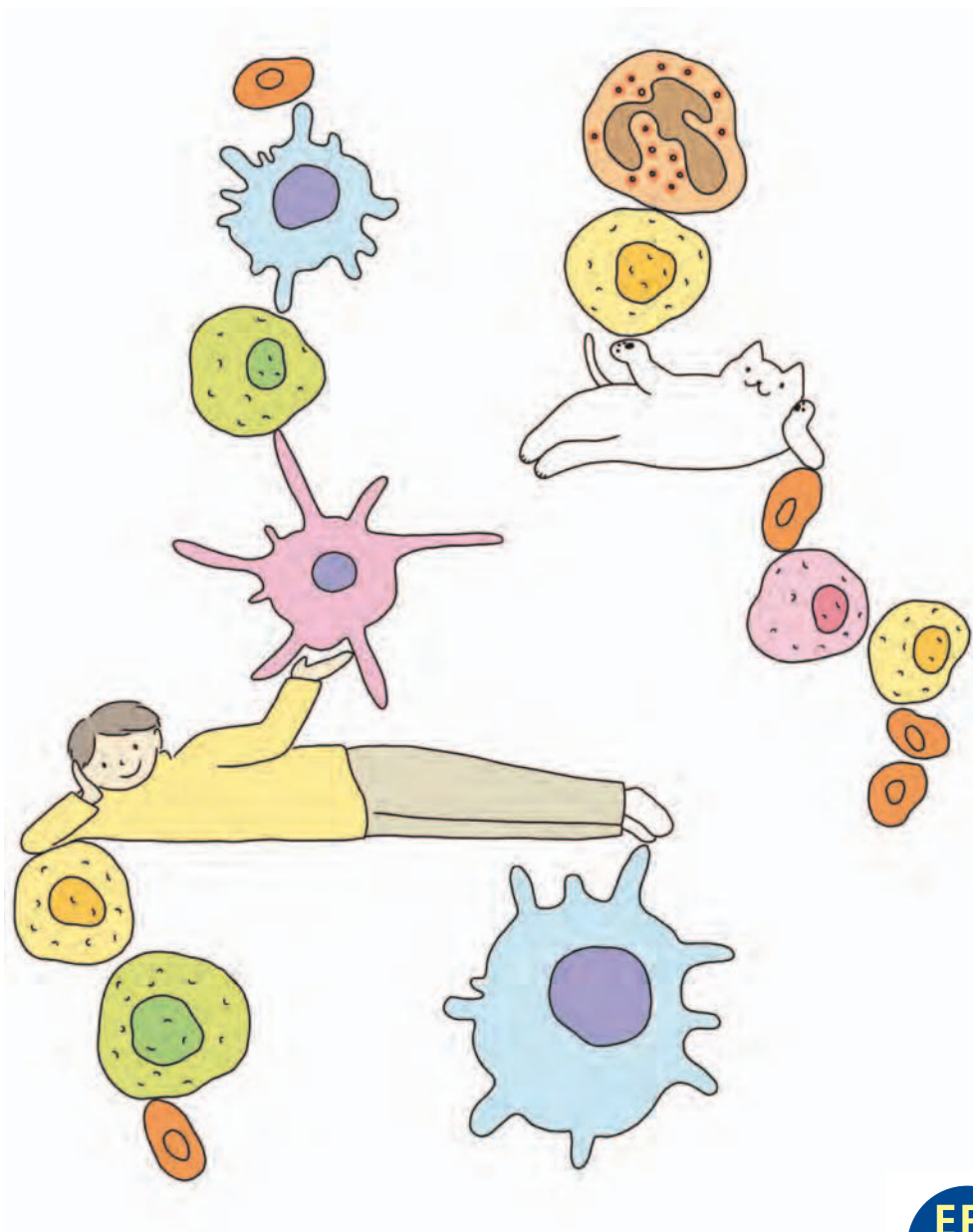


# Your Amazing Immune System

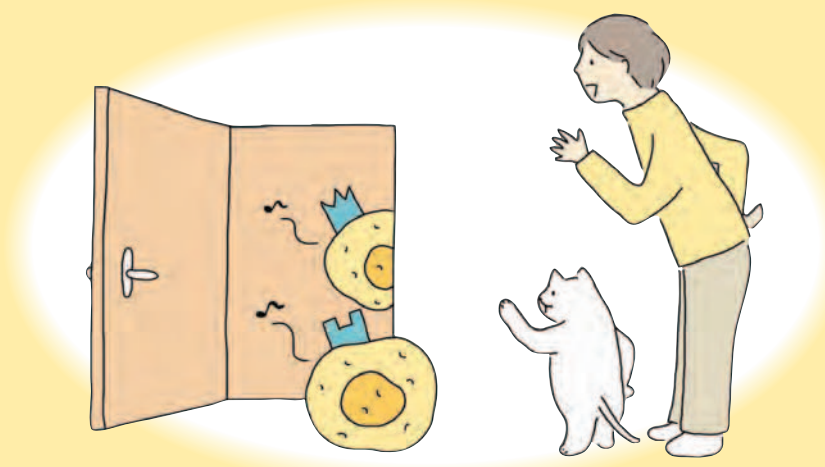
## How it Protects Your Body





# Your Amazing Immune System

## How it Protects Your Body



Compiled by the Japanese Society for Immunology (JSI)  
Illustrated by Tomoko Ishikawa



European Federation of  
Immunological Societies



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## Foreword

This book is designed to help you better understand how the immune system works. It has been compiled by the Japanese Society for Immunology, a group that researches immunity.

The immune system, or the way the body protects itself from germs such as bacteria, is amazingly well put together. The more you get to know about it, the more you will understand what a truly fascinating system it is. It is made up from a myriad of molecules and cells that work together in close co-ordination to protect our bodies from foreign invaders. Yet it is just this complexity that makes some people think the immune system must be too difficult to understand. We hope that by reading this book you will start to think, “Ah, so this is what immunity is all about?” or “So, this is how it works!” and it will make you want to learn more about the subject.

Ms Tomoko Ishikawa kindly illustrated the book. The entire book was created through the dedication and enthusiasm of Dr Yousuke Takahama working together with members of the Education Promotion Committee and the Committee on Public Affairs of the Japanese Society for Immunology. Their efforts were edited with great care by Ms Shinobu Yamashita of the Yodosha editing department. My thanks to all of them.

Finally, I ask that if you find parts of the book are difficult to understand, you will let us know. We would like to use your comments to make this book even better. It is, after all, a book that has been created for all of you so I am looking forward to hearing what you think.

April 2008

*Japanese Society for Immunology*  
*Masayuki Miyasaka*



## Foreword to the English Translation

# Your Amazing Immune System: How it Protects your Body

Every day your immune system is busy protecting you from the thousands of germs around you that can make you sick. Your immune system does its job so efficiently that you don't even notice that it is at work. Vaccinations activate your immune system, enabling it to defend the body against germs that are yet to be encountered. Usually, vaccinations cause no more discomfort than a quick, easily-forgotten prick to your arm or thigh, but they save you from becoming seriously ill or dying from that disease.

Today, many people suffer from allergies such as asthma or hay fever or autoimmune diseases such as rheumatoid arthritis. Of course, those of you who suffer from such ailments are wary having suffered from an overly aggressive response of the immune system. However, don't forget that these complaints are the result of a misdirected immune response which, when all is well, actually prevents you from falling prey to all the infectious agents around you. A look at what can happen if the immune system fails, will help you recognize the importance of this response to your well being. If you grow up without a functioning immune system, you will not only lack any means whatsoever to protect yourself from the germs that cause disease, but your body will also not be able to detect or eliminate or any of its own cells that misbehave. Unchecked, such cells can eventually develop into cancer.

Scientists believe that a better understanding of how the immune system operates will enable us to develop new vaccines. Many are at work seeking a vaccine against infectious diseases such as AIDS, which threatens millions of people, mostly in the developing world. Yet others are trying to understand what goes wrong with the immune response in the case of various autoimmune diseases and allergies, and also why the immune system sometimes fails to combat cancer. With this understanding, scientists hope one day to develop effective vaccines against autoimmune diseases, allergic diseases and cancer, and more effective ones against infectious diseases.

This book, originally entitled "Karada wo Mamoru Meneki no Fushigi", was conceived and created by Japanese researchers working in the field of immunology. It was published by the Japanese Society for Immunology as part of their out-

reach efforts for the **Day of Immunology** 2008, with the aim of making immunology accessible to the public. Recognising a good idea and a good book, researchers working in immunology in Europe thought such a publication would also be of interest to Europeans. Hence, we translated the book into English to raise awareness of the importance of immunology for health and well-being here. The European Federation of Immunological Societies (EFIS), the umbrella organisation of European immunologists, provided financial support for the translation, printing and electronic version of this book. Anjali Patel kindly translated the book into English and helped in its editing. Additional editing support was provided by Mary Louise Grossman. My thanks go to them both for their dedication and hard work in helping us realise this project. In the present edition, a number of Japanese terms and expressions have been simplified for the benefit of a broader readership.

I sincerely hope that you find this book interesting and that it helps you to understand your immune system better. I look forward to hearing how you liked – or didn't like – the book. Your suggestions are valuable because the book was created above all, for you.

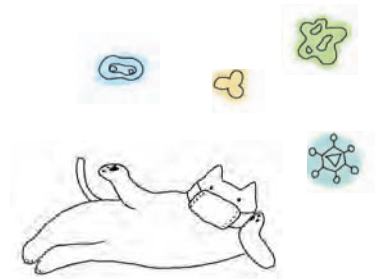
Translations in other languages will follow!

June 2009

*European Federation of Immunological Societies*  
*Stefan H.E. Kaufmann*



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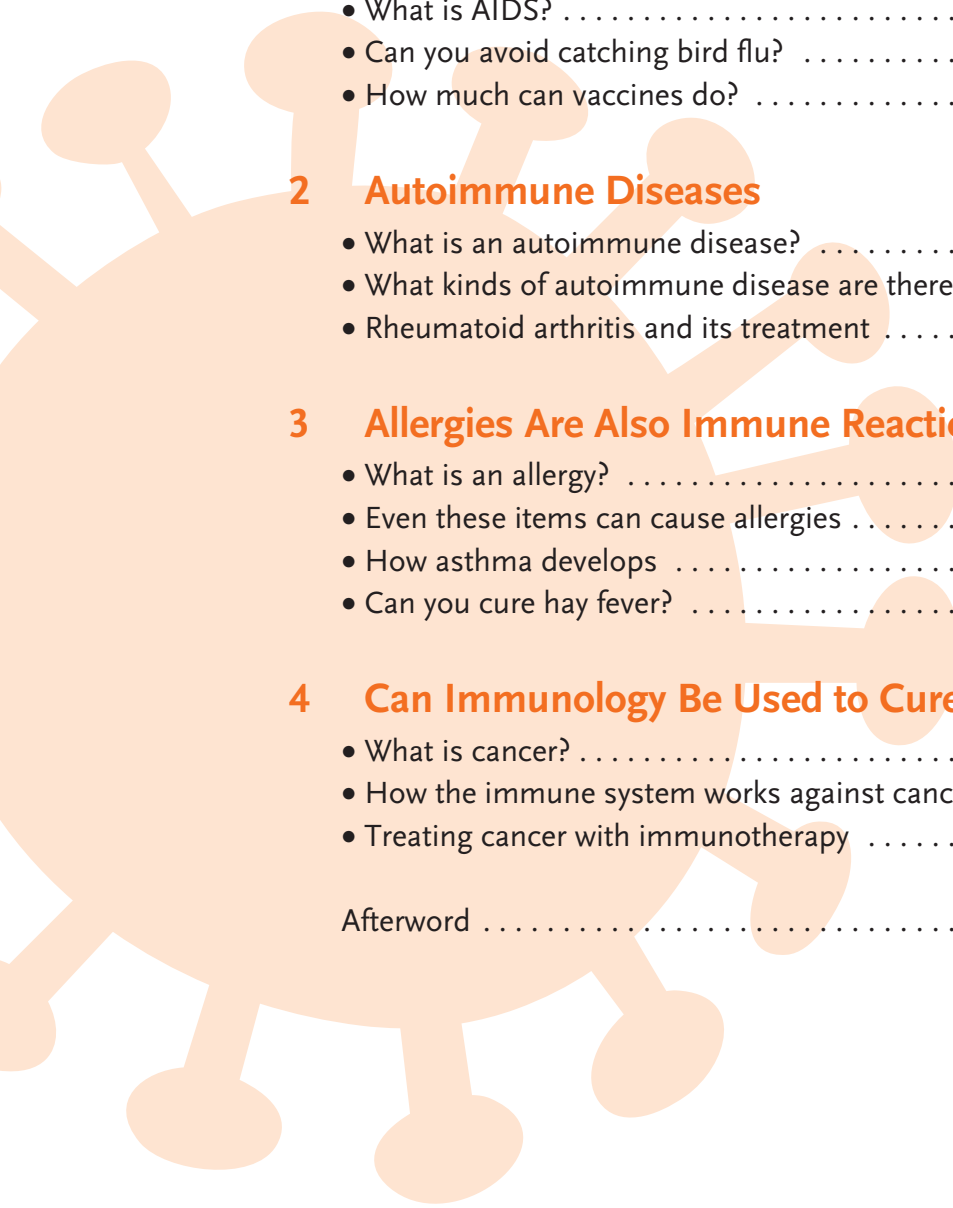
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**Part I**



**All About Immunology**

## 1. The Basics of the Immune System

### What does the immune system do?

Do you know what the immune system is? Do you know where you can find it in the body? And do you know what it does?

When you are feeling well, you don't give much thought to your immune system or what it does. But what do you think would happen to you if you didn't have one?

Well let's see. Roughly one in every hundred thousand babies is born without any immunity whatsoever. This condition is known by the rather long and difficult term of **Severe Combined Immunodeficiency** or **SCID**. Babies born with this condition don't have any of the protection that healthy babies do against pathogens.

By pathogens we mean **germs** like the bacteria, viruses and fungi that can make you sick. This is why babies who have SCID end up getting very sick from infectious diseases.



Severe Combined  
Immunodeficiency

100,000

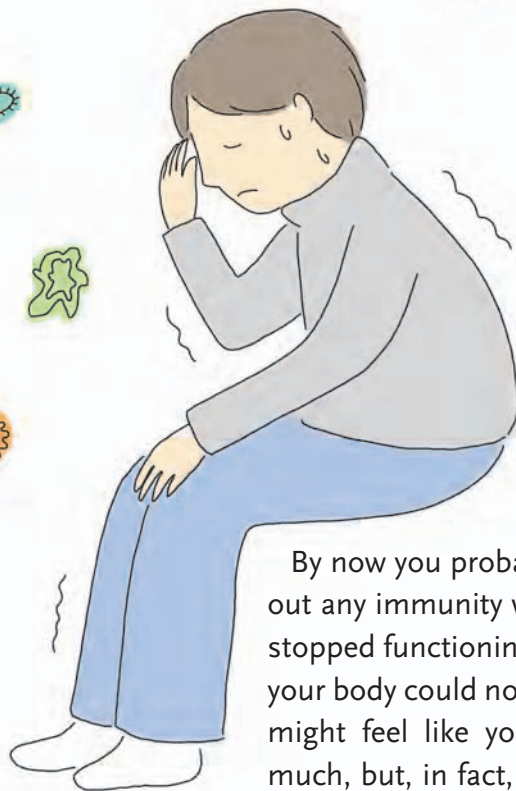
AIDS

HIV

You've no doubt heard about a disease called AIDS. AIDS causes the body to lose its immunity and leaves it unable to protect itself from all sorts of germs.

AIDS does this by knocking out the immune system's ability to function.

There are all sorts of germs floating about in the air.



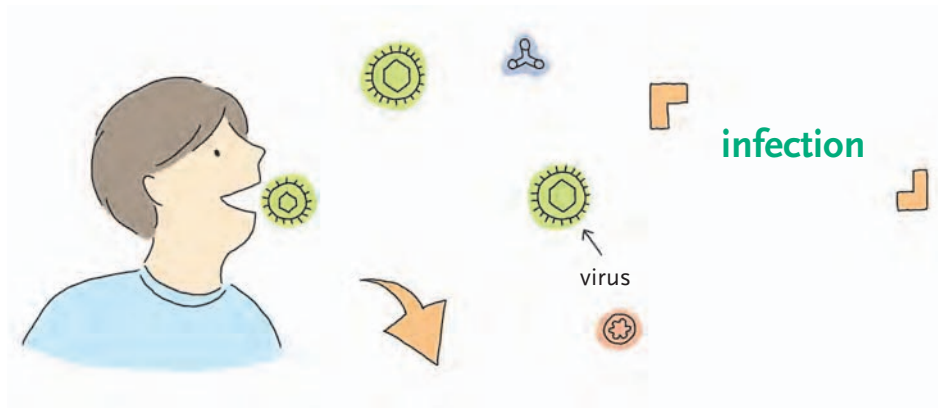
By now you probably realise that if you were born without any immunity whatsoever or if your immune system stopped functioning, you'd be at the mercy of germs that your body could normally protect you from. So you see, it might feel like your immune system doesn't do very much, but, in fact, it is there protecting your body night and day.



## Ever wondered why you don't get the same disease twice?

When germs get into your body, you have what is called an **infection**. Usually, when you get an infection, you'll get a fever and an upset stomach (diarrhoea). However, after you rest for awhile, in most cases, you should get better again.

You have your immune system to thank for this recovery. But this isn't all that your immune system does for you.

