teachers, developed original scripts, which were then translated into comics by professionals in the industry.

The only thing left for us to do is invite young readers to explore the fascinating fields of research presented by *Let's Science!*, which in turn open up opportunities for further questions and insights. Who knows, one of these readers might in turn one day become the one taking important steps forward in understanding the complexity of life and the delicate balance that allows us to be healthy and happy. Enjoy reading!

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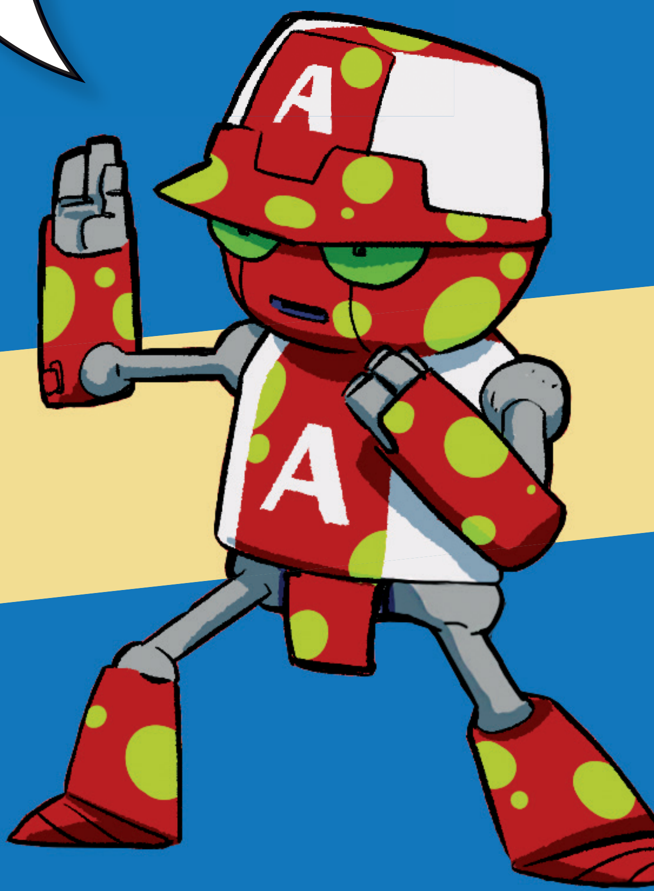
How life circulates

PART ONE



INTRODUCTION

Blood is a fascinating organ. In the course of history, even before its nature and functions were discovered, a huge range of different meanings were attributed to blood, relating to life, death, mood, and family. We can see this plurality of meanings in numerous proverbs and sayings: blood will out, having blue blood, bad blood between people, in one's blood, blood is thicker than water, like blood from a stone, blood feud, in cold blood, bloodthirsty etc. These recurring references to blood are due to the fact that it is the only liquid organ in our body and, as such, is what gives all parts of our body life. In addition, thanks to its colour, it is visible any time we are wounded.

Blood has a huge number of functions, including being a highly efficient communication network between organs and tissues: a kind of **internet of the human body**. Unlike other organs, blood can be regenerated but, due to its complexity, it cannot be produced in a factory or laboratory, especially as efficiently as the human body manages it.

This also explains the importance of the altruistic act of donating blood. In fact, it is possible to remove a certain amount from a vein without harming the donor's health. Some of the components of blood can subsequently be isolated and used to treat patients in various situations.

In this booklet, we will try to find out more about this fascinating organ and follow it on its journey from donor to patient.

BLOOD

Blood is a **liquid organ that flows in the arteries and veins of our body**. Depending on their body mass, an adult contains between 4 and 7 litres of blood. The heart pumps about 5 litres of blood per minute towards all organs and tissues at rest; this amount can increase considerably if the body needs it, for example when exercising.

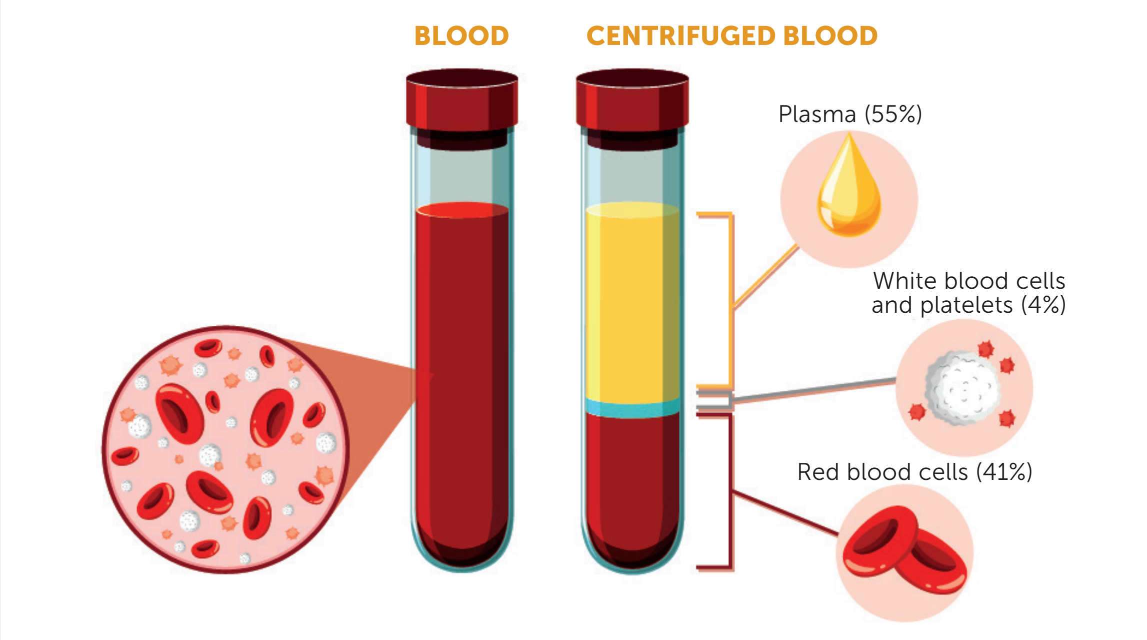
◎ THE COMPOSITION OF BLOOD

What elements make up the blood?

Blood is made up of several elements: plasma, red blood cells, white blood cells, and platelets. If we centrifuge a phial of blood, we will find a light yellow liquid in the upper half, the **plasma**, which represents the actual liquid part of the blood. The corpuscular part is collected in the lower half; this is the part formed by the cells that circulate in our blood vessels, suspended in the plasma. Each type of cell has specific functions, all essential for the survival of the organism [**figure 1**].

The plasma contains thousands of different substances that are transported between the organs and tissues of the body: nutrients that provide the energy needed for survival, substances produced by the metabolism that have to be eliminated, hormones – transported from one organ to another – that regulate

Figure 1 The composition of blood

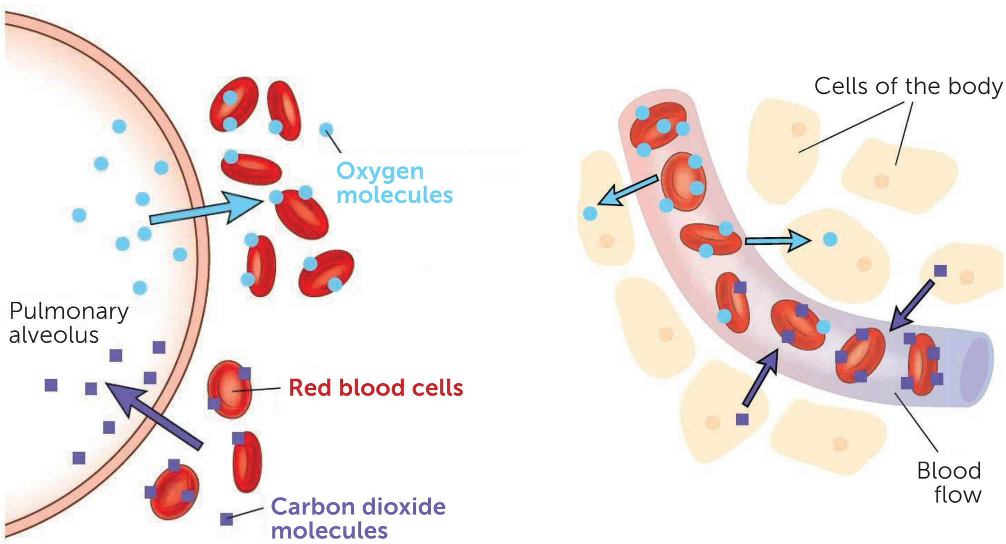


the functioning of our body, antibodies that protect us from the invasion of microorganisms, proteins that cause blood clotting if we are wounded, and many others.

Red blood cells (or erythrocytes) are primarily responsible for **transporting oxygen** from the lungs to the organs that need it to function. The red blood cells perform this task thanks to **haemoglobin**: a molecule that gives the blood its typical red colour and the components of which include iron, which oxygen is bound to. The intake of oxygen in the lungs and its release to the tissues are regulated by a complex mechanism that is not yet fully understood, which enables the body to adapt the supply to the need [**figure 2**].

White blood cells (or leukocytes) are the cells of the immune system. Together with the antibodies, **they are the army that defends our body from unwanted enemies**. In the months after birth, our immune system learns very quickly to distinguish between the specific characteristics of our own body and those of other individuals or other organisms.

Figure 2 Oxygen intake in the lungs and transfer to tissues by the red blood cells



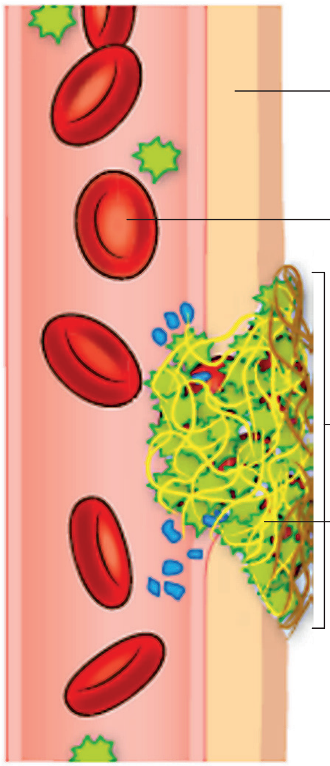
These specific characteristics, which differ from species to species and from person to person, are called **antigens**. Antigens that it recognises as "ours" are tolerated by the immune system, while those identified as "foreign", such as a virus or a transfusion of blood cells from another individual, cause a **reaction by white blood cells**. In this battle, different types of white blood cells take on different roles: recognising the enemy, attacking it directly, or forming antibodies, which in turn will bind to the foreign antigens to eliminate them. The immune system uses two main strategies to defend against foreign bodies: the innate immune response and the adaptive immune response [**table 1**].