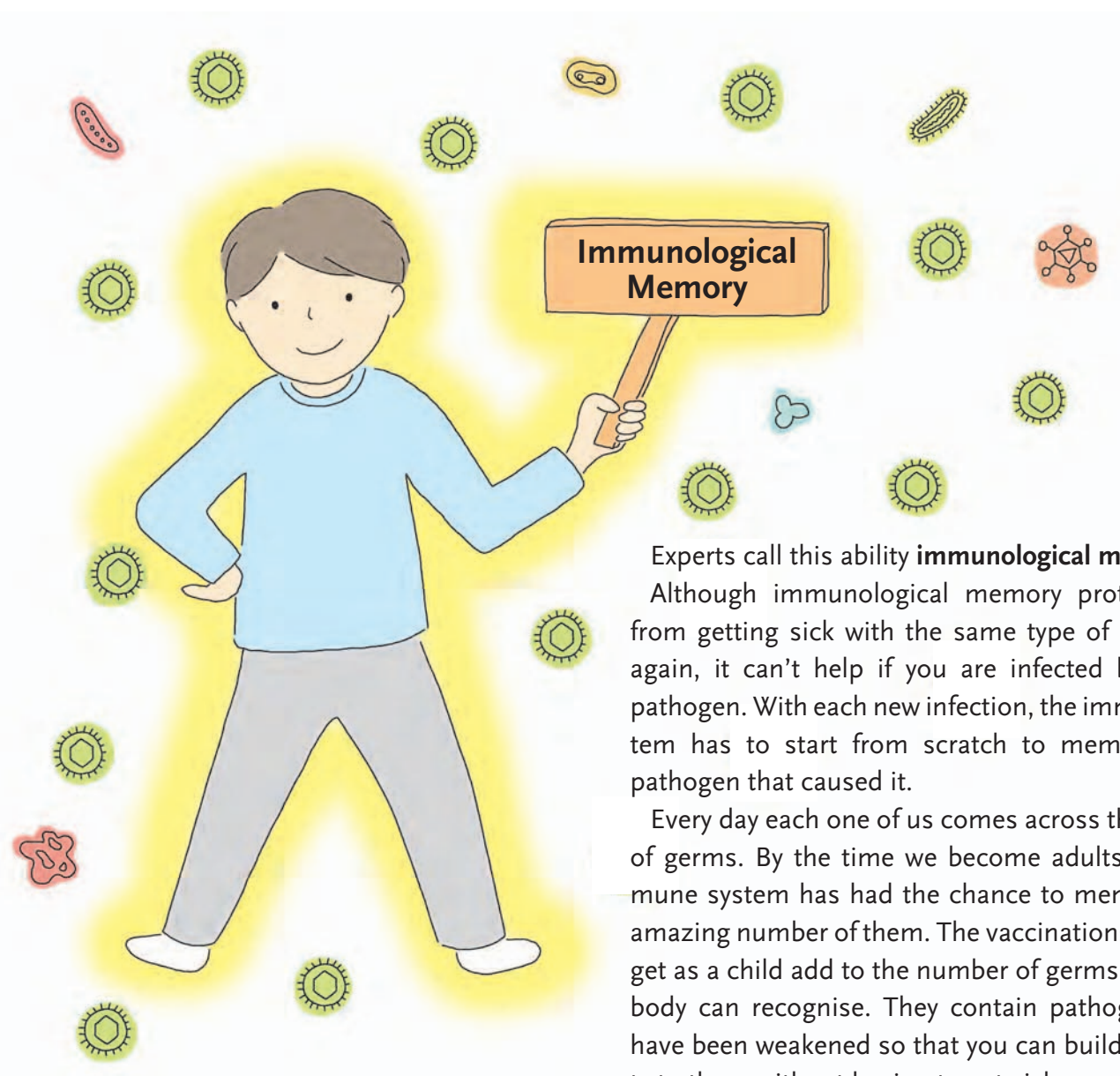


I'm sure you've heard people say things like, "Well, I got the mumps once so I should be okay", or "I've already had the flu this year so I won't catch it again". What people mean when they say this is that if a particular pathogen makes you ill once and you recover, then you won't fall ill with it again.

This ability is another important function of your immune system.

Your immune system remembers all the pathogens that have infected you so that if you were to catch one of these again, you won't fall ill.



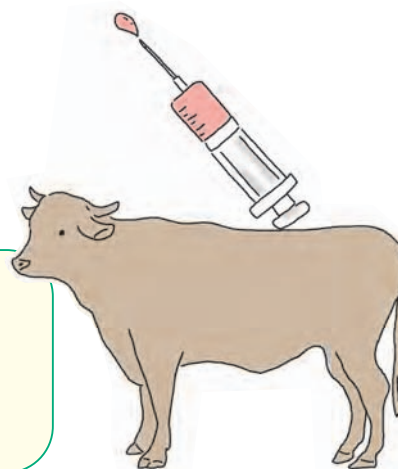


Experts call this ability **immunological memory**.

Although immunological memory protects you from getting sick with the same type of pathogen again, it can't help if you are infected by a new pathogen. With each new infection, the immune system has to start from scratch to memorise the pathogen that caused it.

Every day each one of us comes across thousands of germs. By the time we become adults, our immune system has had the chance to memorise an amazing number of them. The vaccinations that you get as a child add to the number of germs that your body can recognise. They contain pathogens that have been weakened so that you can build immunity to them without having to get sick.

The word vaccine comes from the Latin for cow or *Vacca*. But what have vaccines to do with cows, you ask? Well, Edward Jenner discovered vaccination when he showed that injecting people with the cowpox virus would protect them from a deadly disease called smallpox.



## Where in the body is the immune system?



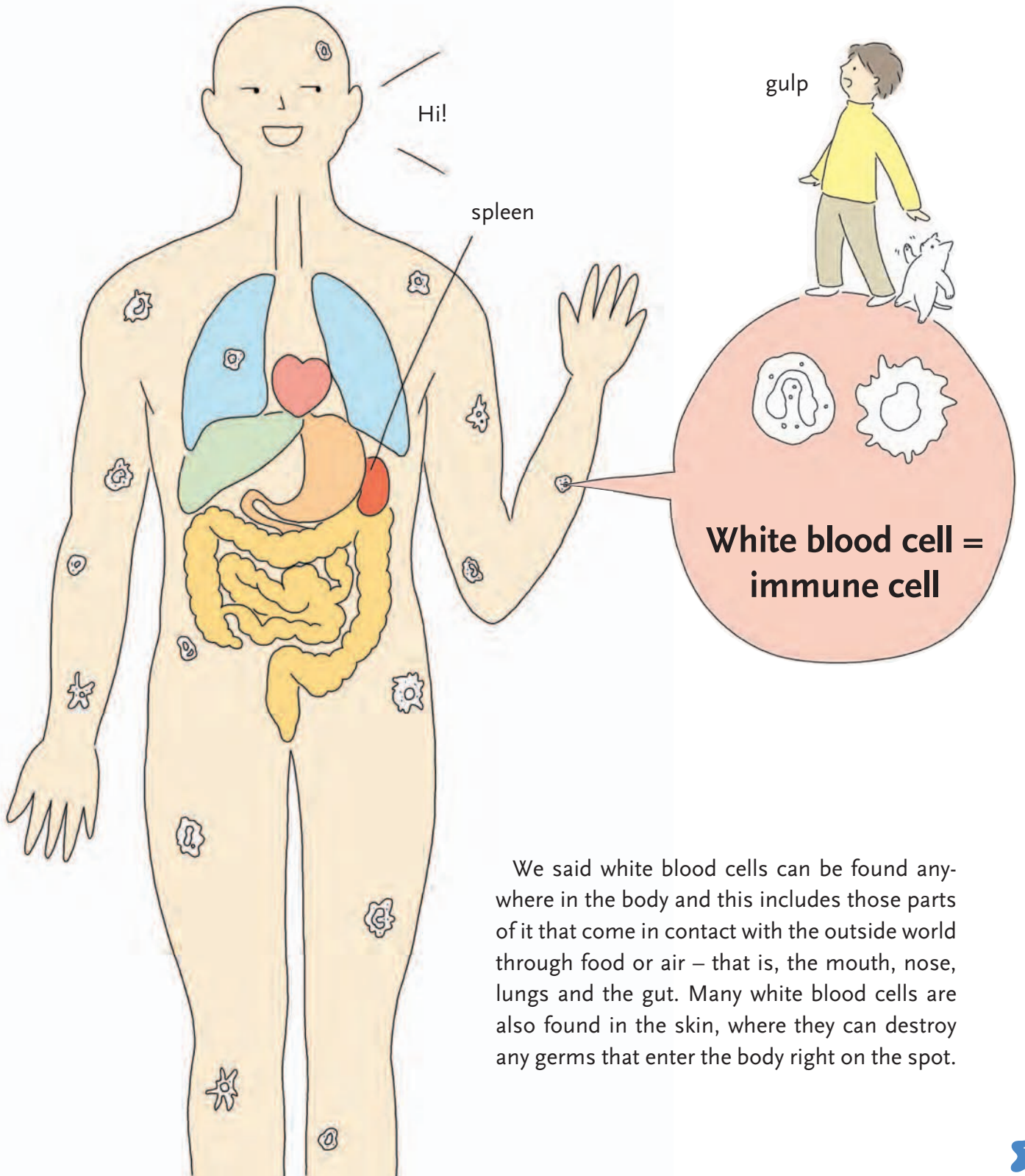
Our bodies are made up of extremely small units called cells, each so small that it can't be seen with the naked eye. Throughout the body there are an amazing variety of cells, each kind performing its own separate function. The immune system too is made up of specialised cells. These cells are called immune cells.

Our blood is red because it contains a great many red blood cells called erythrocytes (eri-throw-sites). However, it also contains white blood cells or leukocytes (loo-co-sites). And it is these white blood cells that work as part of the immune system.



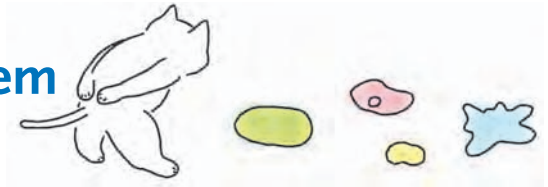
Because blood circulates throughout our entire body, white blood cells are present everywhere too. So, to answer the question, you can find the immune system anywhere and everywhere in your body. However, there are places in the body where white blood cells are particularly concentrated. These places are the lymph nodes and the spleen, and they are important because they are the sites from which the immune system launches when you have an infection. We will tell you more about what the spleen and the lymph nodes do later.





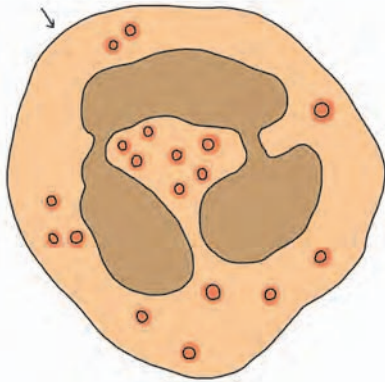
We said white blood cells can be found anywhere in the body and this includes those parts of it that come in contact with the outside world through food or air – that is, the mouth, nose, lungs and the gut. Many white blood cells are also found in the skin, where they can destroy any germs that enter the body right on the spot.

# The many cells of the immune system



So now let's look at some of the different cells that make up the immune system (remember these are white blood cells).

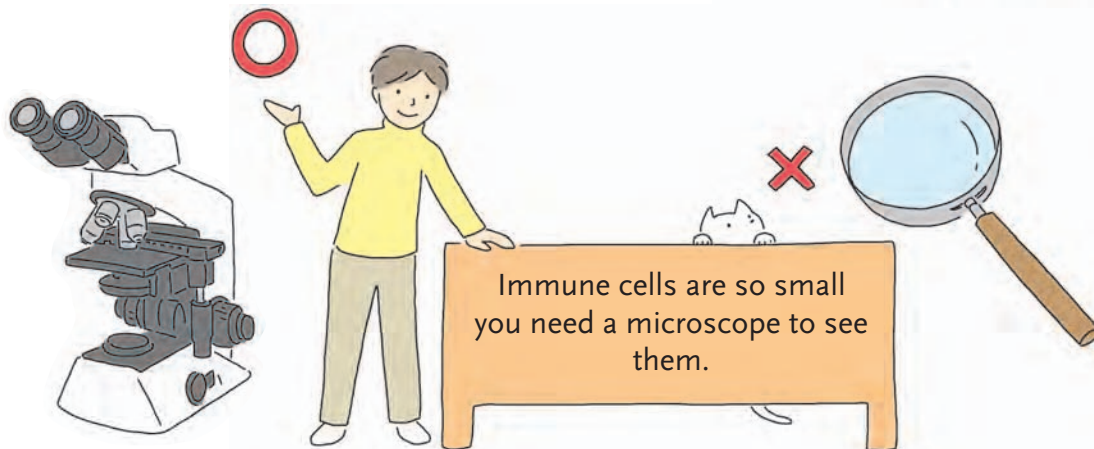
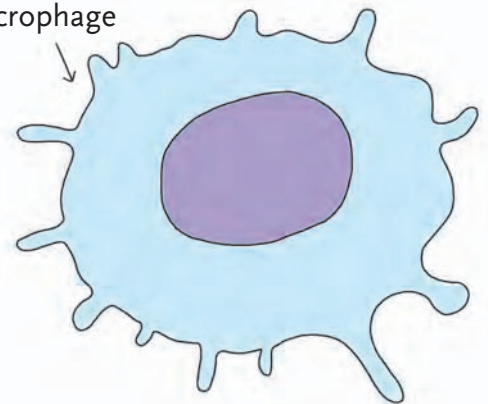
neutrophil



If you get hurt and your skin breaks open, germs can get into your body through the cut. When this happens, neutrophils, a group of white blood cells that are always present in the blood, migrate to the site to destroy the germs.

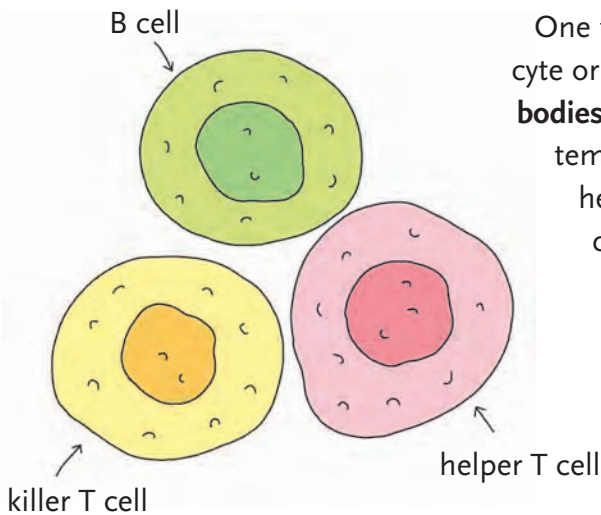
Another type of white blood cell is the macrophage, which destroys pathogens directly by eating them. You'll find macrophages in the lungs, liver, skin and gut.

macrophage

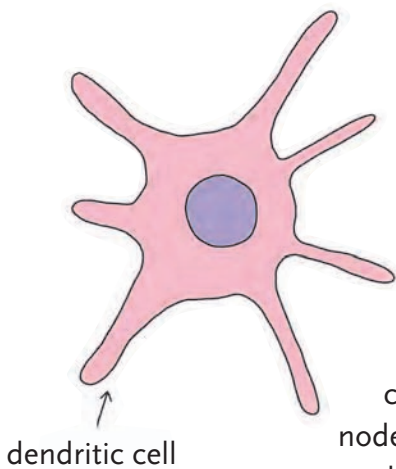


Immune cells are so small you need a microscope to see them.

Lymphocytes are another type of white blood cell, and they are the smallest members of the family. They can measure less than a 100<sup>th</sup> of a millimetre or 10 microns. If you were to look at them under a microscope, they would all look the same. But if you were to investigate a little further, you'd find that there are different types, each with its own specialised function.



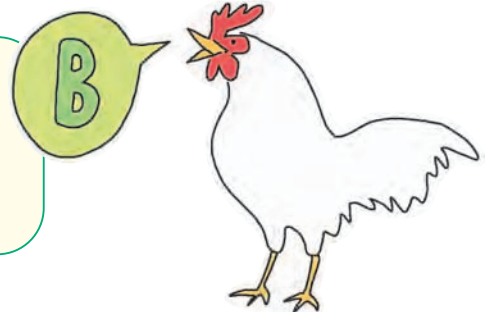
One type of lymphocyte you'd discover is the B lymphocyte or B cell. B cells produce special weapons called **antibodies** which stick to a pathogen and help the immune system to destroy it. Other lymphocytes are known as helper T cells and killer T cells. Helper T cells help B cells to produce antibodies and also boost the ability of macrophages to attack pathogens. Killer T cells, as their name suggests, are hit men of the white blood cell family. They bump off any cells that have been infected by a virus.



One more important type of white blood cell is the dendritic cell. This cell gets its name from all the arms it has that reach out of it like the branches of a tree (Dendron is Greek for "tree"). When germs enter the body, it is the dendritic cells that help helper T cells understand what kind of pathogen it is, and how best to destroy it.

So far we have learnt that different types white blood cells are concentrated in different areas of the body (spleen and lymph nodes). And we also know that while they have distinct roles, they all work together to protect the body.

In humans, the B in B cell stands for bone marrow, where the cells are produced. It also stands for the bursa of Fabricius, where the cells are made in birds. The T in T cells stands for thymus, the organ where these cells develop.



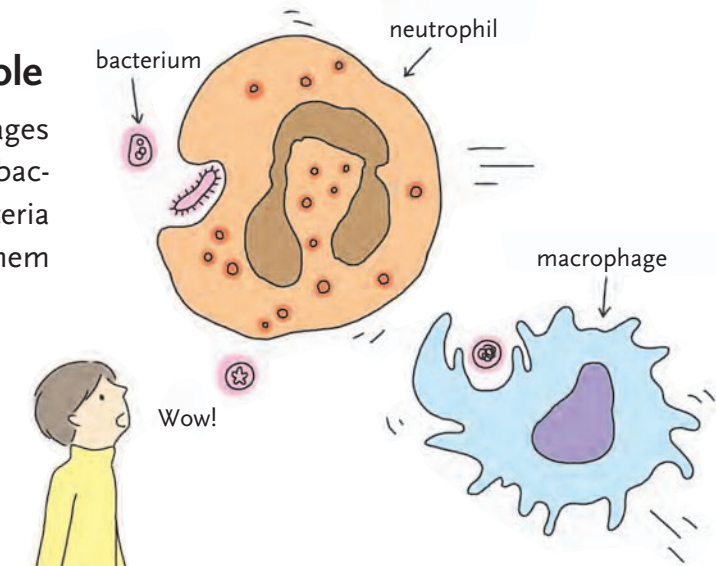
# Three ways of destroying a pathogen



Now let's find out a little more about how white blood cells rid the body of pathogens.

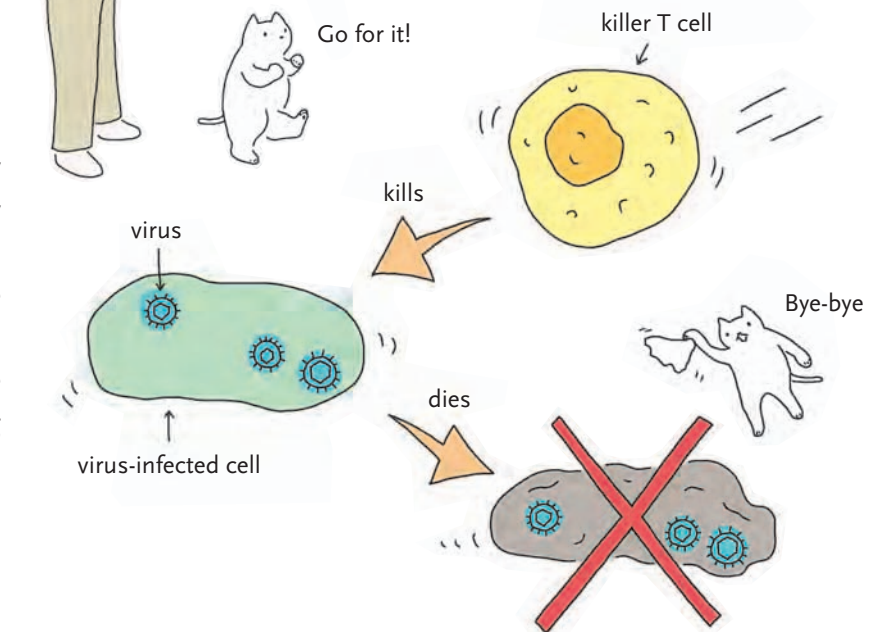
## 1 Swallowing them whole

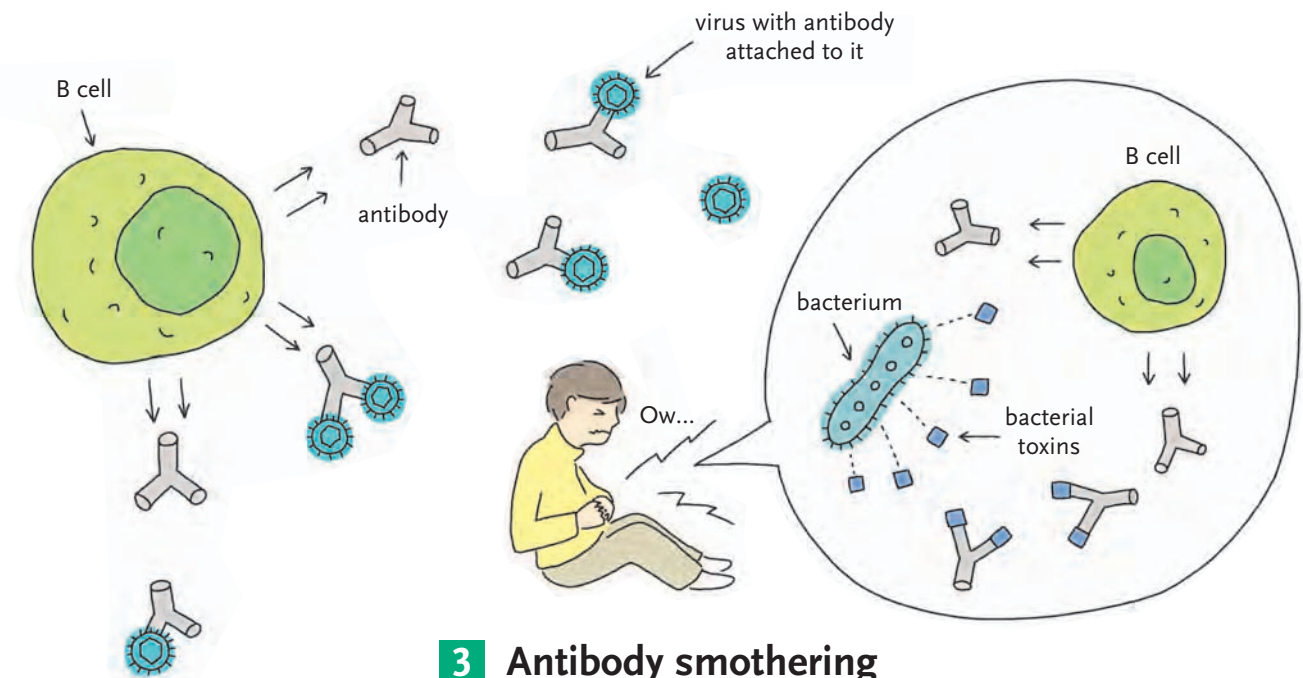
Neutrophils and macrophages swallow pathogens, in particular bacteria, whole. They also kill the bacteria they swallowed by breaking them down into pieces.



## 2 Killing infected cells

Cells that have been infected by a virus are a danger to the body and have to be removed quickly. This is where killer T cells come into play. Killer T cells stop virus that is rapidly multiplying in the cells from spreading by finding the infected cells and killing them.

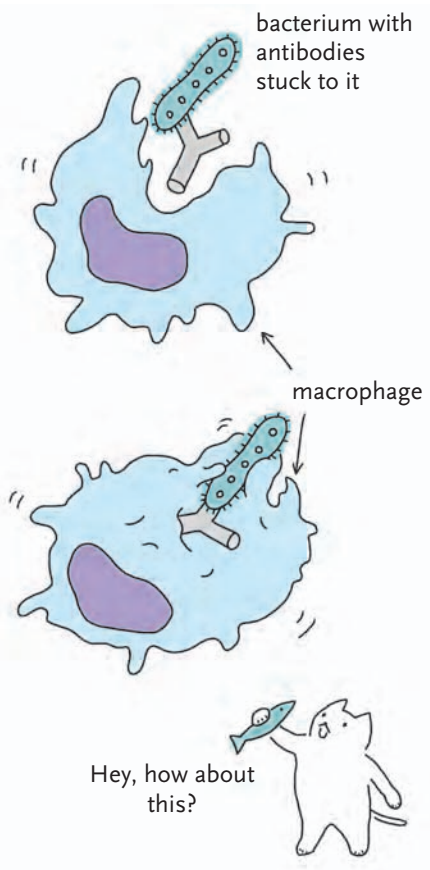




### 3 Antibody smothering

Once inside the body, bacteria not only multiply, but also produce chemicals that are harmful to the body called **bacterial toxins**. To stop bacterial toxins from being able to function, B cells smother them with weapons called antibodies. Antibodies can also attach themselves to viruses to prevent them from penetrating cells. And viruses that can't enter cells, can't multiply.

Antibodies have another important job. They attach themselves to bacteria to flag them as a meal for macrophages. We know that macrophages swallow bacteria anyway, but they can do this job much better when the bacteria are covered in antibodies. Antibodies travel around the whole body via the blood. That means that whatever part of the body is infected, antibodies can move to it quickly to confront the pathogen.



## 2. How the Immune System Works

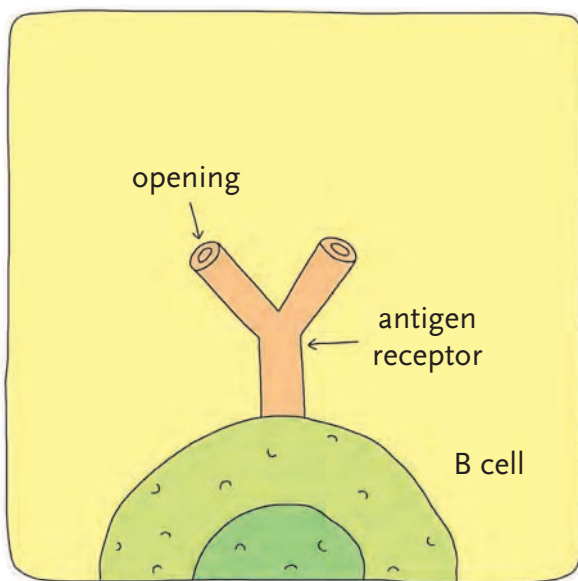
### How the immune system distinguishes among pathogens

The immune system can identify what pathogen has infected your body and decide on the best means to deal with it. Earlier, we learned that because of immune memory, people who'd had mumps once couldn't get sick with it again. But this would not stop them from getting sick from something else, like measles. The cells of the immune system can tell the difference between mumps virus and measles virus because the cells memorise them as two entirely different things.

The immune system's ability to do this is known by the rather difficult term of **antigen specificity**.

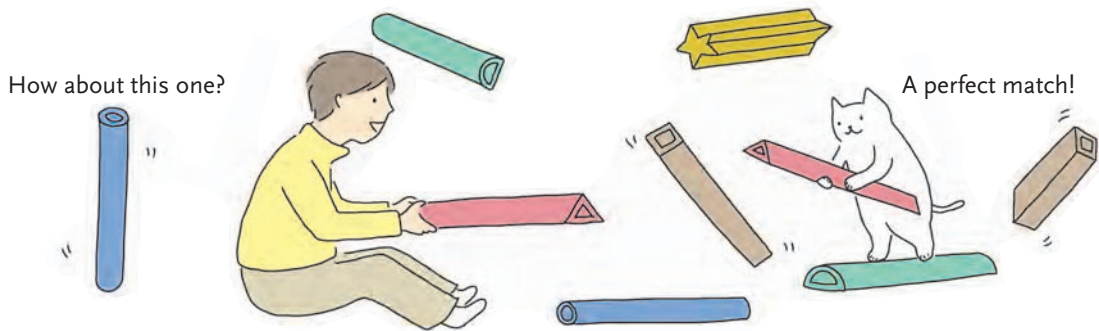
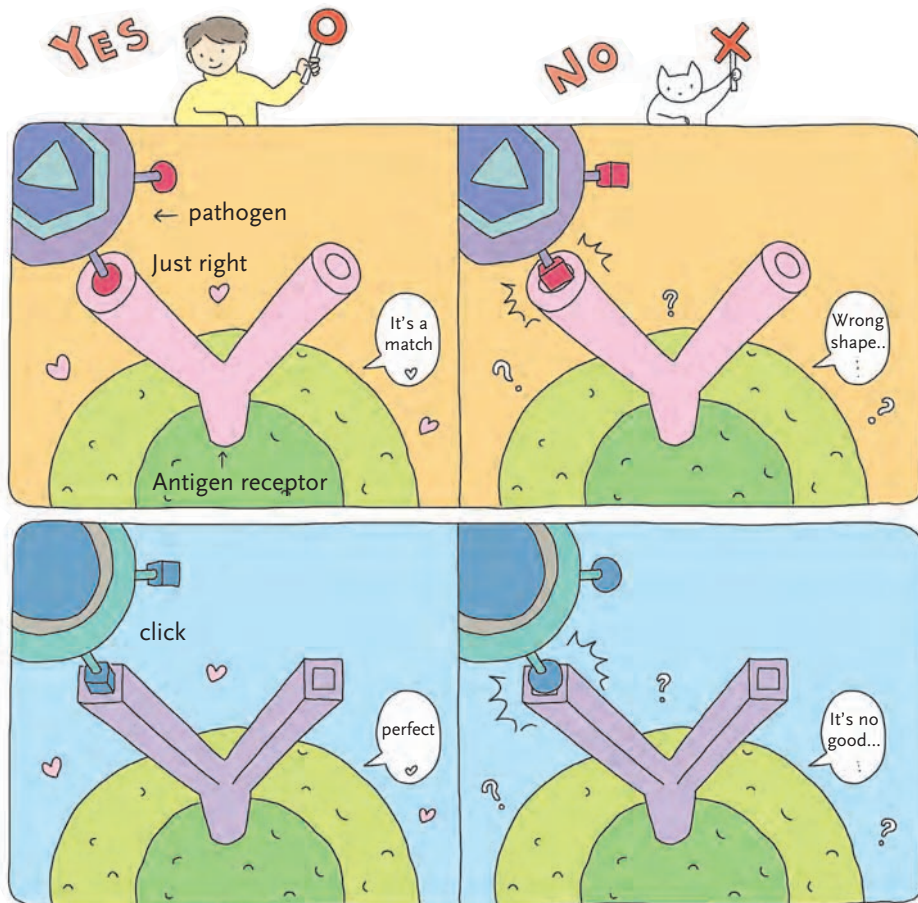


So how exactly does the immune system tell pathogens apart?



The job of distinguishing among different pathogens belongs to the lymphocytes. Both T and B cells have special tools for telling pathogens apart that cover the entire surface of the cell. These tools are called **antigen receptors** and they look like tiny rods with small holes at the end.

Some of the holes are shaped to fit the measles virus exactly, while others are shaped to match the mumps virus or some other pathogen only. The immune system will know if a pathogen has entered the body before, and be able to identify it, based on whether any of its cells possess antigen receptors that match.



Both T cells and B cells have antigen receptors that recognise different pathogens, but their shapes and functions are a little different. B cell antigen receptors look like the letter Y and have a hole at the end of each arm.

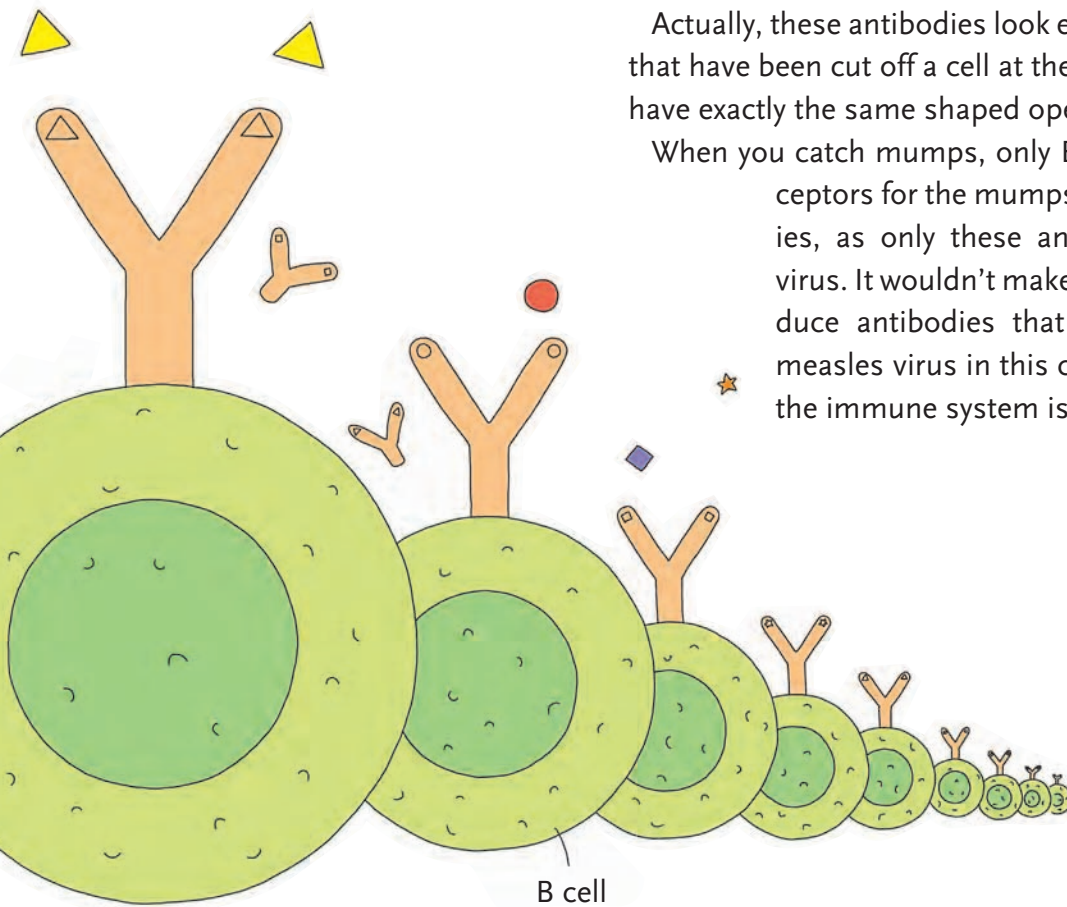


T cells receptors, however, look like rods and have just one hole at the end.

Earlier we told you that B cells get rid of pathogens by producing antibodies that smother them.

Actually, these antibodies look exactly like antigen receptors that have been cut off a cell at the base of the stem. And they have exactly the same shaped openings as B cell receptors.