Platelets (or thrombocytes) are **fragments of cells derived from the megakaryocytes of the bone marrow**; their task is to plug the holes in the walls of the blood vessels when we are injured or when they are damaged by a disease. Platelets are the first responders in the event of **haemorrhage** (primary haemostasis). They are then supported by **clotting factors**, or coagulation factors, proteins found in the plasma that consolidate the clot and stop the bleeding (secondary haemostasis) after a blood vessel has been injured and the platelets have done their work [**figure 3**].

Table 1 White blood cells involved in the two types of immune response

TYPE OF RESPONSE	TYPES OF WHITE BLOOD CELLS INVOLVED	FUNCTION
Innate response	Granulocytes, monocytes, macrophages, Natural Killer cells	The innate response acts immediately against any foreign agent, even if it has never been encountered before. It is immediate but less specific than the adaptive response, which follows shortly thereafter.
Adaptive response	T lymphocytes, B lymphocytes, antibodies, memory lymphocytes	The adaptive response follows the innate response and is activated by monocytes or macrophages if the foreign agent is new. It can be autonomous and activated by memory lymphocytes if the agent has been previously encountered (for example, contact with a virus after being vaccinated). It is specific to the type of agent encountered.

Figure 3 "Plug" formed by platelets and fibrin filaments

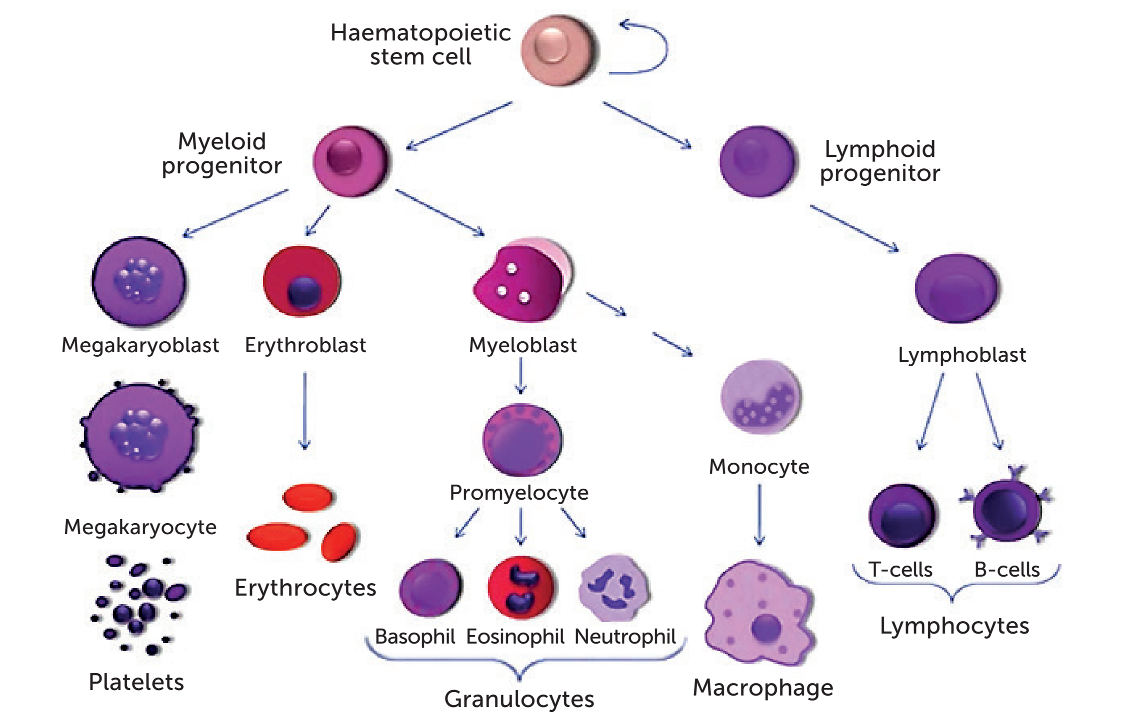


THE BLOOD "FACTORY"

Blood forms in the bone marrow from its stem cells, the **haematopoietic stem cells**. These are able to **regenerate continuously** and differentiate into every type of blood cell very efficiently [**figure 4**]. This means they **can be used for bone marrow or stem cell transplants** in patients with blood diseases such as leukaemia. If we consider that all the red blood cells are regenerated about every 4 months and all the platelets about every 10 days, we can understand why blood is so difficult to reproduce in the laboratory!

Where does blood come from?

Figure 4 Haematopoiesis



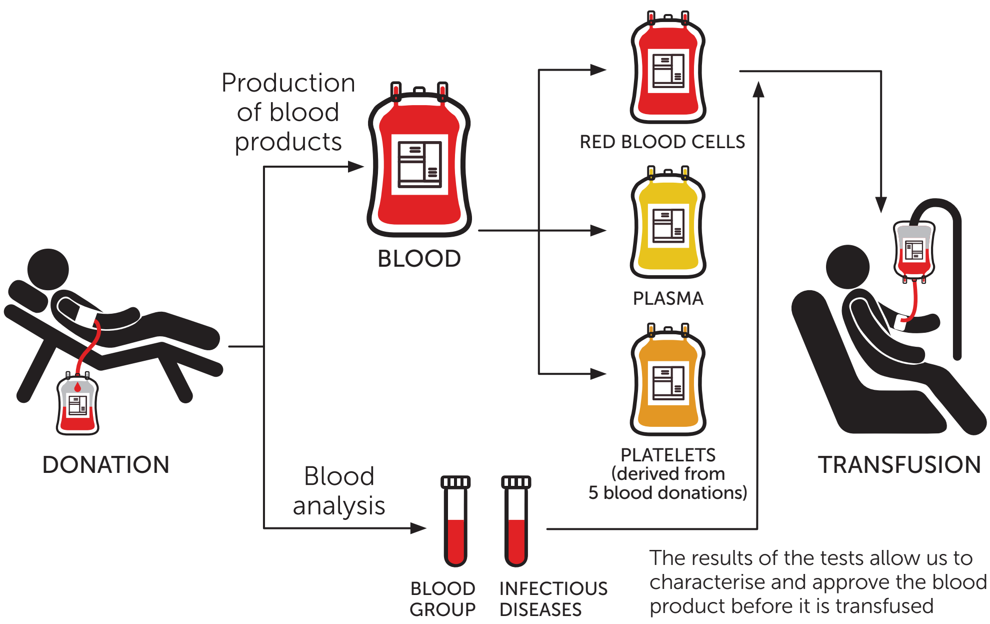
BLOOD DONATION AND TRANSFUSION

Blood can be drawn from a healthy individual in a **blood donation** and administered to a patient for therapeutic purposes with a **transfusion**. Collecting blood from a vein in a donor's arm and infusing it into a patient's vein are simple and generally well tolerated procedures [**figure 5**]. The donor's blood regenerates rapidly and transfusion can thus help save lives in many situations.

We have just seen that every single component of the blood has specific functions. This is why, after donation, the components of the blood are separated and administered to the patient separately, depending on what they need.

We have also seen that our immune system reacts to contact with antigens foreign to our body. This also happens when a patient receives a transfusion of someone else's blood. How can we resolve this problem? In order to give

Figure 5 From donation to transfusion



someone a transfusion of blood – or blood components – it has to be from a compatible **blood group or type**; this means it shares specific characteristics of blood cells that differ between individuals.

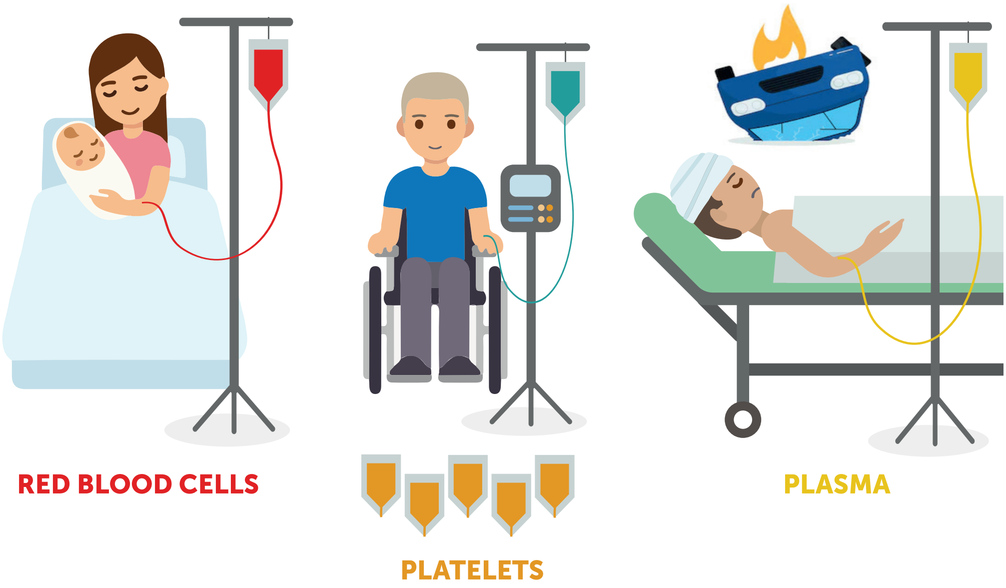
In the next few sections, we will address these issues in more detail. But first let's see what blood is useful for and which patients need it.

INDICATIONS FOR TRANSFUSION OF BLOOD COMPONENTS

We have seen that every component of the blood has specific functions within the body. For this reason, each patient undergoing a transfusion will receive the blood component that's suitable for what they need [**figure 6**]. Let's now look at some practical examples to see which blood components are indicated for transfusion and in which situations.