When you catch mumps, only B cells that have antigen receptors for the mumps virus will produce antibodies, as only these antibodies can attach to the virus. It wouldn't make any sense for B cells to produce antibodies that could attach to, say, the measles virus in this case. So you see, in this way the immune system is very clever.





Unlike antibodies, T cell antigen receptors can't attach themselves to pathogens without help.

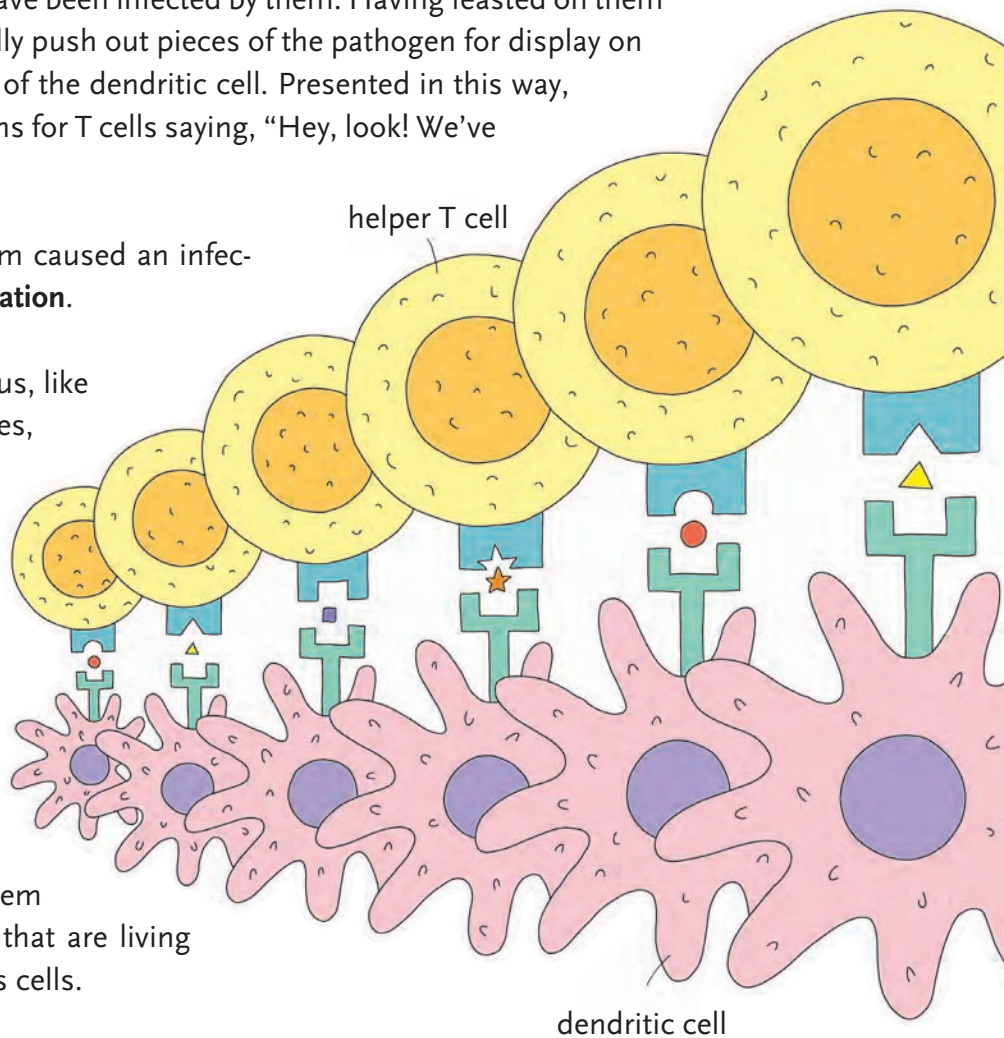
Here, the dendritic cells that we told you about earlier play an important role. Dendritic cells clear the body of pathogens, and they do this in two ways. They swallow pathogens directly or they swallow cells that have been infected by them. Having feasted on them in this way, dendritic cells carefully push out pieces of the pathogen for display on platforms that cover the surface of the dendritic cell. Presented in this way, the pieces of pathogen act as signs for T cells saying, "Hey, look! We've been infected with *this* germ."

This act of signalling what germ caused an infection is known as **antigen presentation**.

And because pieces of each virus, like those for the mumps and measles, are different in shape, a T cell can tell exactly which virus has infected the body.

Once dendritic cells have presented an antigen, T cells can identify it and go ahead and do their work.

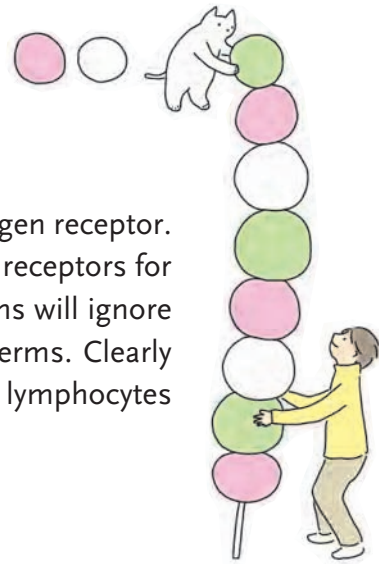
They alert the other cells of the immune system telling them what pathogen they have to deal with. The immune system can now begin to attack germs that are living and multiplying inside the body's cells.



The platform described here is called the Major Histocompatibility Complex, or MHC. It got its name because it determines how well a tissue or organ transplant is accepted by the body. *Histo* is the Latin word for tissue and *compatible* means to match. Improving our understanding of how the MHC works is vital to making progress with transplant medicine or stem cell treatments for degenerative diseases.

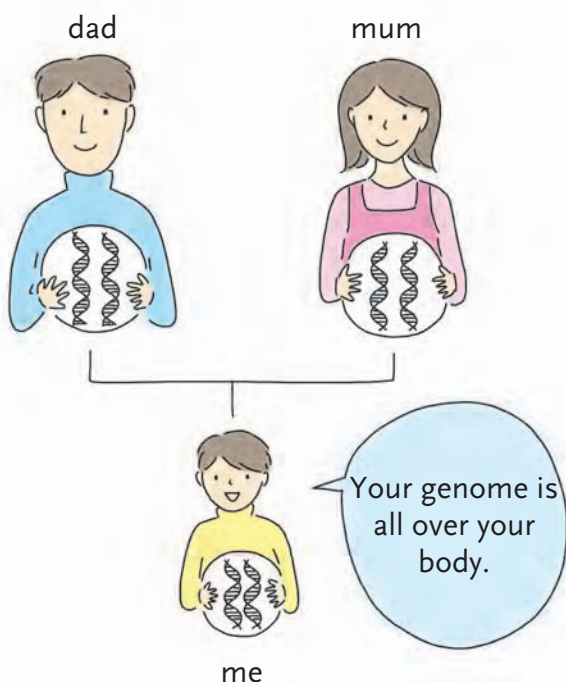
## How the immune system can recognise different germs

We've learned that each lymphocyte has only one type of antigen receptor. So when you catch the mumps, only lymphocytes with antigen receptors for the mumps virus will detect it. Cells that detect other pathogens will ignore it. But all around us are millions upon millions of different germs. Clearly then, the body needs to have an enormous number of different lymphocytes to protect it.



Luckily, it does. If you were to look up how many antigen receptors humans have, you would find that there are over 10 BILLION different kinds! That is 10,000,000,000. With so many different receptors, there is bound to be one lymphocyte in the body that can recognise whatever pathogen enters it. And with all of these lymphocytes working together, the immune system can protect the body from a huge variety of pathogens.

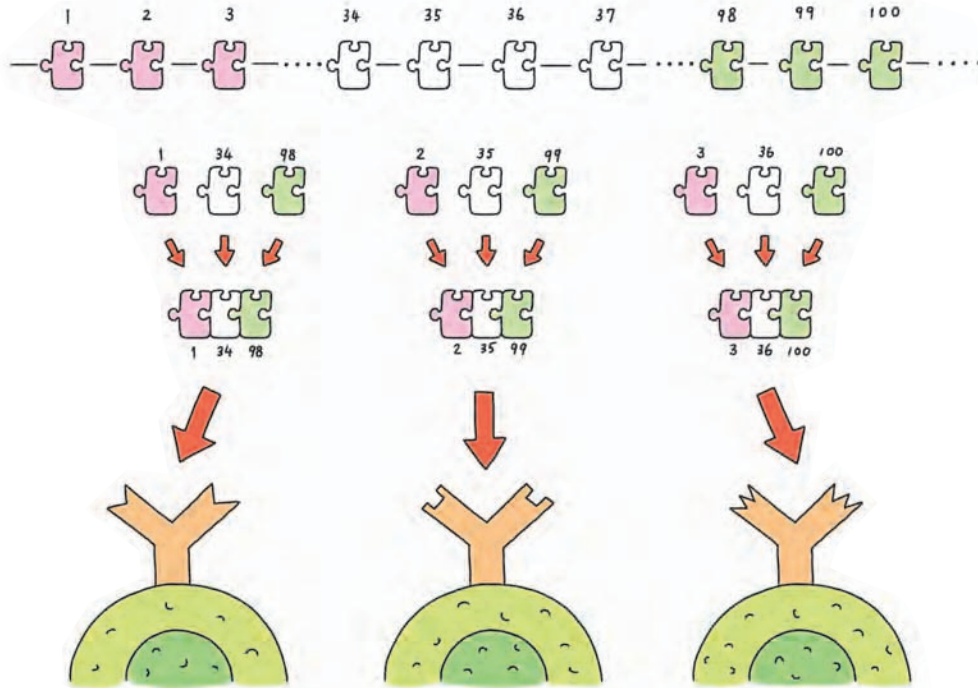
### Genes



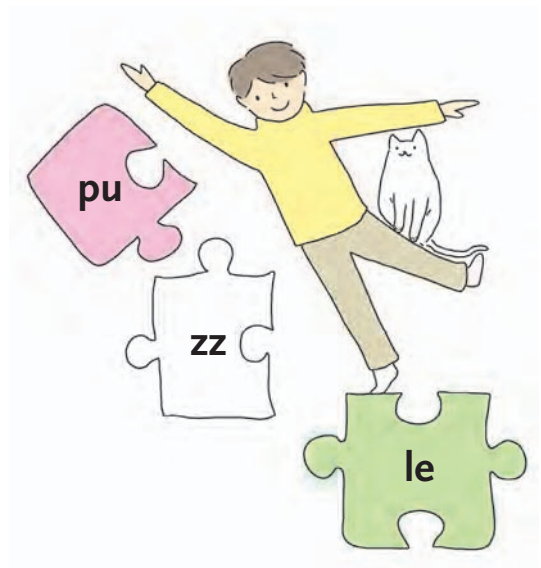
So how does your body make so many different kinds of antigen receptors?

Our parents pass between 30,000 and 40,000 genes on to us, and all of these genes together are known as our **genome**. Within our genome there are genes for making the different parts of our body like muscles, skin, bones and organs. They are also genes for making antigen receptors.

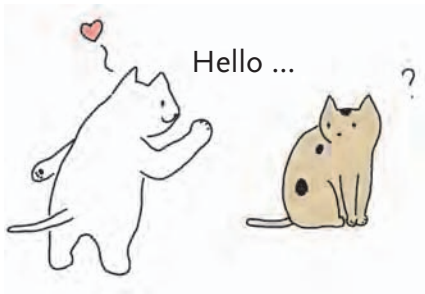
Usually we say that one gene makes one part of the body, but this is not the case with antigen receptors. The genes that make them up are all separated into segments like the pieces of a puzzle. And it's only inside lymphocytes that these pieces of genes can be combined in different ways to produce any number of blueprints for antigen receptors.



From the hundreds of puzzle pieces available, a lymphocyte selects two or three to combine. A lymphocyte can put these pieces together in many different ways, and because there tends to be inaccuracies when the pieces are linked, an extraordinary number of different antigen receptors can be produced.



## How the immune system remembers pathogens it's met before

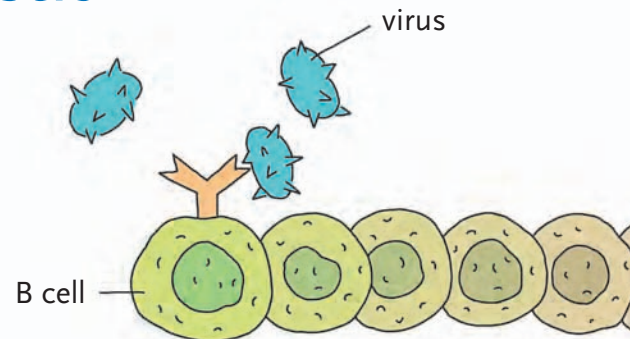


Lymphocytes can remember pathogens that they've met before.

The first time a B cell meets a pathogen, it takes over a week for the cell to produce antibodies against it. During this time the B cell changes itself into a cell that can produce vast amounts of antibody. However, not all B cells become **antibody-producing cells**. Some B cells have the job of remembering the new pathogen. These B cells are known as **memory B cells**.

When a memory B cell again meets the pathogen that it has the job of remembering, it sets to work immediately and produces an enormous amount of antibodies in just a few days.

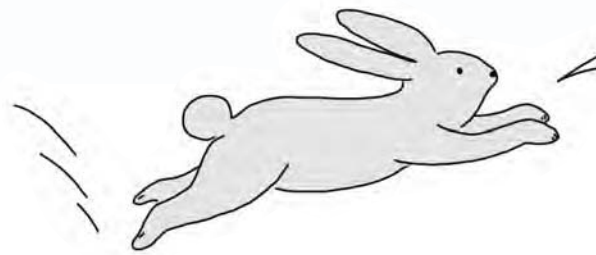
But memory cells aren't just quicker at making antibodies. They also make better quality antibodies than B cells that have encountered a pathogen for the first time. These 'super-antibodies' can attach themselves to bacterial toxins more firmly, and they're also better at flagging bacteria for macrophages to find and eat.

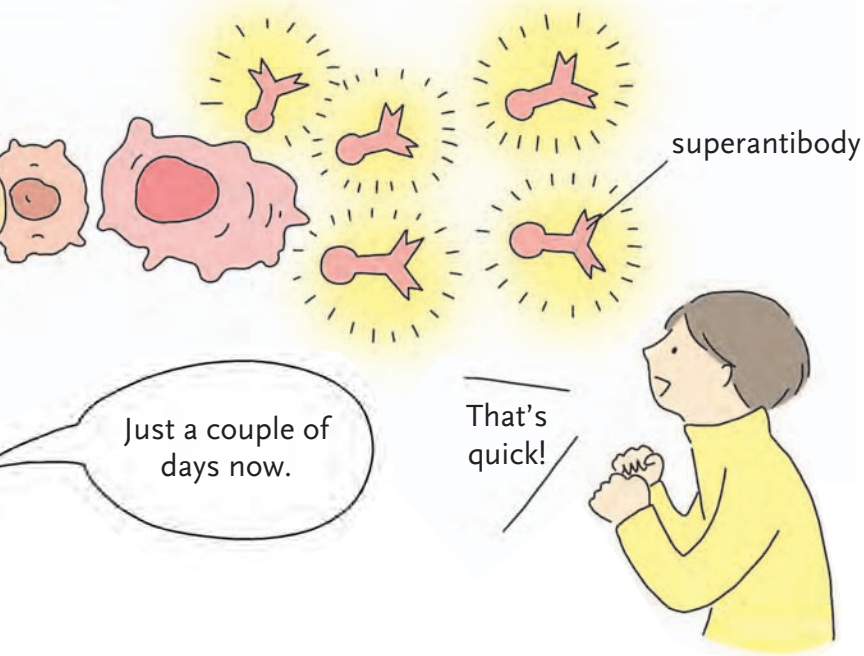
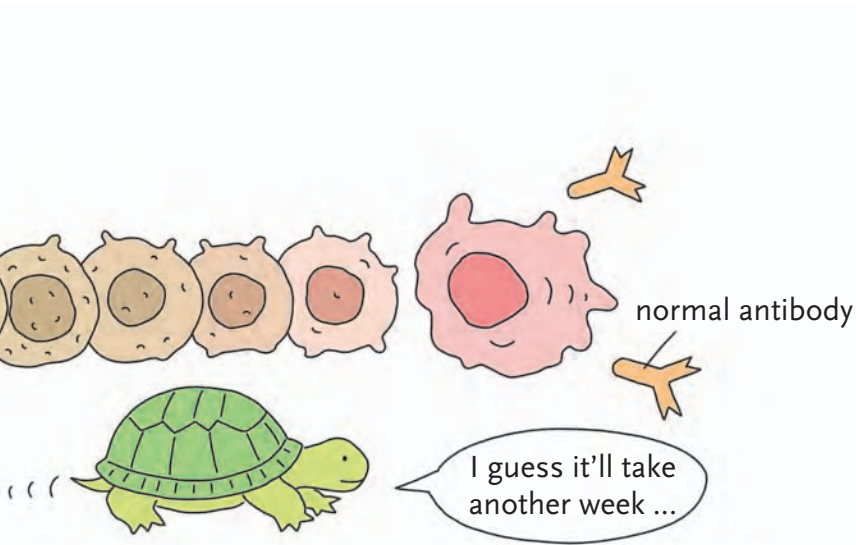