A patient might have a **red blood cell and haemoglobin count that is too low** for several reasons. This condition is called **anaemia**. It can have multiple

Figure 6 Different patients with different needs receive different blood components



causes, such as blood loss (haemorrhage, or bleeding) or a blood disorder. In the latter case, the problem may be either insufficient production in the bone marrow, or premature elimination in the blood vessels or spleen. If the quantity of blood is insufficient, this means it will not be able to transport enough oxygen from the lungs to the organs that need it. The body will try to compensate for this lack with faster breathing and an accelerated heartbeat, as happens when we do sports, causing a feeling of shortness of breath, tiredness, and palpitations. But when this compensation capacity is no longer sufficient, a transfusion of red blood cells will be needed to restore oxygen transportation.

Patients undergoing chemotherapy for **leukaemia** generally have **very low platelet counts**, in addition to anaemia. This is because leukaemia and the treatment prevent the bone marrow from producing blood cells normally. But having too few platelets in circulation increases the risk of bleeding, as there are not enough platelets to seal any damage to the blood vessels (this is the "plug" function we talked about earlier) caused by the leukaemia, the treatment, or other complications that occur during treatment. These patients therefore need transfusions with thrombocyte concentrates that reduce the risk of bleeding throughout the treatment, in addition to red blood cells.

There are situations where it is necessary to transfuse several products simultaneously. A patient who loses several litres of blood following surgery or an accident will need red blood cells, to ensure the supply of oxygen to their organs, as well as platelets and plasma at the same time, so that the blood can clot and the patient will stop bleeding.

Many transfusions are needed in the event of:

- serious accidents involving injuries, lesions to organs, and multiple bone fractures;
- major operations, for example on the heart or large blood vessels;
- severe bleeding during childbirth;
- patients with leukaemia or other blood diseases.

The number of products transfused to a patient can range from one to several dozen. In particularly severe cases, for example in patients with multiple injuries caused by an accident, it may be necessary to transfuse a quantity of products that corresponds to more than the entire volume of their blood, which generally varies between 4 and 7 litres. To cover the need for blood products, about 730 blood donations per day are needed in Switzerland (2021 figure)!

BLOOD DONATION

But where does the blood used for transfusions in Swiss hospitals and clinics come from?

The Swiss Red Cross Transfusion Services are responsible for supplying the country with blood products. **Blood donation is voluntary and unpaid**: it is therefore an **act of solidarity** of healthy individuals towards patients who need it. Blood donation is a simple act but it lets you help others and save lives.

The choice to donate must be made freely, no one must be forced to do so, either with a legal obligation or with incentives. For example, donating blood in exchange for money can push individuals to do so even in situations where this is not appropriate, such as if they are ill. In fact, during an illness (for example, an infection), donation is not only risky to the donor, as it will not be well tolerated, but there is also a risk of transmitting the infection to the recipient and thus endangering their health. The Council of Europe's standards on blood products promote voluntary unpaid donation.

Swiss law and that of most European countries consider blood as a **drug**. This means that it is subject to very strict controls to ensure its quality and safety, just like any other medication. These rules apply during all stages of processing: donation, separation into components, analysis, storage, transport, and use.

The difference compared to other drugs is that blood **cannot be produced in a factory in a standardised way**, but must be obtained from individuals willing to donate it. Each donor, however, is an individual with their own characteristics and this is why it is necessary to check their compatibility with the patient before transfusion, a test that is not necessary when we administer other medications.

Who can donate blood?

A donation corresponds to 450 ml of blood, as well as an additional 30-40 ml to be used for the necessary tests to check it [**figure 7**]. Based on the donor's body mass, this amount **represents between 8 and 12% of their total blood volume**. This means that individuals with a higher body weight and mass can tolerate donating better. Anyone between the ages of 18 and 60 who weighs over 50 kg and is in good health can therefore donate blood. However, anyone who is already a donor at 60 can continue to donate up to the age of 75, if their state of health allows it.

Before each donation, a **medical questionnaire** must be completed, which is evaluated by a skilled nurse [**figure 8**]. Next, the donor's **pulse**, **blood pressure**, and **haemoglobin** are measured. This is to make sure the donor has "enough" blood to donate safely. The checks carried out and the evaluation criteria serve to ensure that blood donation does not pose a risk to the donor or the recipient of the blood. For example, an individual with heart disease will tolerate the donation less well, because it will stimulate their heart excessively.

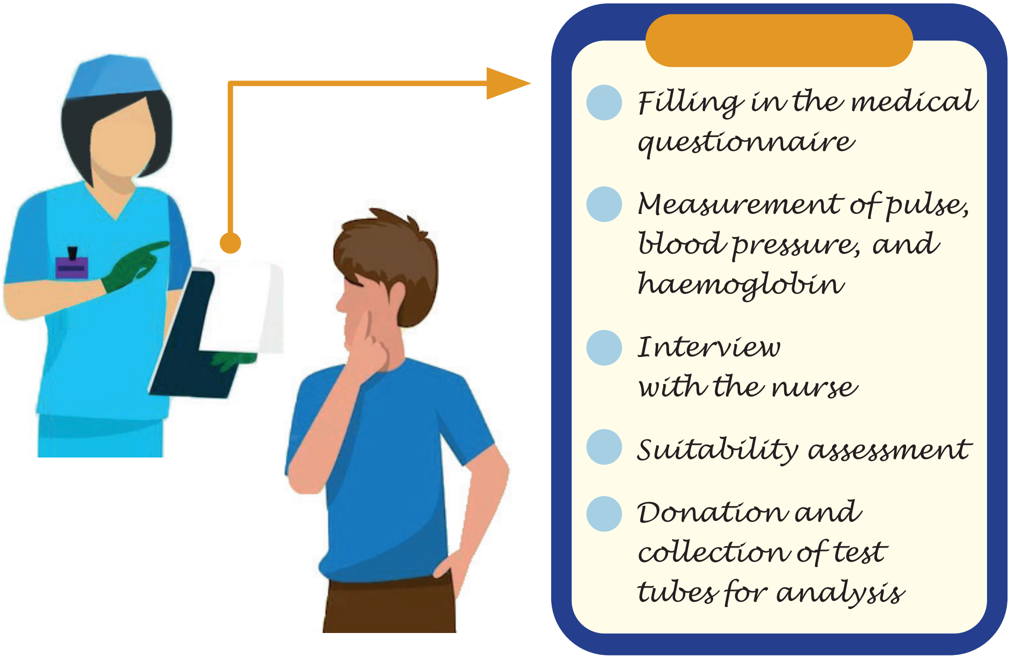
Figure 7 Test tubes of blood taken from the donor for analysis

Source: Transfusion Service of Italian Switzerland, Swiss Red Cross (CRS).

Or, if an individual has a viral liver disease (called hepatitis), they cannot donate blood because it would put the recipient at risk, because this disease can be transmitted via the blood.

Once their suitability has been verified, the donor can proceed with the donation. This – like all the subsequent processing of the blood – takes place in a closed system of plastic bags and tubes sealed to a needle. This prevents possible contamination with microorganisms during processing. After disinfecting their skin, the needle sealed to the bag is inserted into a vein in the donor's arm. First, the test tubes for the analyses are filled; then, the blood flows into the collection bag containing an anticoagulant, which prevents the blood from clotting. The bag is placed on a

Figure 8 Steps of donor assessment



special scale that oscillates it, mixing the blood with the anticoagulant, which stops the collection automatically when 450 ml have been drawn [**figure 9**].

Donating blood is not dangerous. To avoid symptoms related to the reduction of blood volume, however, it is important to prepare properly and follow some simple rules:

- drink water or other soft drinks before and after donation;
- do not donate on an empty stomach;
- have a small snack after donating;
- avoid extreme exertion or overly strenuous workouts on the same day.

These measures have proven to be effective in reducing the risk of dizziness or fainting, a risk that is very low but cannot be totally prevented.

Figure 9 Blood donation from a vein in the arm

Source: Transfusion Service of Italian Switzerland, Swiss Red Cross (CRS).

THE ANALYSES

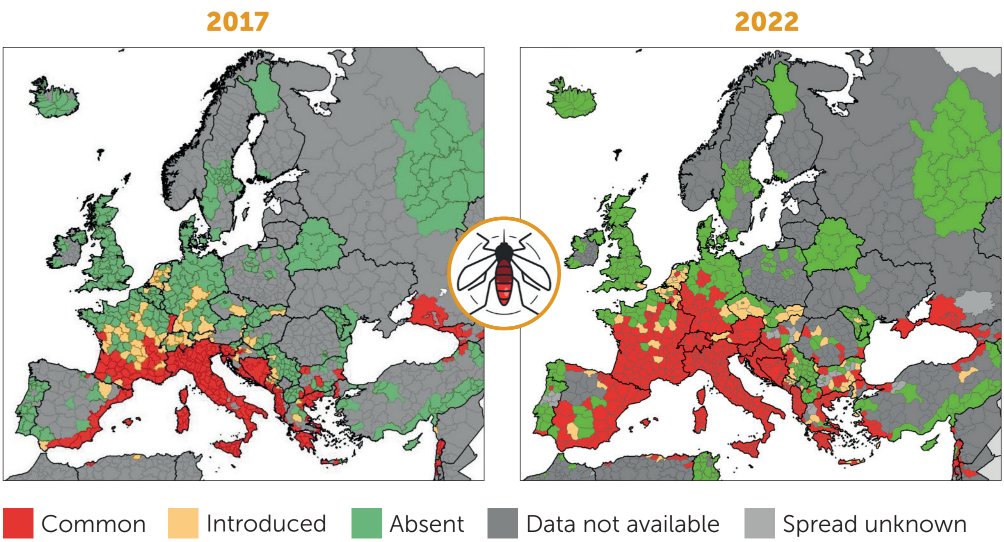
As we have seen, during each donation, 30-40 ml of blood are drawn to perform laboratory tests that have two main purposes.