### 1<sup>st</sup> time

### 2<sup>nd</sup> time

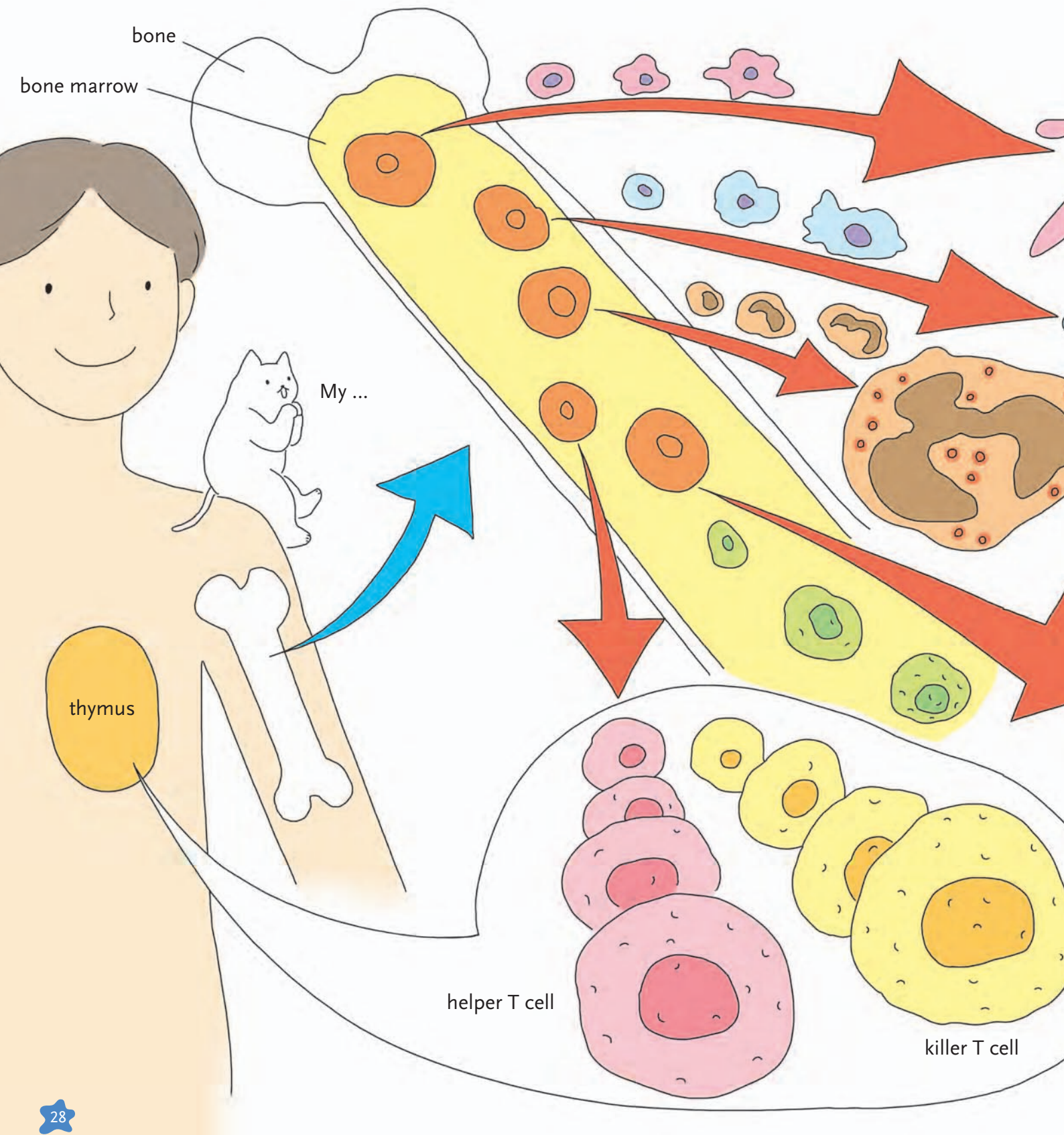
memory B cell





T cells also make memory cells. Helper T cells and killer T cells normally just travel around the body patrolling it. When they do come across a pathogen, the T cells with antigen receptors that match the antigen begin to divide rapidly and get ready for work. It takes about a week for all of this to happen. During that time, some of the helper T cells change into memory T cells. And if they meet the same pathogen again, they are primed to go to work immediately.

In this way people who have recovered from the mumps have a large number of memory T and B cells that can recognise just that virus. Similarly, people who've recovered from any other infection will have large numbers of just those memory T and B cells that can identify the specific pathogens involved.



bone

bone marrow

My ...

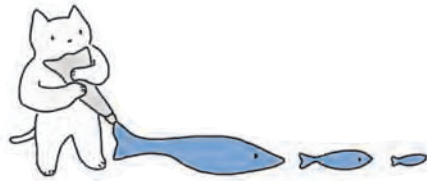
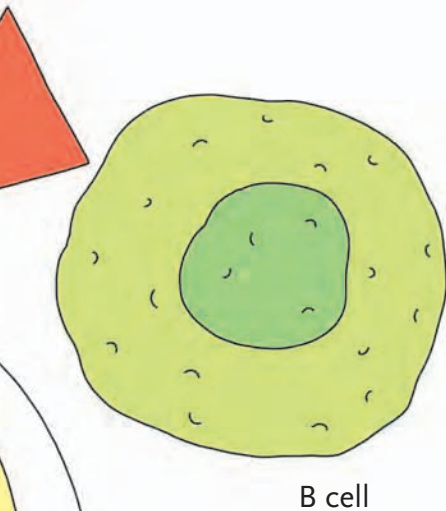
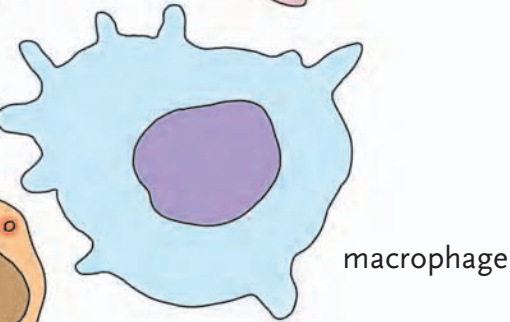
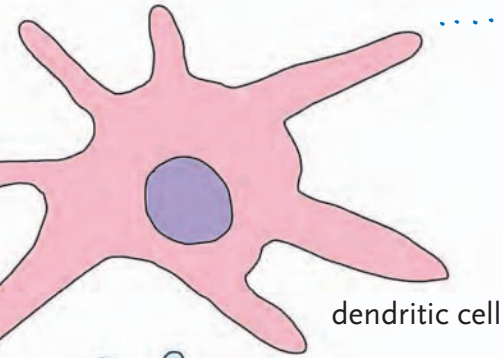
thymus

helper T cell

killer T cell

### 3. Where the Cells of the Immune System are Made and Where They Work

#### Where are immune cells made?



All immune cells are white blood cells, and they are made in the bones. Bones are very hard, but they have a soft, spongy core called the **bone marrow**. Blood cells are made from special cells in the bone marrow called **haematopoietic (he-ma-toe-po-etic) or blood stem cells**. Just one stem cell can make any number or any type of immune cell.

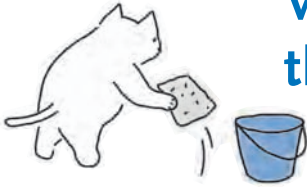
Like red blood cells and platelets, most immune cells like neutrophils, B cells and macrophages are made in the bone marrow. Only T cells are different. They are made in a special organ near the heart called the **thymus**. Blood stem cells that are destined to be T cells move to this organ to mature.

Newly made immune cells stream out into the body from the marrow and thymus via blood vessels. The cells then migrate to the lymph nodes and spleen – the sites from which the immune response is launched – to begin their work.

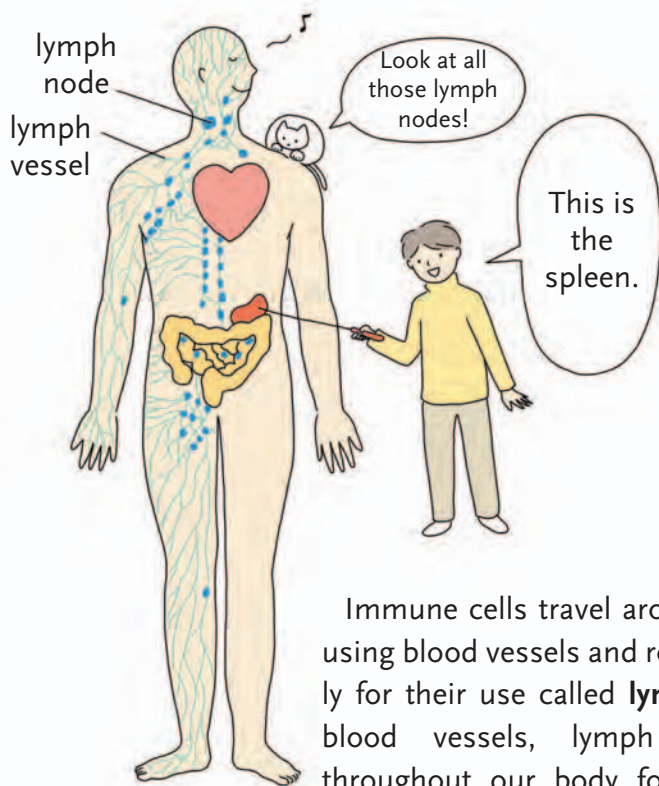
How did the thymus get its name? Some people think it's because the thymus of a cow, which is sometimes used in cooking, smells just like the herb thyme.



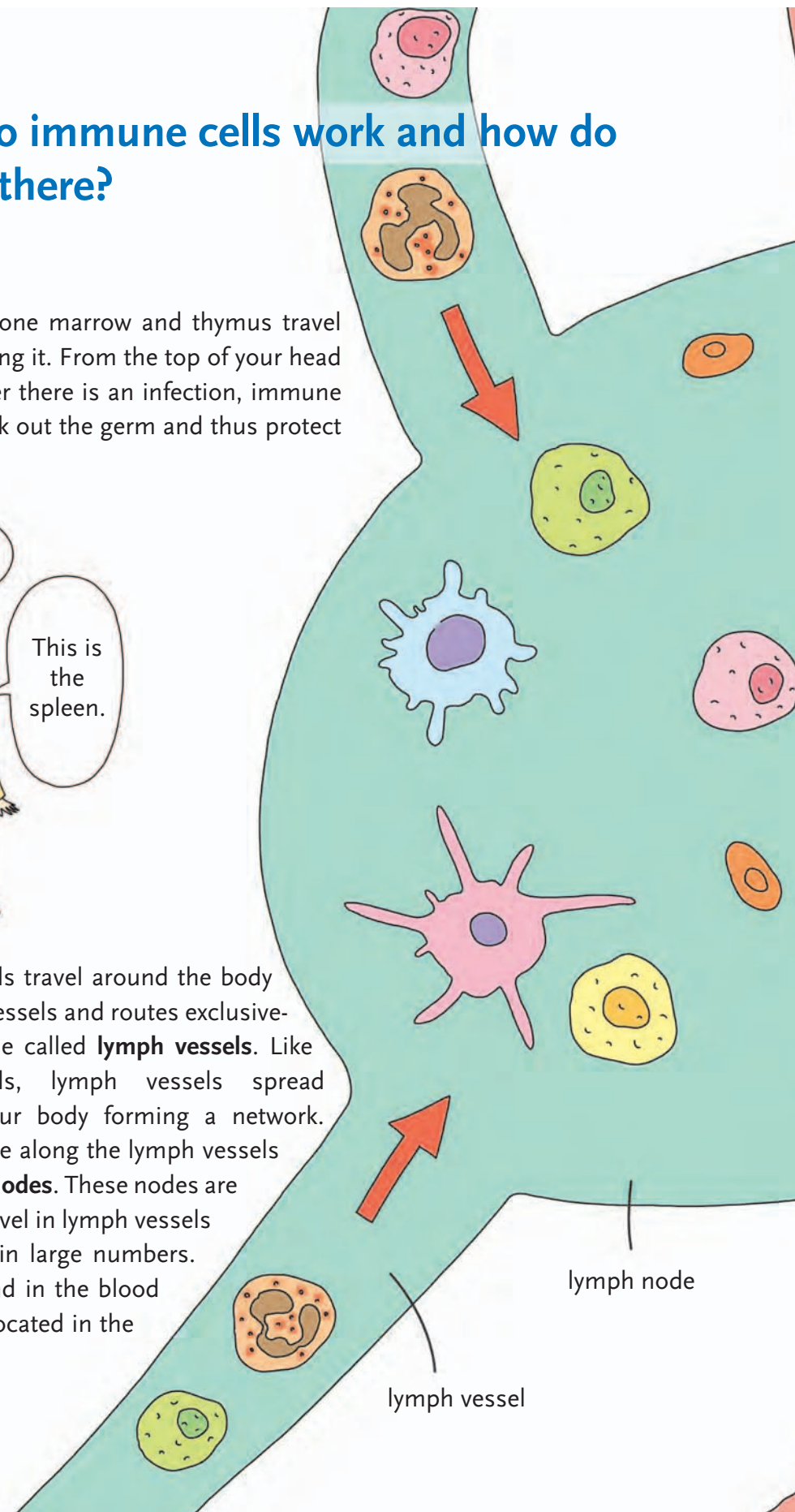
## Where do immune cells work and how do they get there?



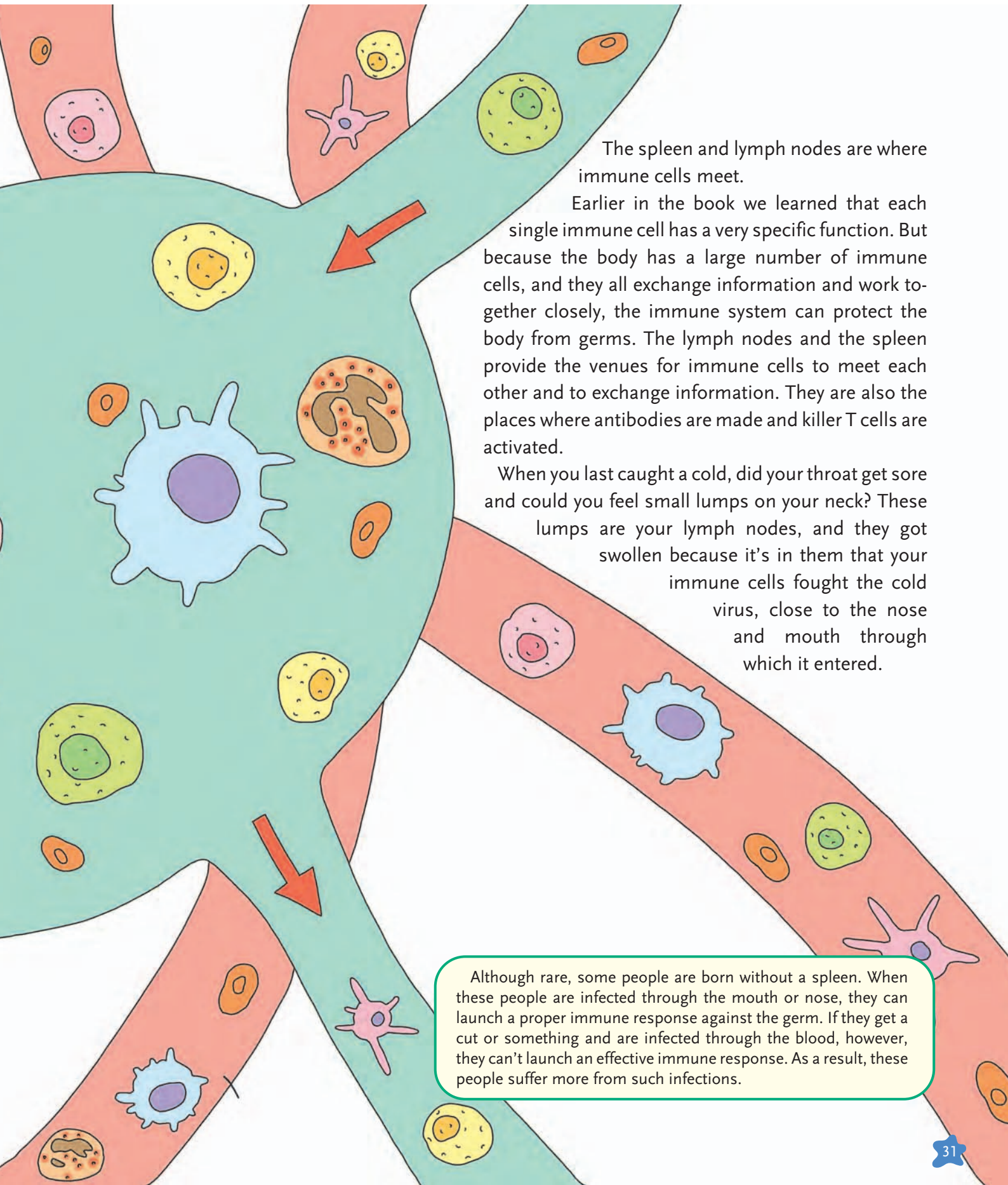
Immune cells made in the bone marrow and thymus travel around the whole body, patrolling it. From the top of your head to the tip of your toes, wherever there is an infection, immune cells rush over to the site, knock out the germ and thus protect the body.



Immune cells travel around the body using blood vessels and routes exclusively for their use called **lymph vessels**. Like blood vessels, lymph vessels spread throughout our body forming a network. Here and there along the lymph vessels are staging posts called **lymph nodes**. These nodes are where the immune cells that travel in lymph vessels and blood vessels can gather in large numbers. Immune cells that travel around in the blood gather in the spleen, which is located in the abdomen.