1. **Identifying possible blood-borne infectious diseases.** Obviously, it is not possible to test for every possible type of naturally occurring micro-organism that could cause disease in humans. The tests are limited to infectious diseases of a certain severity that have been shown to be transmissible

through blood transfusion, such as various forms of hepatitis (hepatitis B, hepatitis C, and hepatitis E), which are caused by different types of viruses that can circulate in the blood and cause inflammation of the liver. With global warming underway and the extreme mobility of the population, diseases typical of warmer regions that are spreading to our latitudes have also been added in recent years. Some of these are transmitted by carriers known as vectors, for example mosquitoes. Some species of native mosquitoes can be infected with viruses from tropical regions (e.g. West Nile fever). Other species are of tropical origin but are increasingly spreading to our latitudes, such as the tiger mosquito [**figure 10**], thus facilitating the spread of new viruses such as Dengue fever or the Chikungunya virus.

2. **Determining the donor's blood type** so it can then be compared with that of the patient before the transfusion to ensure that the patient's blood and the donor's are compatible. In the next chapter, we will learn more about blood groups and types and what they mean.

Figure 10 Spread of the tiger mosquito in Europe 2017-2022



Source: European Centre for Disease Prevention and Control.
https://www.ecdc.europa.eu/en/publications-data/aedes-albopictus-current-known-distribution-europe-april-2017
https://www.ecdc.europa.eu/en/publications-data/aedes-invasive-mosquitoes-current-known-distribution-march-2022

A BRIEF HISTORY

The first transfusion attempts were made in the seventeenth century and carried out with sheep's blood. Among the various theories in vogue at that time, it was thought that transfusions of sheep's or lamb's blood were able to calm the spirits of people suffering from mental disorders with a particularly agitated spirit. In 1667, **Jean-Baptiste Denis**, the court physician of King Louis XIV of France, and Richard Lower and Edmund King, in England, surprisingly reported some successes with this procedure, probably due to the minimum amount of blood transfused, which was not sufficient to produce side effects [**figure 11**]. It was soon realised, however, that in most cases, transfusing animal blood led to serious complications, even death. About 10 years later, it was therefore banned by law. Today, we know that these reactions are caused by the immune system, which recognises the differences between the red blood cells of different animal species, and thus also between humans and sheep.

Figure 11 First attempts at transfusion with sheep's blood

Source: Matthias Gottfried Purmann, *Grosser und gantz neugewundener Lorbeer-Krantz, oder Wund Artzney... Zum andern Mahl vermehrt heraus gegeben* (1705).

> When was the first transfusion carried out?

In 1818, **James Blundell**, an English obstetrician, first transfused human blood into a woman who was bleeding heavily after childbirth. The blood was taken from her husband with a syringe and transfused directly into the woman. In the following years, Blundell gave several other patients transfusions this way, and it seems that he also became very wealthy doing so. However, Blundell had to acknowledge that although in some cases the transfusion was successful, in others it caused serious complications, even the death of the patient. Why was that?

To solve this riddle, we would have to wait until 1900, when the Austrian doctor **Karl Landsteiner** observed that when mixing the blood of several individuals, the blood of some of them reacted selectively with that of others, while in other cases no reaction was observed. This observation led to the discovery of the first blood groups, which make up the ABO group system. This discovery earned Landsteiner the Nobel Prize for Medicine in 1930. Even today, the ABO group remains the most important that must be compatible when giving patients transfusions.

Between the years 1939-40, the Rhesus factor was discovered, an antigen belonging to what is now called the Rh blood group system. More groups have been discovered increasingly rapidly until today, when there are 43 known blood group systems.

◎ THE PRINCIPLE OF COMPATIBILITY

We have seen that our immune system is able to distinguish between its own characteristics and characteristics foreign to our body. These characteristics are called **antigens**. The white blood cells and antibodies circulating in our blood are able to recognise antigens that are different to ours and react against them. This means that if we transfuse red blood cells from a donor that carry antigens different to those of the patient, the latter may undergo a transfusion complication that manifests as a **haemolytic transfusion reaction** (HTR), in which the antibodies cause the destruction of the transfused red blood cells. The severity of this reaction is variable: some foreign antigens do not cause any problems, others can lead to reactions so serious as to endanger the patient's life.

That is why before a transfusion you must always check the compatibility between the donor and the patient.

◎ CLASSIFICATION OF BLOOD GROUPS

Which blood groups have to be compatible?

Today, we know about **43 blood group systems**, which together cover more than **360 different antigens** located on the surface of red blood cells [figure 12]. Fortunately, not all of these groups need to be identified before carrying out a transfusion, because only some of them cause a transfusion reaction if they are not compatible between the donor and the recipient. The most important groups to match are the **ABO group** and the **D antigen**, which is part of the **Rh** (Rhesus) **blood group system**.

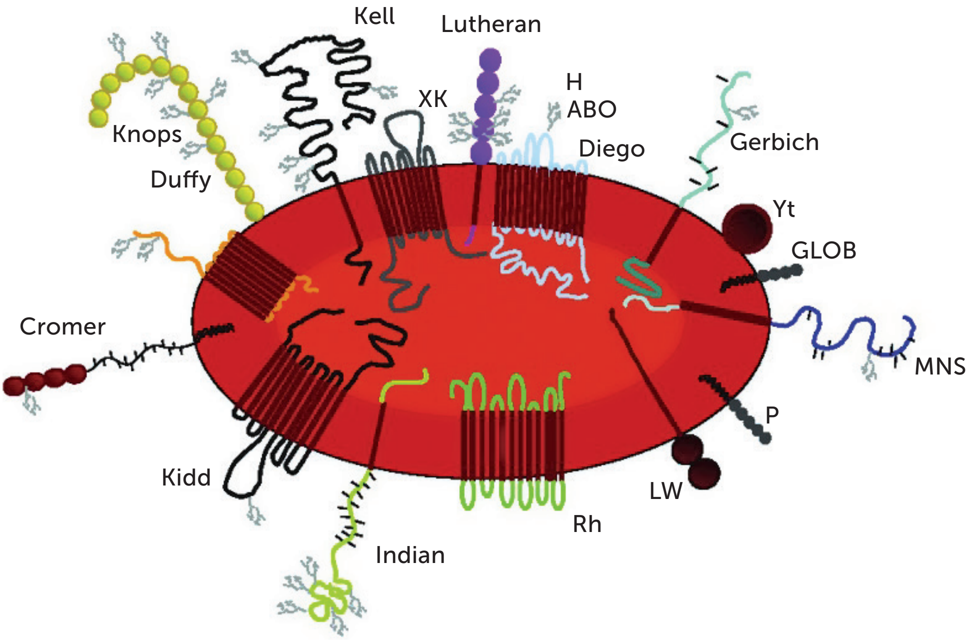
In the ABO group system, red blood cells can carry antigen A, or B, or both, or neither. The antigen determines the specific group, so those who carry neither A nor B are in group O, while those who carry antigen A are in group A etc. [figure 13]. In the months after birth, our body forms antibodies against foreign antigens, i.e. anti-B antibodies in group A, anti-A in group B, anti-A and anti-B in group O, and neither in group AB.

If we transfuse **erythrocytes**, we need to make sure **they don't carry antigens that the patient has antibodies against**. Thus, for example, group O erythrocytes may be transfused to patients of any group, while A erythrocytes may be transfused to patients of groups A and AB. The rules applicable to erythrocytes are summarised in figure 14.

For plasma, the rules apply in reverse: for example, group AB plasma, containing neither anti-A nor anti-B antibodies, can be transfused to all patients, whereas group B plasma (containing anti-A) can only be transfused to B or O patients.

The second group system in order of importance is called the **Rhesus factor** (Rh group); it comprises several different antigens, of which the most important is the D antigen. **Anyone who has the D antigen is Rh-positive, anyone who does not is Rh-negative. Rh-negative people** can form anti-D antibodies,

Figure 12 Schematic representation of some antigens showing the names of the blood group systems



Source: Blood group systems. ISBT Science Series, 2020.
https://onlinelibrary.wiley.com/doi/epdf/10.1111/voxs.12593

Figure 13 The ABO group system

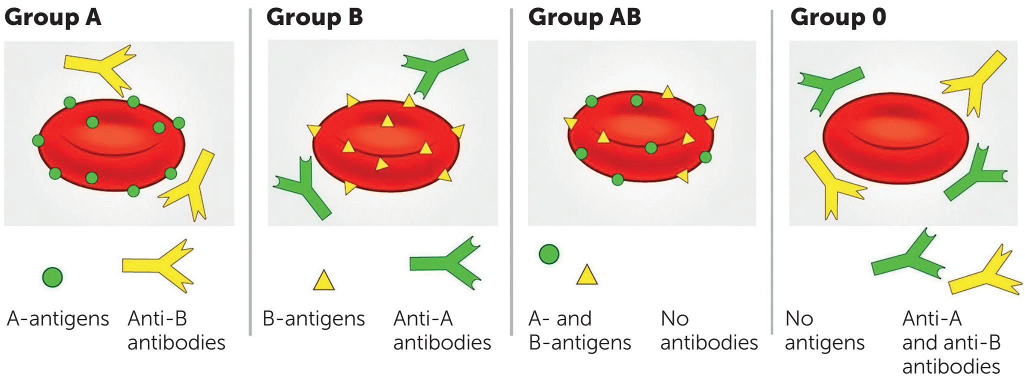
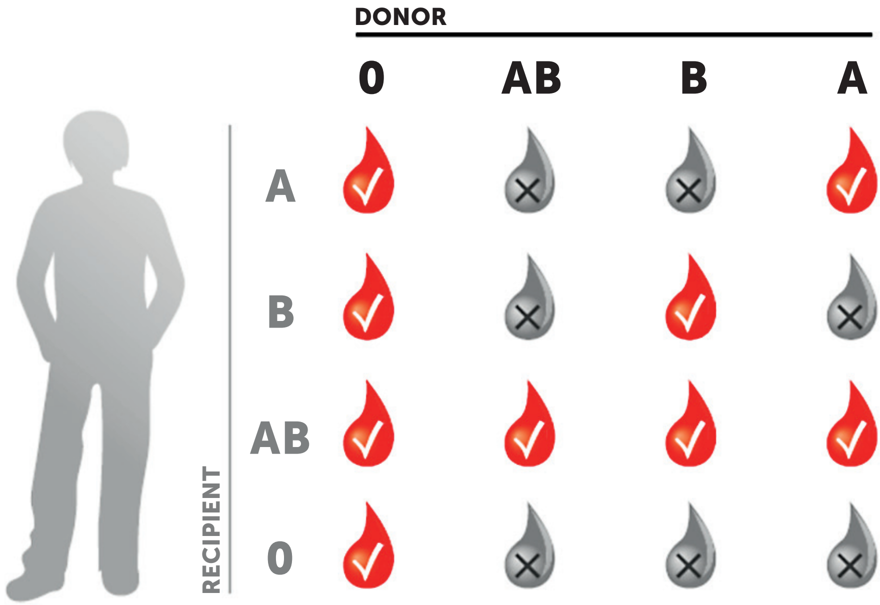


Figure 14 Donor-recipient compatibility rules for red blood cell transfusion



People with blood group AB can donate blood to recipients with the same blood group. People with blood group O, on the other hand, can also donate their blood to people with different blood groups. This is why they are particularly suitable for donation.

so they **must receive Rh-negative blood**. **People who are Rh-positive can receive both.**

This explains why **type O Rh-negative** donors are so in demand: they represent less than 7% of the population in our country and **anyone can receive a transfusion of their erythrocytes**. In fact, an O-negative transfusion is used in urgent cases, when the patient's blood group is not yet known. As soon as the laboratory has determined the group, products from the same group are used.

BLOOD PRODUCTS

After donation, the blood is separated into its components. Centrifugation enables us to separate out red blood cells (at the bottom), plasma (at the top), and other cells (in the middle) [figure 15].

Figure 15 A blood donation after centrifugation: the plasma at the top, the erythrocytes at the bottom, with leukocytes and platelets in the thin middle layer

Source: Transfusion Service of Italian Switzerland, Swiss Red Cross (CRS).

Erythrocyte concentrate. It is useful to remember that the cells in our body are alive and need sustenance if they are stored in a plastic container outside our body. After donation and separation from other cells, the red blood cells are then transferred into a bag with a nutrient solution that allows them **to be stored at 4°C for 42 days**. Filtration allows **residual white blood cells to be eliminated** and a purer erythrocyte concentrate to be obtained, with minimal contamination of other cells [**figure 16**].

Fresh frozen plasma. Plasma is also transferred into a bag and frozen at -25°C, to be **stored for up to 2 years** [**figure 17**].

Thrombocyte concentrate. The **platelets** are extracted from the intermediate layer, which consists of platelets, white blood cells, and residual red blood cells. The platelets of 4-5 donors are pooled to obtain a sufficient dose for a

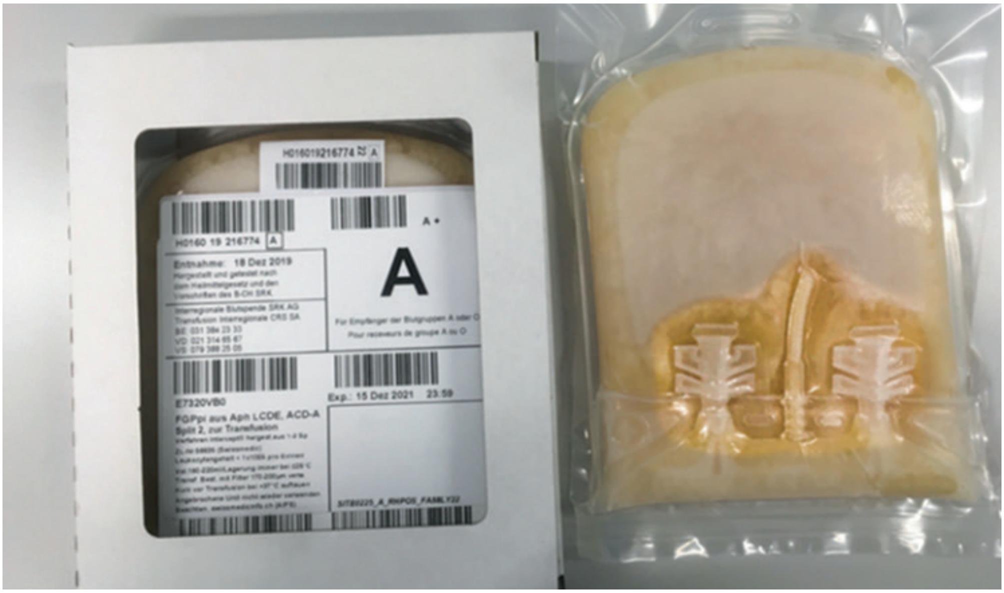
Figure 16 Fridge containing erythrocyte concentrates of different groups at 4°C

Source: Transfusion Service of Italian Switzerland, Swiss Red Cross (CRS).

transfusion. The resulting product is subjected to a special procedure to **eliminate any micro-organisms** (inactivation of pathogens) and stored at room temperature for a maximum of 7 days [**figure 18**].

In addition, antibodies or clotting factors can be extracted from the plasma to produce drugs used to treat patients with immune system diseases, infections, or clotting disorders. A typical example is **haemophilia**, a genetic disease that causes bleeding, whose carriers lack a specific clotting factor. When they bleed, these patients can be treated with this factor, which can be extracted from plasma.

Figure 17 Fresh frozen plasma, stored in a freezer below -25°C



Source: Transfusion Service of Italian Switzerland, Swiss Red Cross (CRS).

Figure 18 Two thrombocyte concentrates stored at room temperature (20-24°C)

Source: Transfusion Service of Italian Switzerland, Swiss Red Cross (CRS).

CONCLUSIONS AND FUTURE PROSPECTS: WHY IS THERE NO ARTIFICIAL BLOOD?

The first attempts to produce artificial blood date back over 50 years. The initial approach, which seemed like the simplest, was to develop forms of **artificial haemoglobin** that could transport oxygen from the lungs to the tissues, just like the haemoglobin in our red blood cells does.

Later, completely different substances that were able to bind oxygen were also studied. A class of substances, **perfluorocarbons** (PFCs), was found on which several studies were carried out. However, despite numerous attempts, none of these substances was able to replace the transfusion of red blood cells, due to both their lack of efficacy and, above all, their toxicity: most of the studies were interrupted due to serious side effects.

The problem with these approaches is that they did not consider the complexity of the mechanism for oxygen transportation, which is based not only on haemoglobin, but on **a balance produced by the interaction between blood vessels, erythrocytes, haemoglobin, oxygen, and other substances present in the blood**, the result of an evolutionary process that took place over millions of years and is difficult to imitate.

We've seen that blood comes from **blood stem cells**. Growing these cells in the lab and maturing them into red blood cells or platelets, reproducing as closely as possible what our body does, could be a way to produce blood in the lab.

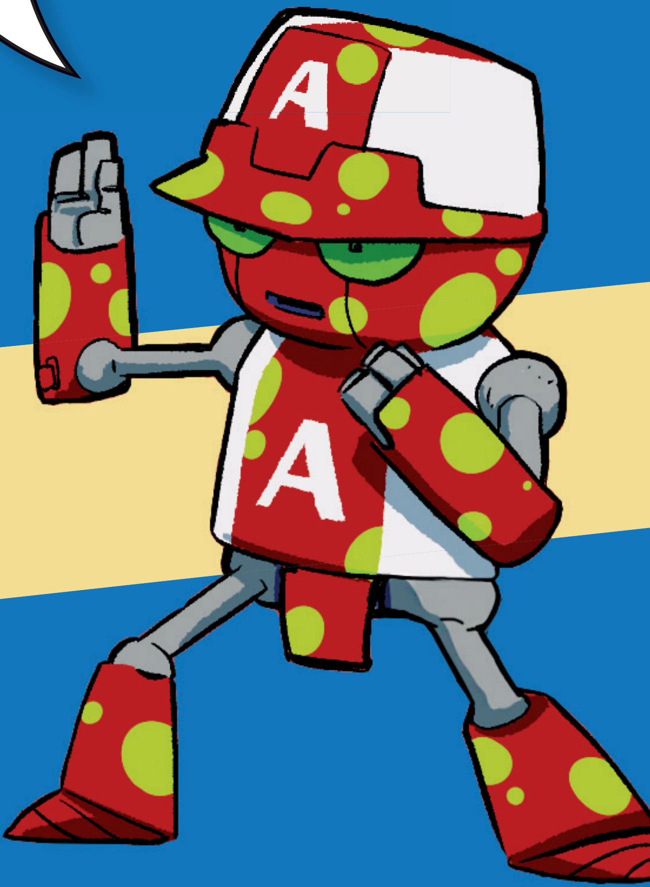
Progress has been made in recent years in cultivating and differentiating different types of stem cells. The difficulties of this approach consist in obtaining cells that correspond 100% to red blood cells, without any immature forms that are not suitable for their function, cells that carry a form of haemoglobin not suitable for transporting oxygen, or antigens foreign to the human body that could cause side effects if transfused into a patient being left in the blood.

So far, some laboratories have managed to produce a few millilitres of blood. We are still a long way from producing blood industrially and safely, following standardised processes, in the amount needed to supply an entire country. Before these new products can be used in daily practice, clinical trials will then be necessary to ensure their efficacy and safety. However, this stem cell-based approach could be fine-tuned in the coming years to **produce blood for patients with very rare blood types**, of which there are few donors across Europe. If we had the stem cells of a few individuals with rare types always available, it would be possible to produce a sufficient amount of blood of this type; although the costs would be high, they would be justifiable in the absence of valid alternatives.

In conclusion, it will still be a long time before we are able to produce blood in a factory in the quantities necessary to meet the needs of patients, while providing the same guarantee of safety as donor blood at sustainable costs. Until then, our bodies will remain the most efficient and safe blood factories and donation will remain a necessary activity for the survival of many human beings.