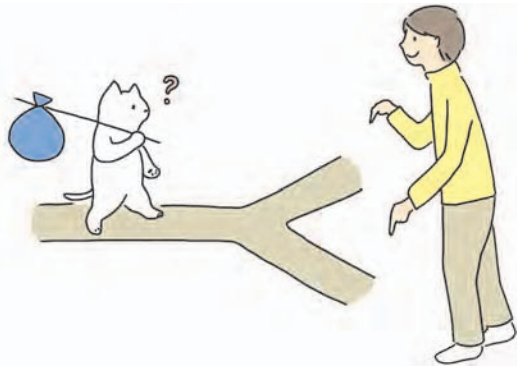
The spleen and lymph nodes are where immune cells meet.

Earlier in the book we learned that each single immune cell has a very specific function. But because the body has a large number of immune cells, and they all exchange information and work together closely, the immune system can protect the body from germs. The lymph nodes and the spleen provide the venues for immune cells to meet each other and to exchange information. They are also the places where antibodies are made and killer T cells are activated.

When you last caught a cold, did your throat get sore and could you feel small lumps on your neck? These lumps are your lymph nodes, and they got swollen because it's in them that your immune cells fought the cold virus, close to the nose and mouth through which it entered.

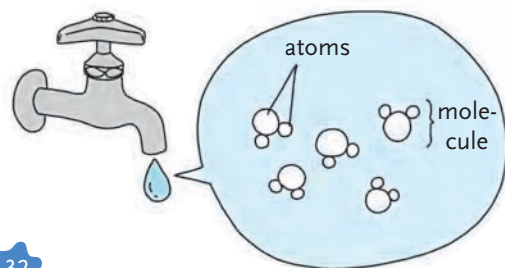
Although rare, some people are born without a spleen. When these people are infected through the mouth or nose, they can launch a proper immune response against the germ. If they get a cut or something and are infected through the blood, however, they can't launch an effective immune response. As a result, these people suffer more from such infections.

We mentioned that immune cells use blood and lymph vessels to patrol the body. But how do these immune cells manage to find their way to the lymph nodes? And, when there is an infection, how do they manage to find out exactly where the pathogens have invaded the body?



## How immune cells find their way around

Immune cells can find lymph nodes because the nodes make molecules that act as signs that read, “this is a lymph node”. Immune cells patrolling the body come across these signs, recognise where they are and respond by entering the nodes.

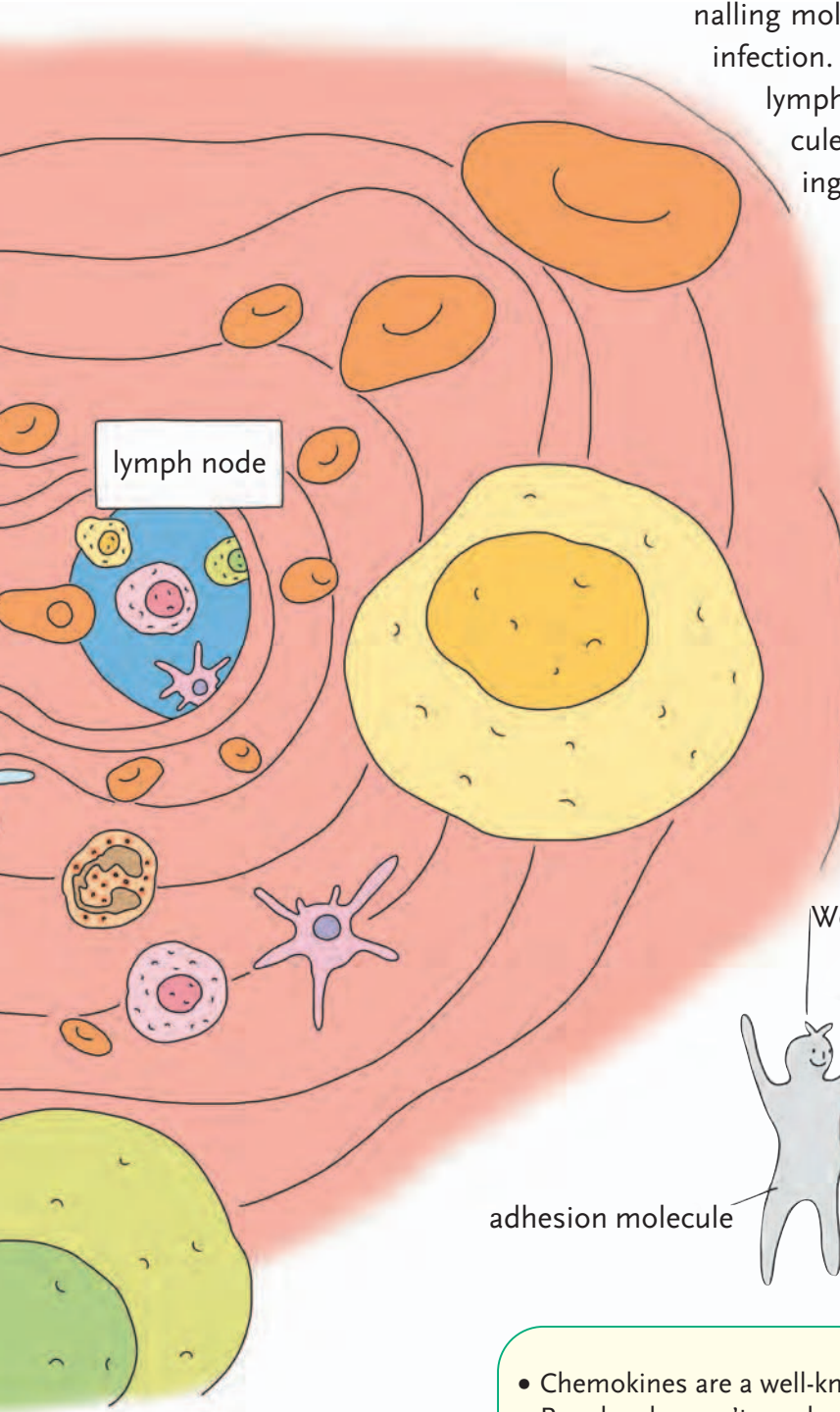


\* Molecules are groups of atoms. They are smallest units into which you can breakdown a substance and still recognise what it is from its physical and chemical properties.



During an infection, dendritic cells, don't just tell T cells what germ is the cause. They also release signalling molecules that alert their surroundings to the infection. Immune cells that pass through blood and lymph vessels nearby respond to these molecules by migrating to site of infection and dealing with the germs.

Such signalling molecules located on cell surfaces are called adhesion molecules, and they show immune cells that approach exactly where they are by sticking to these cells. Other signalling molecules, called chemo-attractants, are discharged by cells and can travel some distance to invite over immune cells that they meet on their journey. It's just like a shop that tries to grab your attention by putting up a large sign (adhesion molecules) over the door and then having people (chemo-attractants) at the entrance to invite you in.



- Chemokines are a well-known group of chemo-attractants.
- People who can't produce any adhesion molecules can't launch a proper immune response because their lymphocytes find it difficult to get into the lymph nodes.

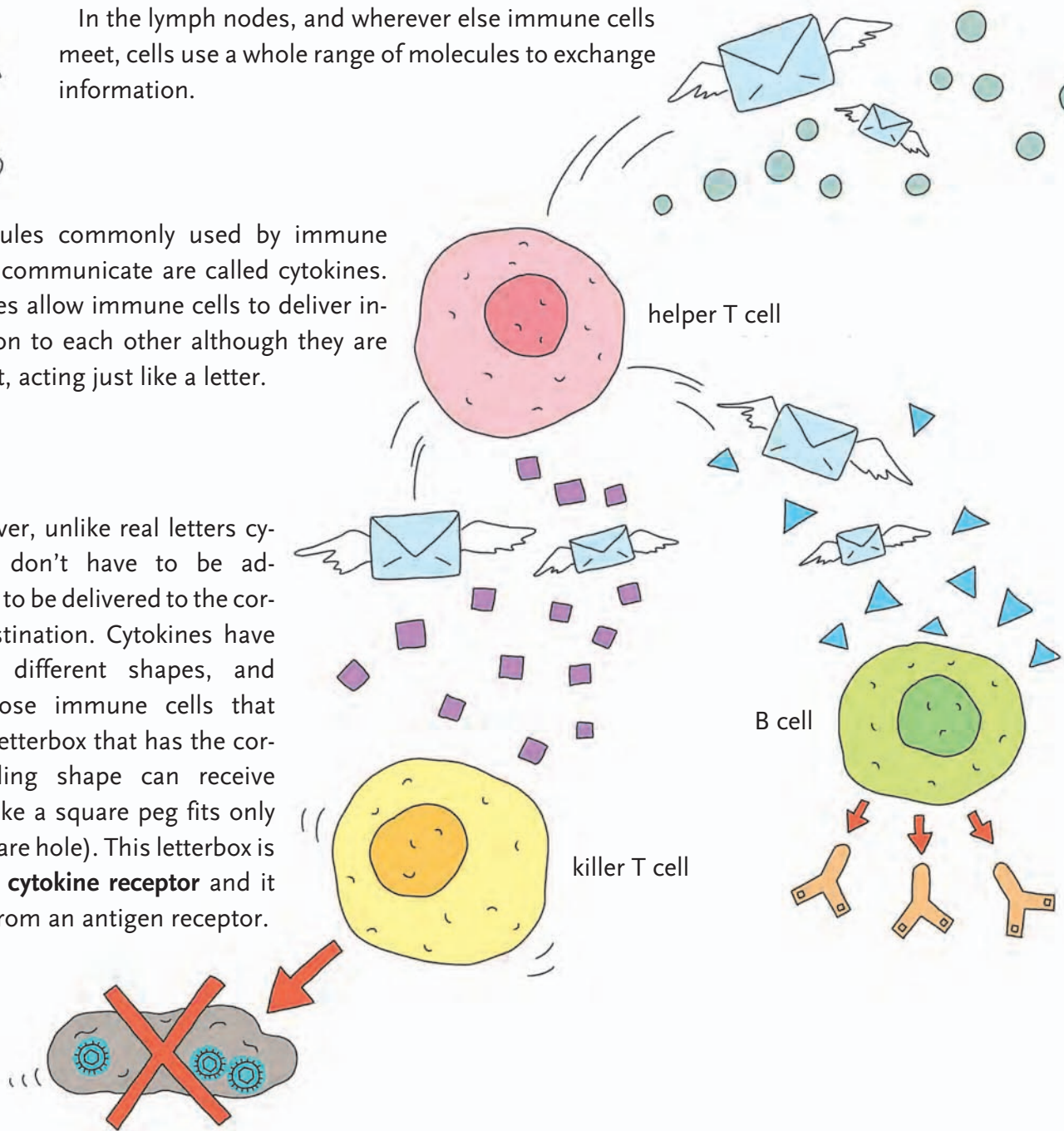
## How immune cells help each other



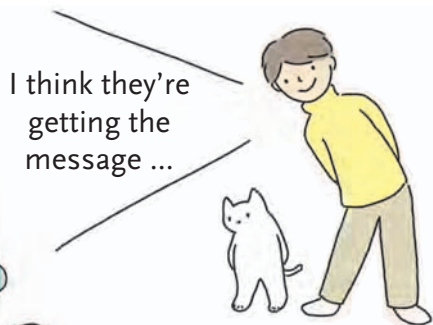
In the lymph nodes, and wherever else immune cells meet, cells use a whole range of molecules to exchange information.

Molecules commonly used by immune cells to communicate are called cytokines. Cytokines allow immune cells to deliver information to each other although they are far apart, acting just like a letter.

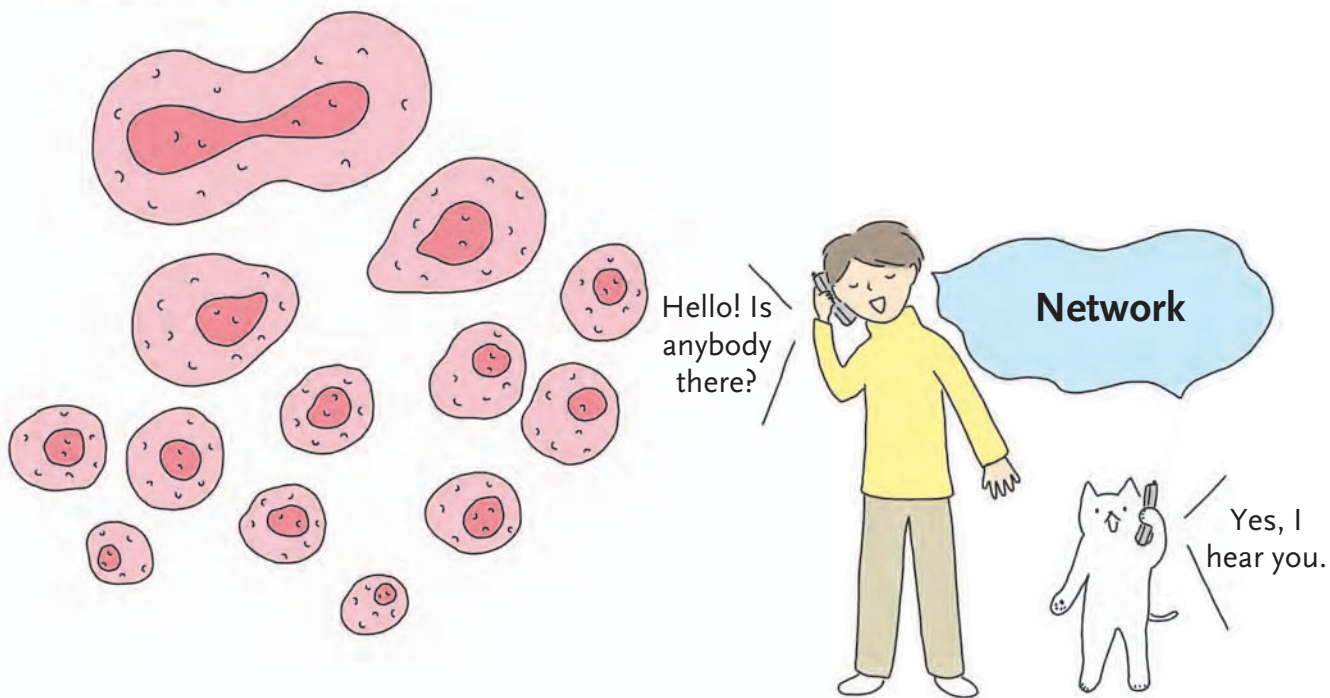
However, unlike real letters cytokines don't have to be addressed to be delivered to the correct destination. Cytokines have various different shapes, and only those immune cells that have a letterbox that has the corresponding shape can receive them (like a square peg fits only in a square hole). This letterbox is called a **cytokine receptor** and it differs from an antigen receptor.



Now, some cytokines deliver commands like “Wake up!” or “Divide!” to cells. Yet other cytokines tell cells to slow down and rest or to self destruct. When cells read a message that orders them to get to work, some respond by beavering away furiously. Depending on the situation, however, others respond by dying on the spot.

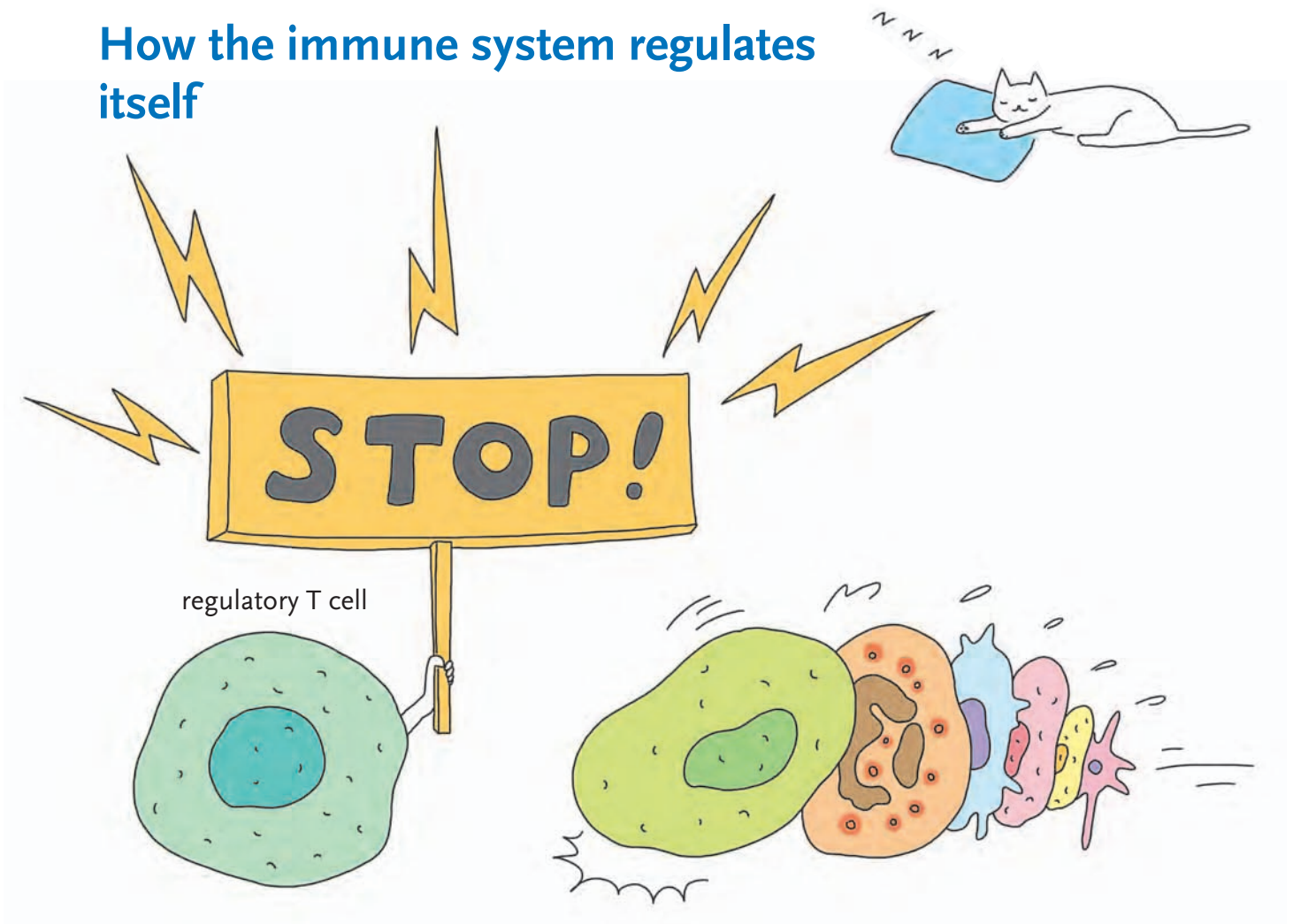


By using cytokines to send messages, immune cells are able to build a sophisticated information network. Just like people who use mobile phones and e-mail to connect with those beyond their immediate surroundings, immune cells continue to communicate with one another via the cytokine network while they patrol all around the body to protect it.



Researchers have discovered quite a few different types of cytokines. One type, interferon, became well known after doctors started using it to treat cancer and hepatitis C. Interferon helps the immune cells in our bodies to communicate with one another.

## How the immune system regulates itself



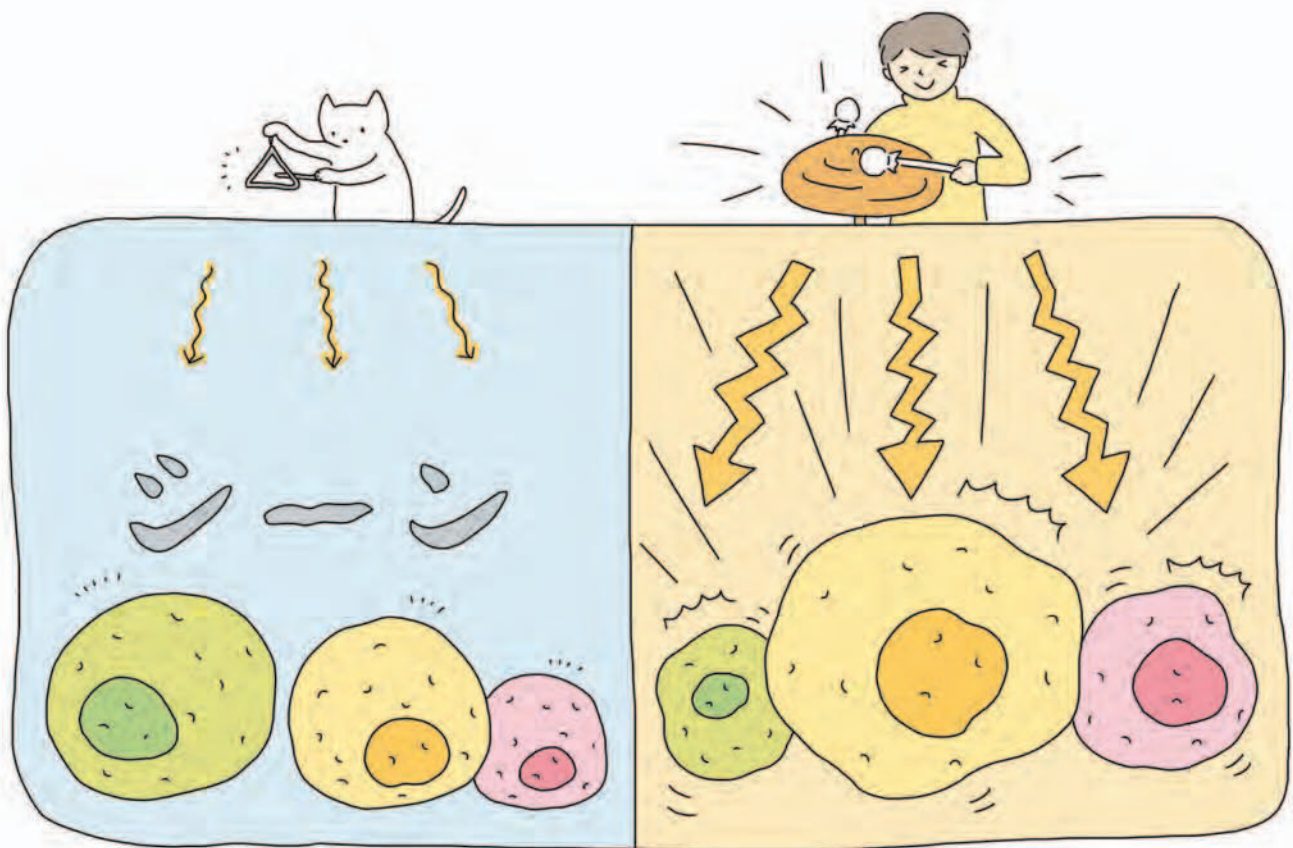
The attack that immune cells launch to rid the body of pathogens is called an **immune response**.

By now you probably realise that you'd be in trouble if your immune system didn't launch a response when you needed it. However, it'd be just as bad if it responded to each and every little thing. What you need is an immune response that launches *when* needed, *as* needed. The fever you get when you have a cold is caused by the immune response, but think what would happen to your body if your temperature didn't drop even after the virus had been fought off.

The immune system has a number of ways to stop an overblown response from launching. It possesses molecules and cells that have the role of suppressing the immune response. One cell that specialises in this task is the **regulatory T cell**.

The immune system not only can halt a response already underway, it can also prevent an unnecessary one from launching. Antigen receptors on lymphocytes are ultra-sensitive and can detect very faint signals. However, when cells receive a weak signal, they just respond by waiting and standing at the ready. Only when they get a strong signal caused by an infection, do they kick off into action.

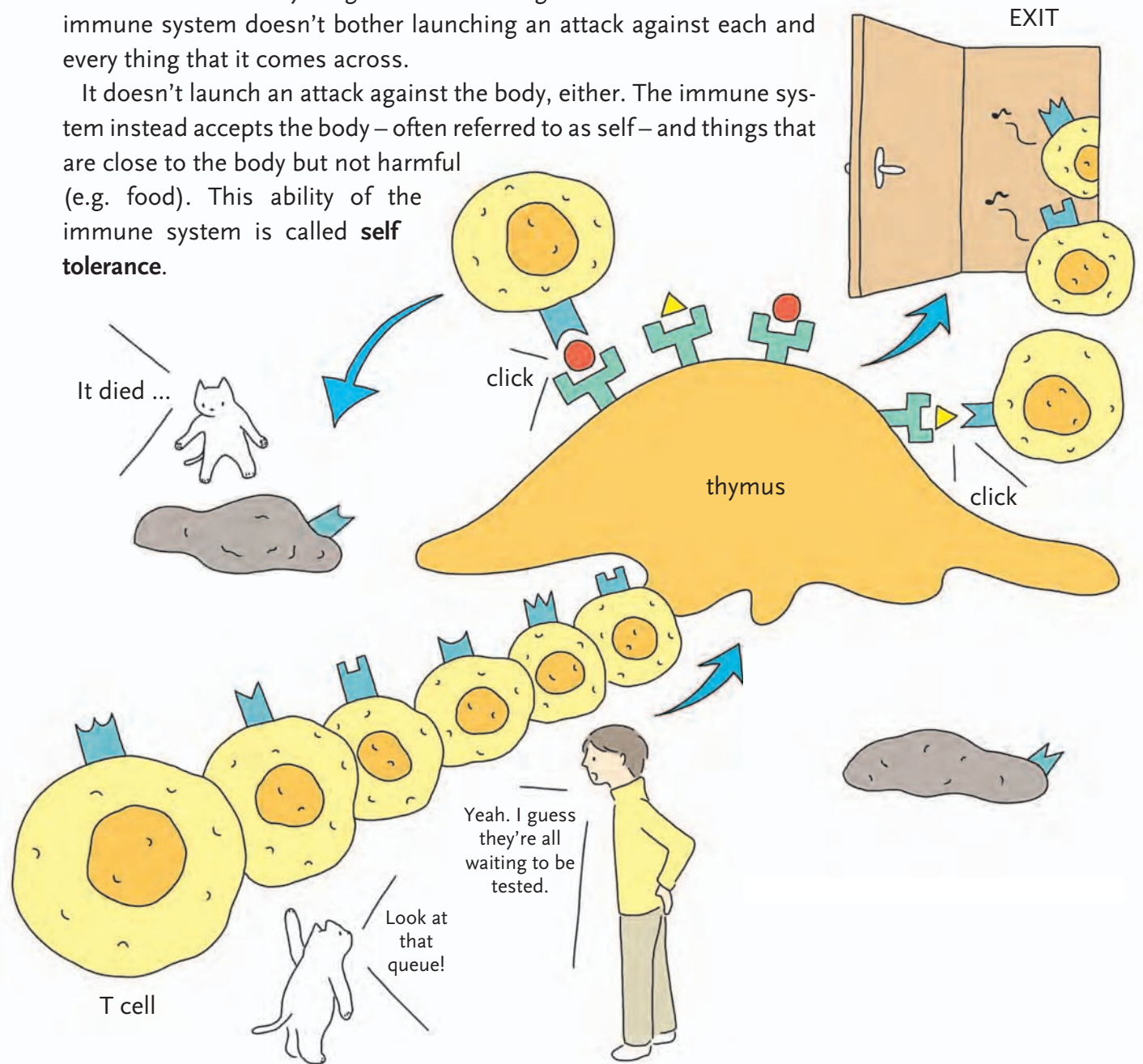
The immune system provides the body with an extremely reliable defence system. It's manned with specialised cells, equipped with a sophisticated communications system and armed with weapons such as antibodies. And now you know that the system also has a whole host of safety measures that make sure that it doesn't start any needless fights, nor harm the body by wielding more force than necessary.



## Why the immune system doesn't attack the body or food

Every day a host of things other than germs enter your body. From the body's point of view the food that you eat or the millions of microbes that make a home in your gut could be thought of as invaders. But the immune system doesn't bother launching an attack against each and every thing that it comes across.

It doesn't launch an attack against the body, either. The immune system instead accepts the body – often referred to as self – and things that are close to the body but not harmful (e.g. food). This ability of the immune system is called **self tolerance**.





So, let's find out first why the body doesn't attack itself.

Remember we told you that B cells and T cells have well over 10 billion different antigen receptors? With so many types, there could just be an antigen receptor that matches one of the body's own antigens among them. If a lymphocyte with such an antigen receptor did enter the blood, the cell would begin to attack the body and that could spell disaster.

To stop this from happening, lymphocytes are tested to see if their antigen receptors match the body's own antigens before they are released into the blood. For B cells this test takes place in the bone marrow. For T cells, it takes place in the thymus. Cells that have dangerous antigen receptors are destroyed on the spot.

But if some of these dangerous lymphocytes did make it out of the test sites and into rest of the body, not all would be lost. Those mechanisms we told you about earlier – the ones that stop unnecessary immune responses – would take care of these cells.

As for the food you eat and all those beneficial microbes that live in your stomach and bowel, the immune system has special mechanisms that allow it to tolerate them.





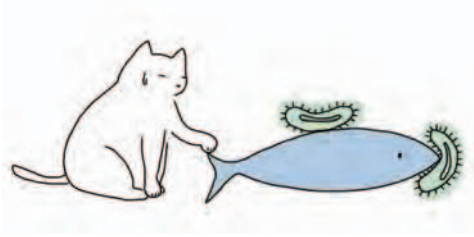


**Part II**

# **All about Diseases**

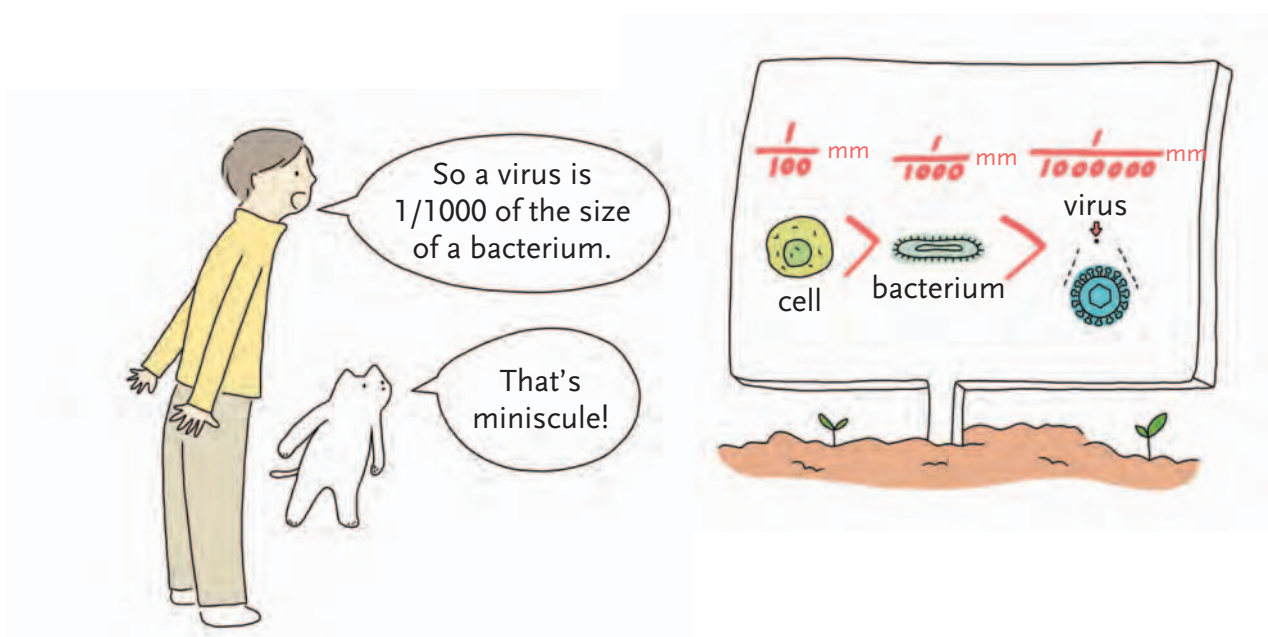
## 7. Fighting Infectious Diseases

### All about pathogens

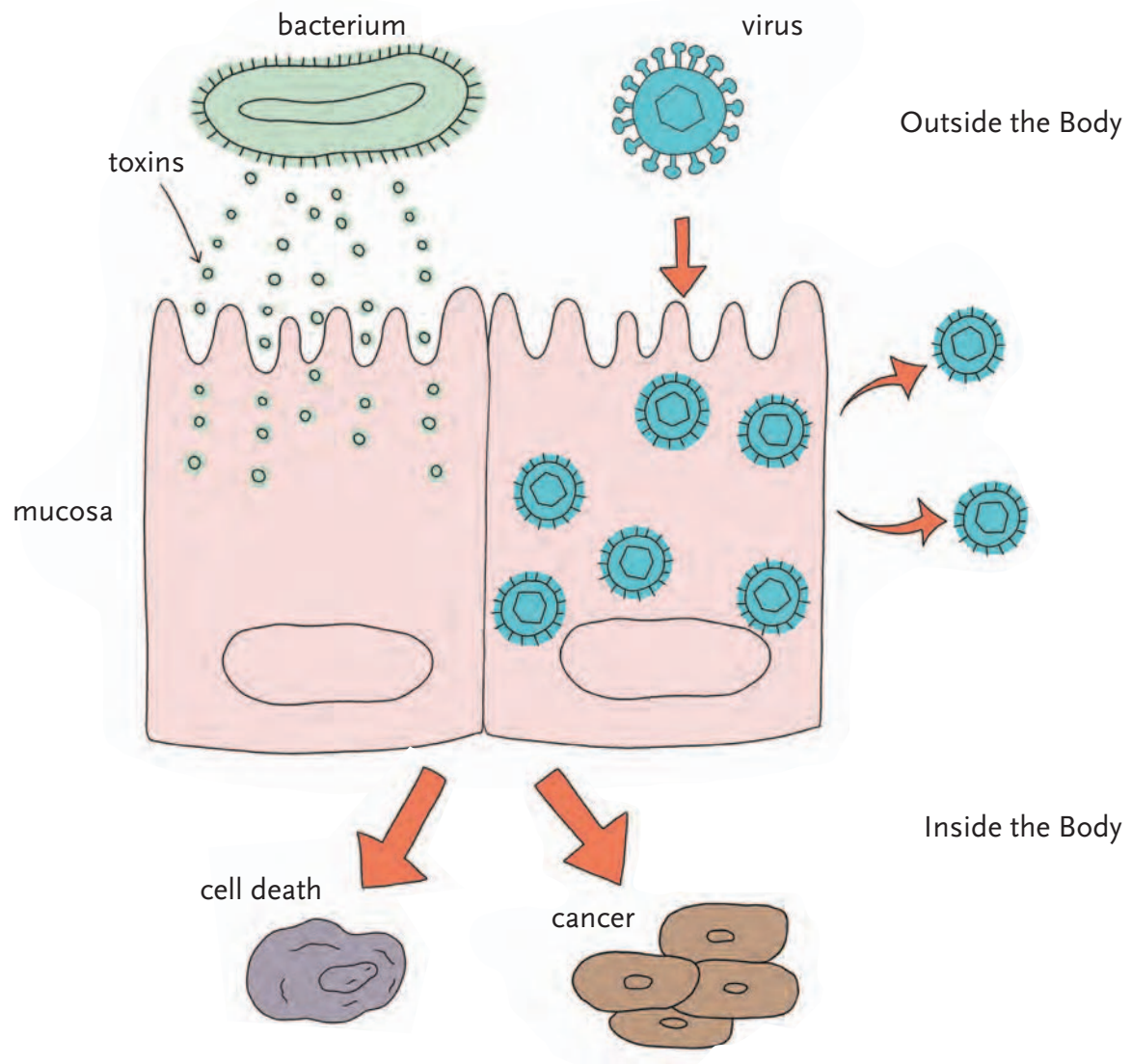


Infectious diseases are caused by invisible microorganisms that enter the body and multiply there. The history of immunology, which began in the 18<sup>th</sup> century with Jenner's discovery of vaccines, is also the history of the fight against infectious diseases. Thanks to the worldwide use of the vaccine Jenner discovered, the disease smallpox has vanished. And thanks to the many excellent vaccines that have been developed since, we are safe from a large variety of infectious diseases.