PART TWO

Blood



TEXTS

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ILLUSTRATIONS

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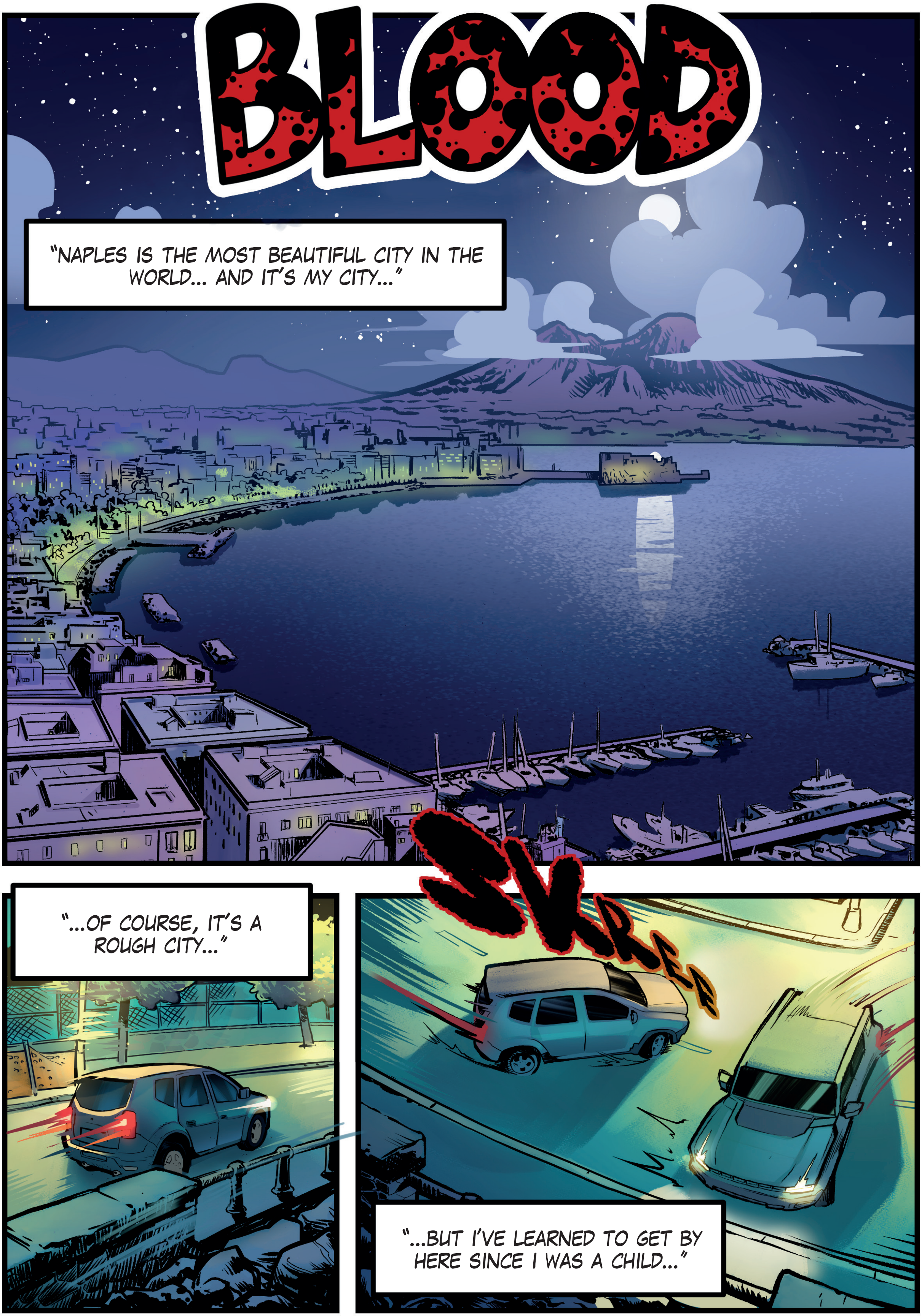
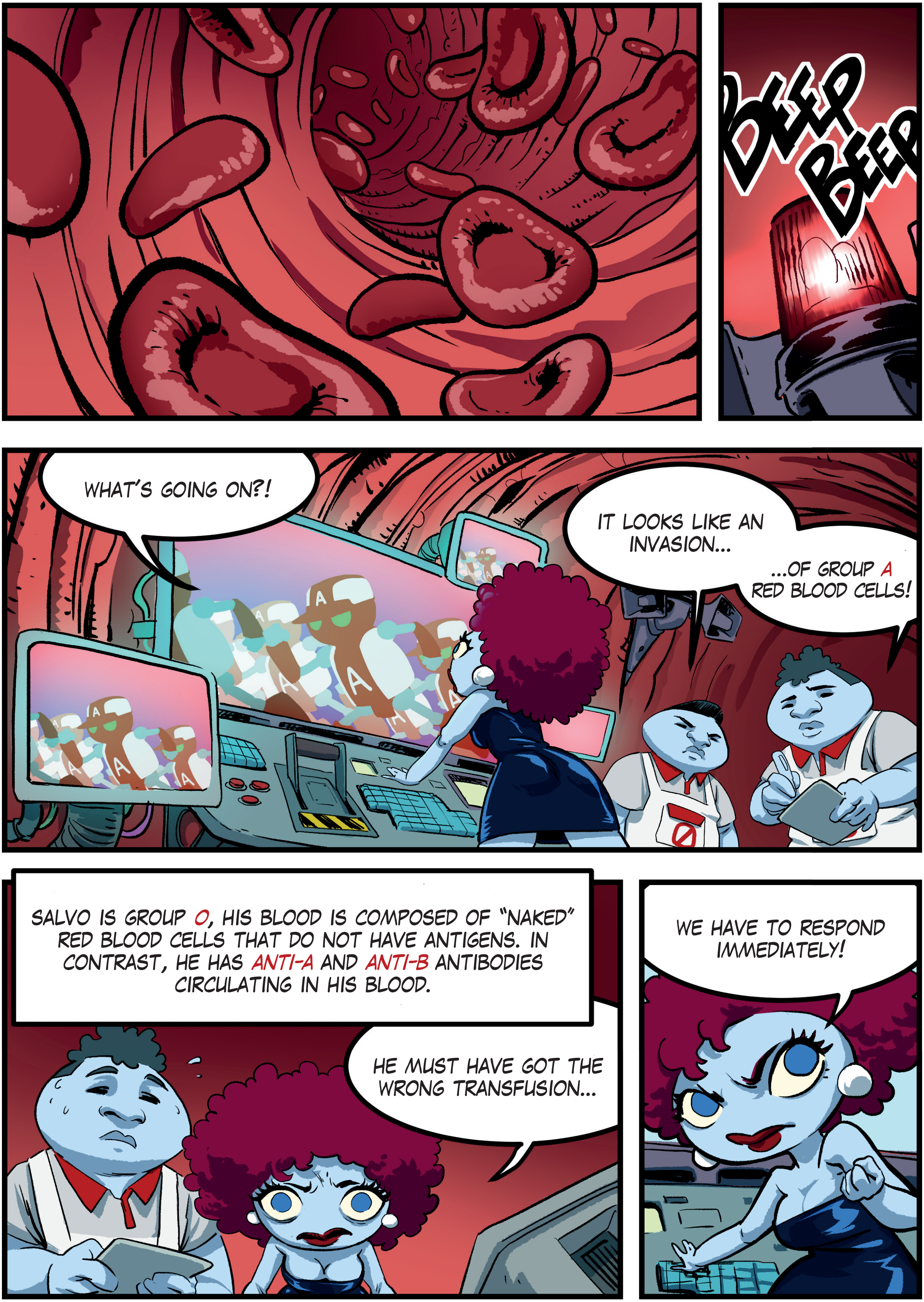

BLOOD
"NAPLES IS THE MOST BEAUTIFUL CITY IN THE WORLD... AND IT'S MY CITY..."
"...OF COURSE, IT'S A ROUGH CITY..."
SKREE
"...BUT I'VE LEARNED TO GET BY HERE SINCE I WAS A CHILD..."


"...MY NAME IS SALVATORE... SALVO TO MY FRIENDS..."
"...AND I HAVE MY GANG..."
LET'S KILL THEM ALL!
"...AND WE KNOW HOW TO MAKE RIVAL GANGS RESPECT US!"
BANG BANG
BANG
BANG
BANG BANG


IT'S BULLETPROOF!
BANG
BANG
AH
THE BOSS IS HURT... LET'S GET HIM AWAY!
COME ON, QUICK!
BLAM


YOU'RE LOSING A LOT OF BLOOD... WE'RE TAKING YOU TO THE HOSPITAL!
NO... THEY WOULD ARREST ME...
TAKE ME TO THE DOC!
BUT HE'S NOT EVEN A REAL DOCTOR!
HIS SISTER IS ENGAGED TO A DOCTOR AT CARDARELLI HOSPITAL... HE KNOWS ABOUT MEDICINE...
THAT'S AN ORDER, ABDUL!

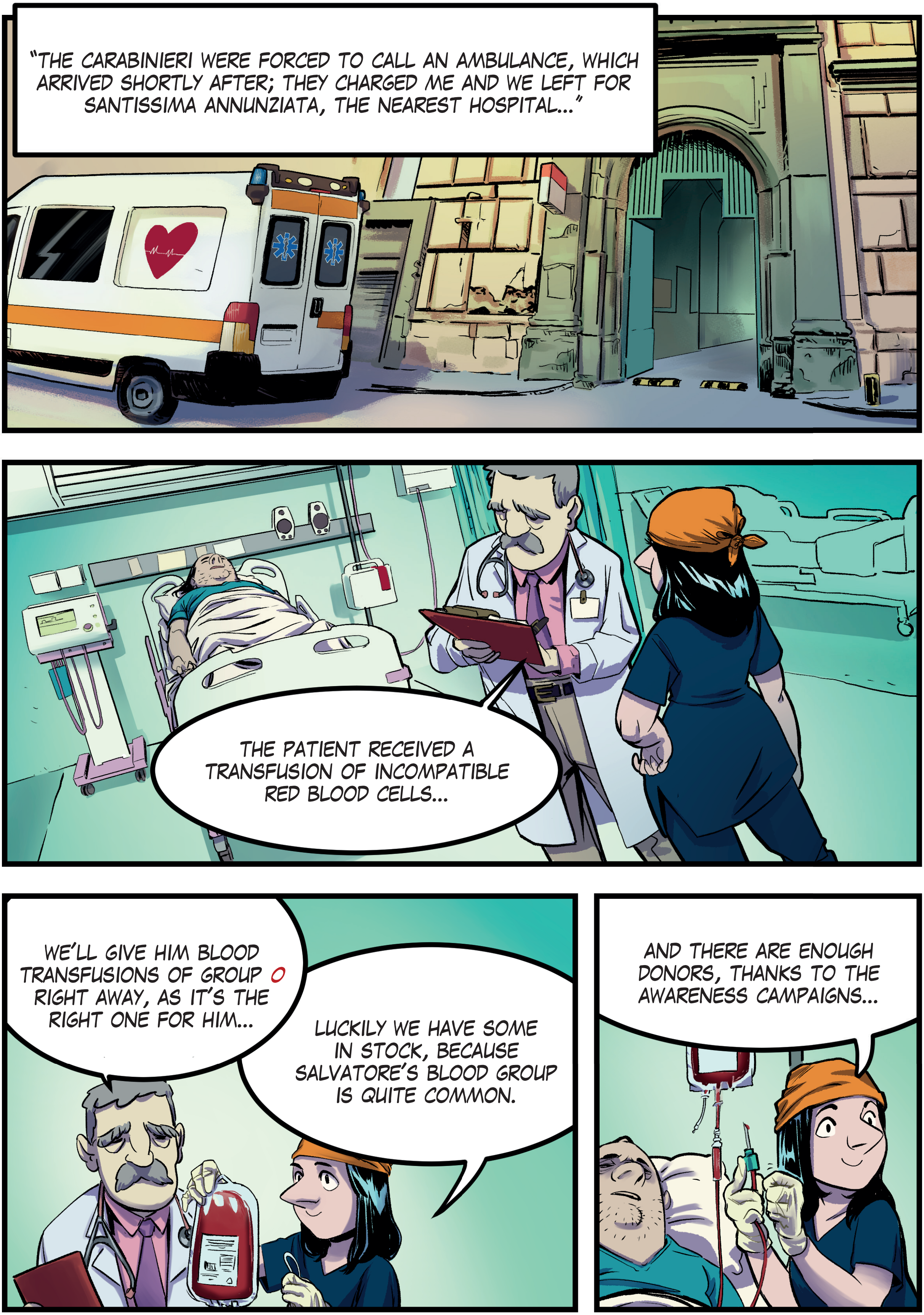

"AND SO I WAS BROUGHT TO THE DOC..."
WE NEED A TRANSFUSION HERE IMMEDIATELY...
BUT THAT BLOOD IS A AND I'M GROUP O...
A
A
DON'T WORRY... BLOOD IS BLOOD... AND THE BEST, I CAN ASSURE YOU, DON SALVO!

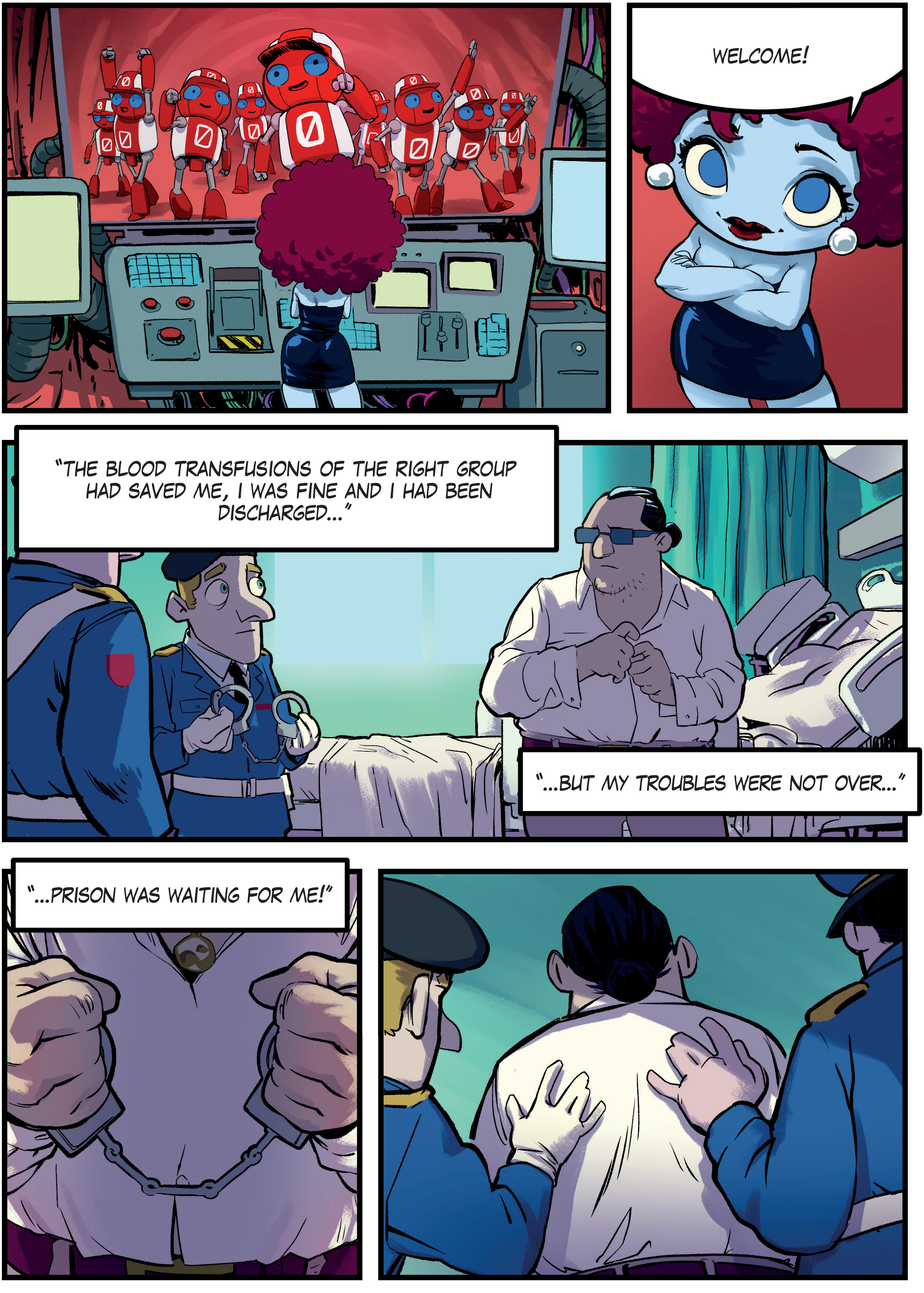

BEEP BEEP
WHAT'S GOING ON?!
IT LOOKS LIKE AN INVASION...
...OF GROUP A RED BLOOD CELLS!
SALVO IS GROUP O, HIS BLOOD IS COMPOSED OF "NAKED" RED BLOOD CELLS THAT DO NOT HAVE ANTIGENS. IN CONTRAST, HE HAS ANTI-A AND ANTI-B ANTIBODIES CIRCULATING IN HIS BLOOD.
HE MUST HAVE GOT THE WRONG TRANSFUSION...
WE HAVE TO RESPOND IMMEDIATELY!

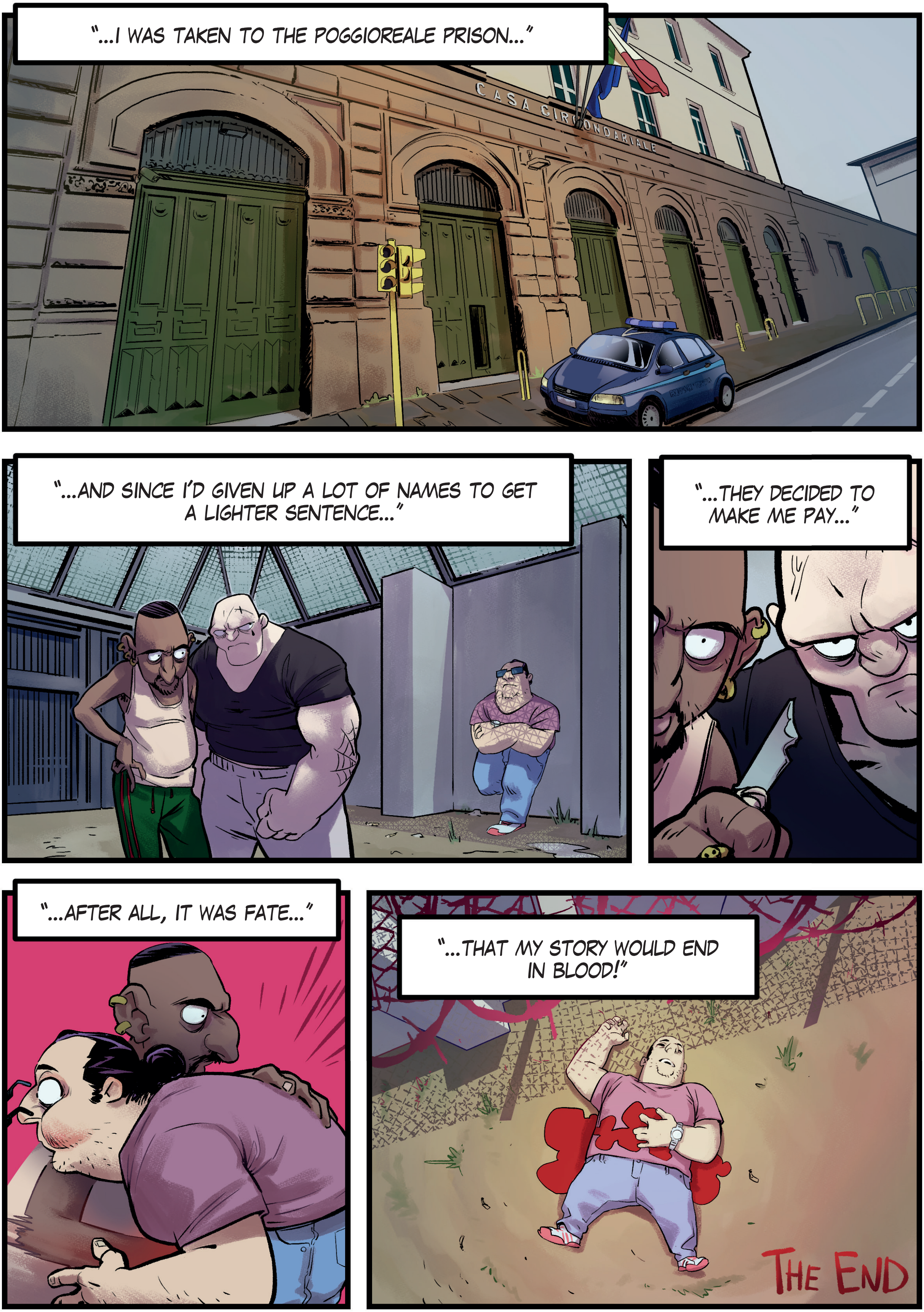

THE PROBLEM IS NOT ACTUALLY THE GROUP A RED BLOOD CELLS, WHICH ARE HARMLESS TO GROUP O BLOOD CELLS, BUT THE ANTI-A ANTIBODIES...
BECAUSE SALVO'S IMMUNE SYSTEM THINKS IT'S BEING ATTACKED EVEN THOUGH A-CELLS WON'T DESTROY O-CELLS...
THERE ARE BILLIONS OF THEM... THEY'RE ATTACKING US...
LUCKILY, YOU CAN RECOGNISE THEM EASILY, WITH ALL THOSE LITTLE DOTS...
YES, LET'S BEGIN THE PROCESS OF DESTRUCTION...
LET'S UNLEASH OUR ANTI-A ANTIBODIES!


"...IT WAS CLEAR THAT THE DOC HAD TRICKED ME AND TRIED TO KILL ME ON BEHALF OF THE RIVAL GANG..."
"...I HAD TO GET OUT OF THERE... I FELT WEAKER AND WEAKER..."
"...WAS I ALSO IN WITHDRAWAL?"
"DON GENNARO WOULD GIVE ME THE ANSWER..."
"...HE HAS THE BEST COCAINE IN NAPLES..."


STOP, HANDS UP!
"...THAT SCUM BAG HAD SOLD ME OUT TO THE COPS..."
"I DIDN'T RUN, IT WASN'T WORTH IT. I KNEW THE GAME WAS OVER, THE COPS HAD ME CORNERED AND VERY SOON, THEY WOULD INEVITABLY ARREST THE WHOLE GANG..."
ANF ANF
"FROM THAT MOMENT, EVERYTHING SLOWED DOWN AROUND ME, IT WAS ALL OVER NOW..."
"I FAINTED, AND THAT JUST MIGHT HAVE SAVED ME..."


"THE CARABINIERI WERE FORCED TO CALL AN AMBULANCE, WHICH ARRIVED SHORTLY AFTER; THEY CHARGED ME AND WE LEFT FOR SANTISSIMA ANNUNZIATA, THE NEAREST HOSPITAL..."
THE PATIENT RECEIVED A TRANSFUSION OF INCOMPATIBLE RED BLOOD CELLS...
WE'LL GIVE HIM BLOOD TRANSFUSIONS OF GROUP O RIGHT AWAY, AS IT'S THE RIGHT ONE FOR HIM...
LUCKILY WE HAVE SOME IN STOCK, BECAUSE SALVATORE'S BLOOD GROUP IS QUITE COMMON.
AND THERE ARE ENOUGH DONORS, THANKS TO THE AWARENESS CAMPAIGNS...


WELCOME!
"THE BLOOD TRANSFUSIONS OF THE RIGHT GROUP HAD SAVED ME, I WAS FINE AND I HAD BEEN DISCHARGED..."
"...BUT MY TROUBLES WERE NOT OVER..."
"...PRISON WAS WAITING FOR ME!"


"...I WAS TAKEN TO THE POGGIOREALE PRISON..."
CASA CIRCONDARIALE
"...AND SINCE I'D GIVEN UP A LOT OF NAMES TO GET A LIGHTER SENTENCE..."
"...THEY DECIDED TO MAKE ME PAY..."
"...AFTER ALL, IT WAS FATE..."
"...THAT MY STORY WOULD END IN BLOOD!"
THE END

GLOSSARY

Adaptive immune response Our body's second line of defence: it acts in a very specific way against foreign antigens and is able to form a memory of them, in case it encounters them again in the future.

Anaemia A condition in which the level of haemoglobin in the blood is below normal. There can be many causes for this: from iron deficiency to one of the many blood diseases, to bleeding after an accident or surgery. The condition reduces the blood's ability to supply oxygen to the tissues.

Antibody A protein produced by a specific category of lymphocytes (called B lymphocytes) that is able to bind to an antigen, helping the immune system to eliminate it.

Anti-coagulant A substance capable of inhibiting the blood clotting process. There are anticoagulant drugs, given to prevent the formation of blood clots in the blood vessels (thrombosis), and anticoagulants used to prevent the clotting of blood taken for analysis or transfusion. The latter are found in blood donation bags or the test tubes used for laboratory analyses.

Antigen The structure of an organism that our immune system is able to recognise as foreign. The reaction that this causes, aimed at eliminating the foreign organism, includes the formation of antibodies, among other things.

Blood donation Voluntary provision of a set amount of your blood, the components of which can be used for therapeutic purposes. The most commonly used blood products derived from donation have a short shelf life; this is why the constant availability of donors is very important.

Blood group or type A set of antigens controlled by the same gene, present in different forms in different individuals (e.g., the ABO group system). Transfusion of blood from a donor with a different group to the patient may activate the patient's immune system, causing haemolysis.

Chikungunya A virus transmitted by mosquito bites that causes fever and severe pain in the muscles and joints. It is a virus characteristic of warmer regions (especially Asia and Africa), but travel and climate change are increasing the risk of it spreading to Europe as well.

Coagulation factors, or clotting factors Proteins dissolved in the plasma that interact with platelets and with each other, causing clots to form. Lacking one or more of these proteins can lead to excessive bleeding. In diseases where the individual has a deficiency of a specific factor, such as haemophilia, bleeding can be treated by administering the missing factor (factor VIII or factor IX). Following a major blood loss, for example due to an accident, plasma must be transfused to ensure a balanced supply of all clotting factors.

Dengue A virus transmitted by mosquito bite that causes fever, headache, joint pain, and rashes. It is widespread in tropical and subtropical regions, but in recent years, the first cases have been observed in southern Europe due to climate change.

Erythrocytes (red blood cells) Blood cells whose main function is to transport oxygen from the lungs to the tissues. They can be obtained from a blood donation and transfused into a patient with anaemia, if this is of such severity that it no longer allows a sufficient supply of oxygen to the tissues.

Fibrin An essential component of clots that forms following the activation of clotting factors. Fibrin consolidates the primary clot, which is formed by platelets following injury to a blood vessel.

Haematopoietic stem cells Stem cells are undifferentiated cells that have the capacity to mature into various types of cells in our body. Haematopoietic stem cells are found in the bone marrow and can develop into red blood cells, white blood cells, and platelets.

Haemoglobin The main component of red blood cells. It is responsible for transporting oxygen around the body and is the substance that gives the blood its typical red colour.

Haemolysis The process of premature destruction of red blood cells. It can be the consequence of a blood disease, consuming drugs or toxic substances, or a transfusion, if the patient has antibodies against an antigen located on the surface of the transfused red blood cells.

Haemophilia A genetic disease caused by the lack of a protein necessary for the blood to clot (factor VIII or factor IX). The absence of this protein causes a tendency to bleed spontaneously or as a result of minor trauma.

Hepatitis Inflammatory liver disease. Its causes include several viruses, some of which can be transmitted through blood transfusion (hepatitis B, hepatitis C, and hepatitis E). Fortunately, the current preventive measures reduce this risk to almost zero.

Innate immune response Our body's first line of defence: it recognises a limited number of antigens, but acts immediately and activates the adaptive immune response.

Leukaemia A bone marrow disease consisting of an uncontrolled proliferation of pathological blood cells, which prevent the formation of normal cells. There are various forms of leukaemia, with different courses and prognoses, depending on the type of cell altered and the type of abnormality found. In general, patients can suffer from anaemia, haemorrhage, and infections, as well as a number of other complications. The purpose of chemotherapy is to eliminate pathological cells, restoring normal haematopoiesis. During treatment, it is often necessary to transfuse patients with erythrocyte or thrombocyte concentrates.

Leukocytes (white blood cells) Immune system cells that defend the body from microorganisms or foreign bodies. There are several types, each with specific tasks; the blood contains lymphocytes, monocytes, and various categories of granulocytes.

Perfluorocarbons Chemicals potentially capable of carrying oxygen. They have long been investigated as possible substitutes for erythrocyte transfusions, but so far without success, not least because of the risks associated with their administration.

Thrombocytes (platelets) Fragments of cells that circulate in the blood, whose main function is to activate clotting by aggregating where a blood vessel has been injured, thus stopping the bleeding. Their action is followed by that of the clotting factors present in the plasma, which cause fibrin to form, thus stabilising the clot. Thrombocytes can be obtained from blood donors and transfused to patients with an insufficient number of platelets.

Transfusion Administration of blood or blood components from a donor to a patient for therapeutic purposes.

Vector In the biological sense of the term, it is an organism capable of transferring infectious agents to other organisms. As a result of travel and climate change, some vectors (for example, certain mosquito species such as the tiger mosquito) are expanding from tropical and subtropical regions to Europe, causing the spread of viral diseases that were not previously observed at our latitudes.

West Nile Virus A virus transmitted by mosquito bites that in most cases does not cause symptoms, but can lead to flu-like symptoms and occasionally to inflammation of the meninges and brain tissue. In recent years, it has appeared regularly in southern and eastern Europe, in summer and autumn.

Inside our body, the blood performs a lot of essential functions: it transports oxygen and nutrients to the cells, it carries carbon dioxide away from them, and it connects organs and tissues. Pumped by the heart, it circulates continuously, bringing life to all parts of the body.

But when we think about our blood, it is important to remember that it is not only essential for us, but can save the lives of others: if we choose to donate it, in fact, it can help someone who needs it for therapeutic reasons, helping them get better.

Even a small amount can make a difference: this is why donating blood is one of the highest acts of altruism a person can perform.

Stefano Fontana, Foundation of the Transfusion Service of Italian Switzerland, Swiss Red Cross (CRS); University of Lausanne (UNIL).

Inside the comic:

Blood

Texts by the students of class 3B of the Biasca Middle School, Ticino, Switzerland.

Illustrations by Matteo Perilli for the Scuola Romana dei Fumetti.

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