The microorganisms that cause infectious diseases are called **pathogens** or, more commonly, **germs**. Pathogens include bacteria and viruses. Bacteria are single-celled and are a few microns in size. (1 micron is 1/1000 of a millimetre.)



- Smallpox is an infectious disease caused by the smallpox virus. If you catch the disease, you get a fever of 40 degrees and your whole body becomes covered in pustules and blisters. Many people used to die of this disease, but thanks to Jenner's vaccine, not a single person has developed the disease since 1977.
- Virus is the Latin word for poison. In ancient Greece, Hippocrates used the word virus to mean a poison that causes illness.

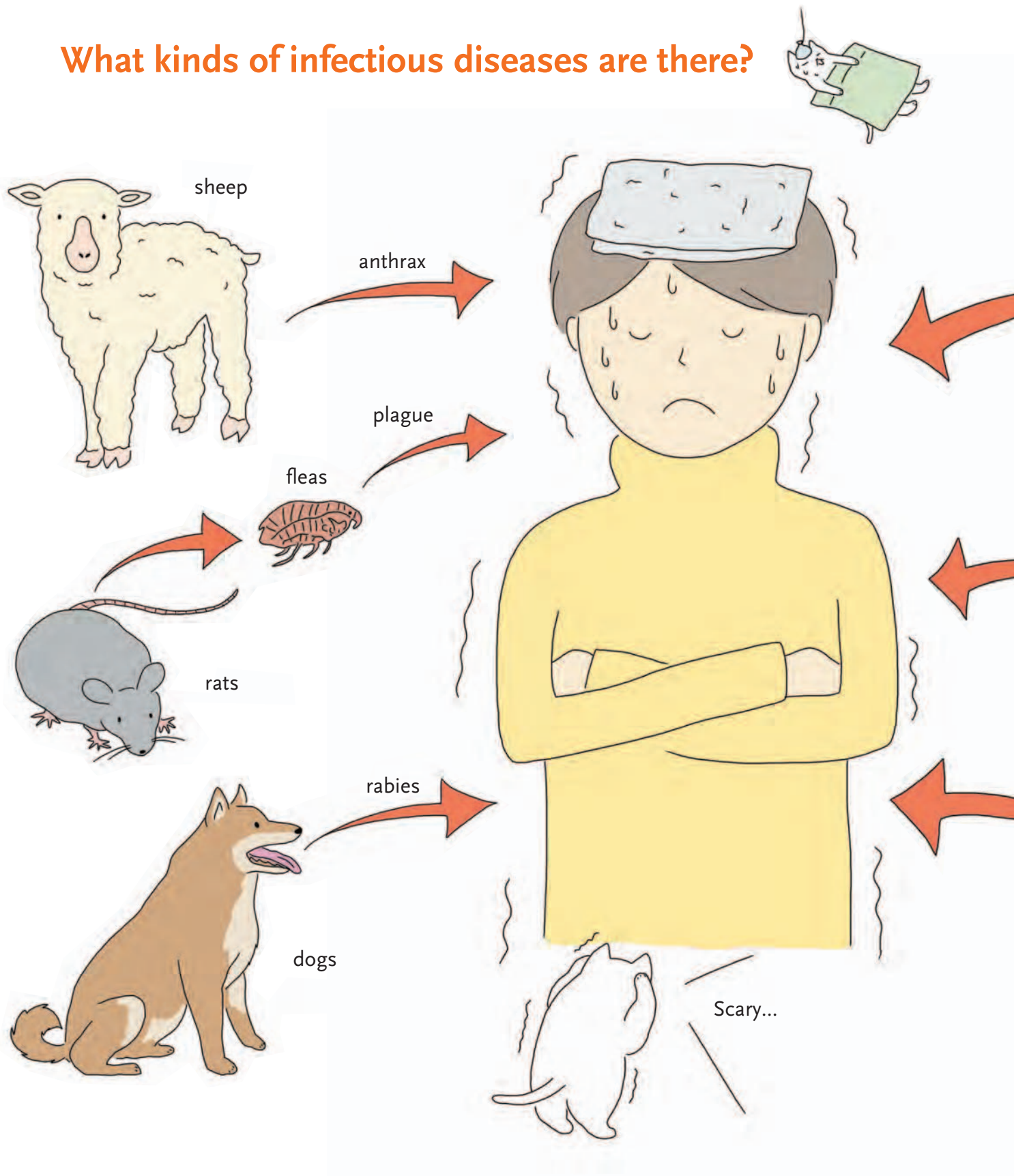


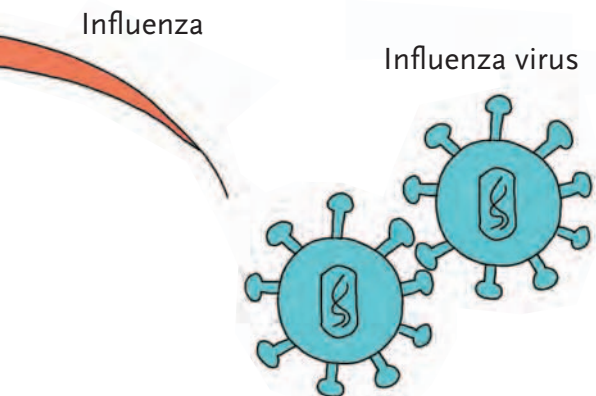
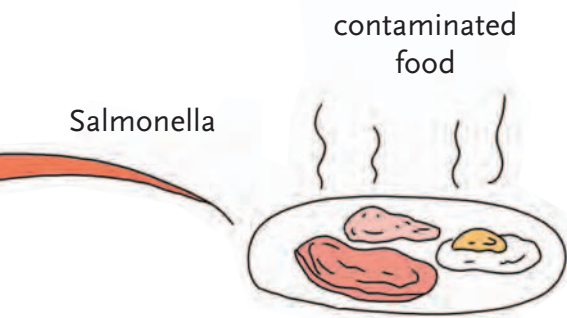
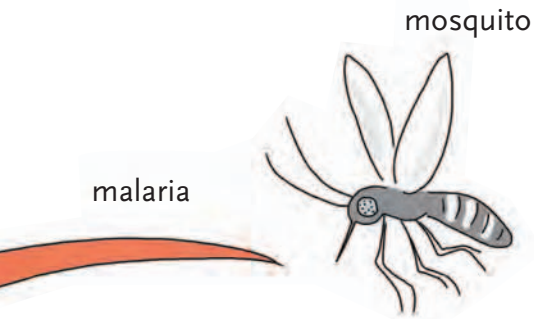
How do the bacteria that invade your body cause disease?

Bacteria produce toxins that destroy cells or paralyse them. They also have toxins incorporated into their cell walls that can cause fever, diarrhoea, or a drop in blood pressure. As well as toxins, bacteria have a whole host of other weapons that can cause you harm.

Viruses are between 100 and 1000 times smaller than bacteria and they can invade a whole range of cells. Once inside the cell they begin to multiply rapidly. Viral infection can either derail the normal functioning of a cell, causing it to die, or it can make a cell multiply uncontrollably so that it turns into a cancer cell. Following infection, some types of viruses multiply slowly to cause a **persistent infection**. Yet others stop multiplying all together and cause what is known as a **latent infection**.

# What kinds of infectious diseases are there?






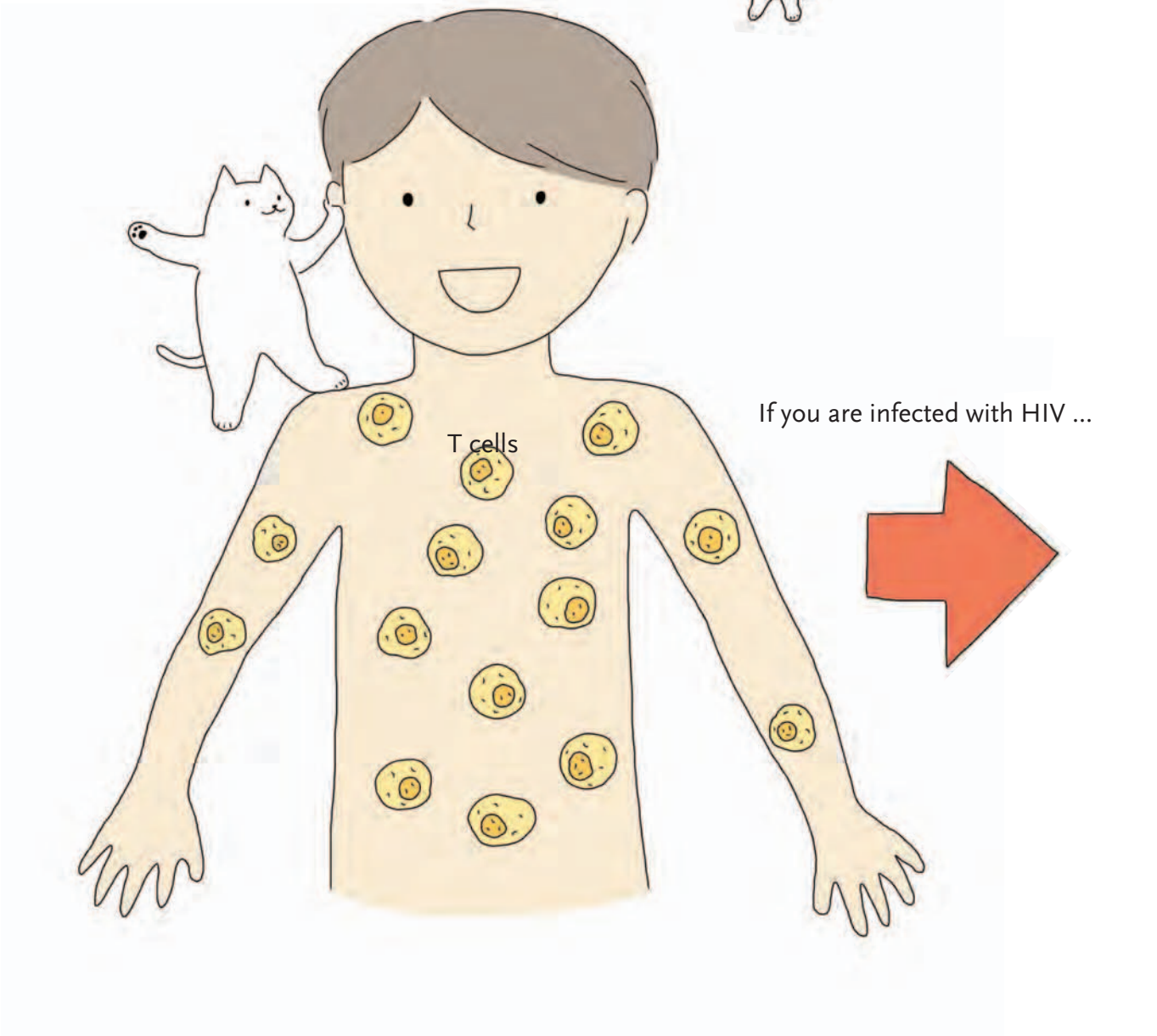
All over the world, there are many diseases that are still difficult to control. Of particular concern are **zoonotic diseases** that are caused by pathogens that can infect both animals and humans and newly **emerging diseases**, which were first reported in the 1970s.

Zoonotic diseases caused by bacteria include anthrax from goats or sheep, the plague from fleas that live on rats, tuberculosis from the air around us when a patient coughs, and salmonella from contaminated food. They can also include diseases caused by viruses, like influenza which is common in winter, rabies which you catch if bitten by an infected animal, and malaria which you can get from mosquito bites. Other zoonotic diseases are caused by parasites.

Emerging diseases include SARS (Severe Acute Respiratory Syndrome) which is caused by a new coronavirus, Ebola which is a haemorrhagic (he-mo-ra-jic) fever that causes your intestines to bleed and kills 50 to 90% of people who catch it, AIDS which kills more people than any other infectious disease, and avian influenza, a disease could develop into a pandemic, that is, a disease that afflicts many people all over the world like the Spanish flu.

## What is AIDS?

AIDS? 

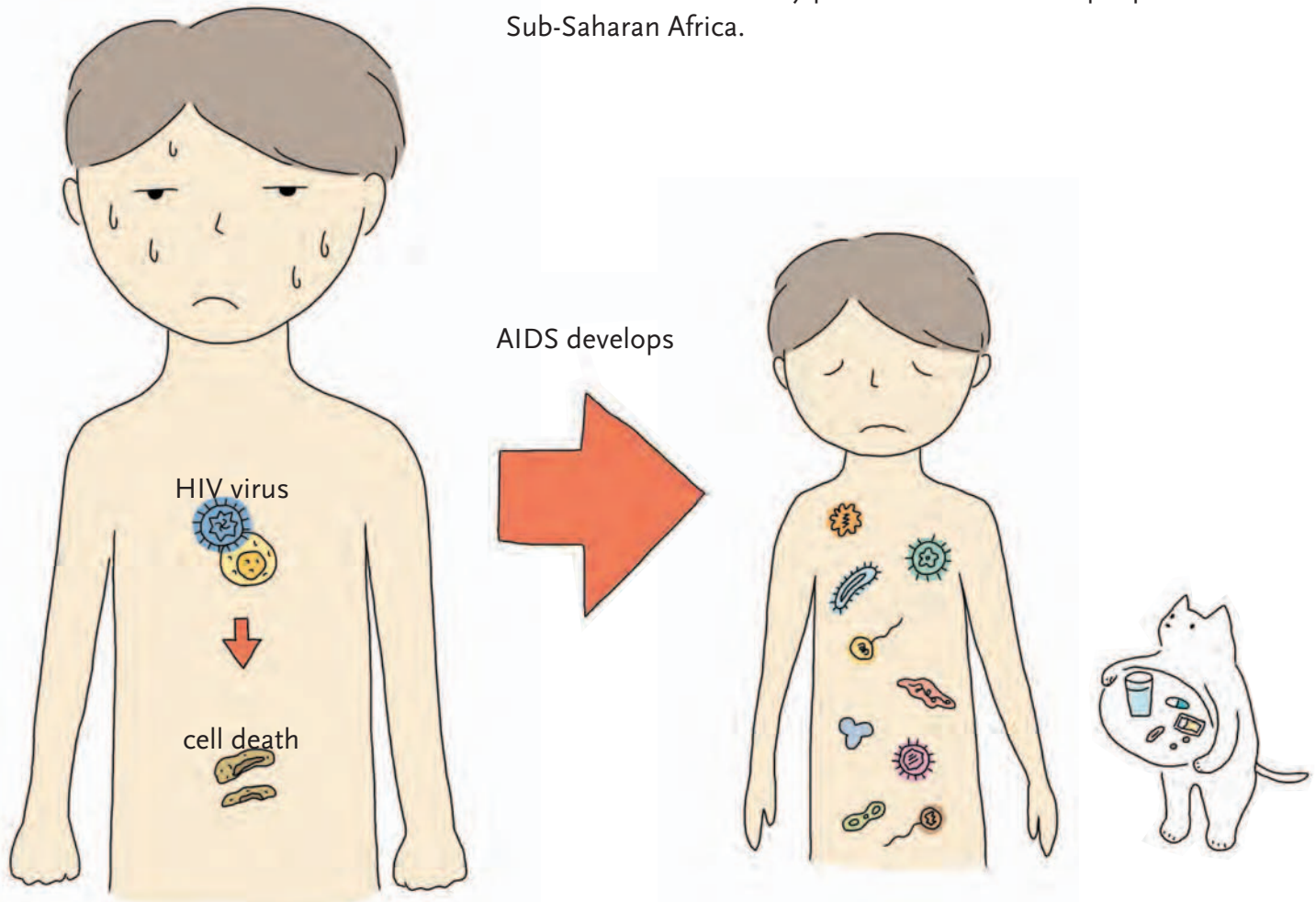


The Human Immunodeficiency Virus (HIV) is a virus that infects helper T cells and destroys them. With fewer T cells, your immune system is weakened and you can get sick from germs that would not cause disease in healthy people.

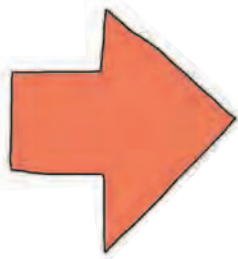
When this happens, the person has what is called AIDS or Acquired Immunodeficiency Syndrome. Her/his blood and bodily fluids will still contain the HIV virus, and she can pass it to her children at birth or she/he can pass it to others through having sex.



Scientists believe that HIV developed from a chimpanzee immunodeficiency virus that mutated several hundred years ago and became able to infect humans. By the end of 2007, the number of people infected by HIV around the world had reached 30 million. Sixty percent of all infected people live in Sub-Saharan Africa.



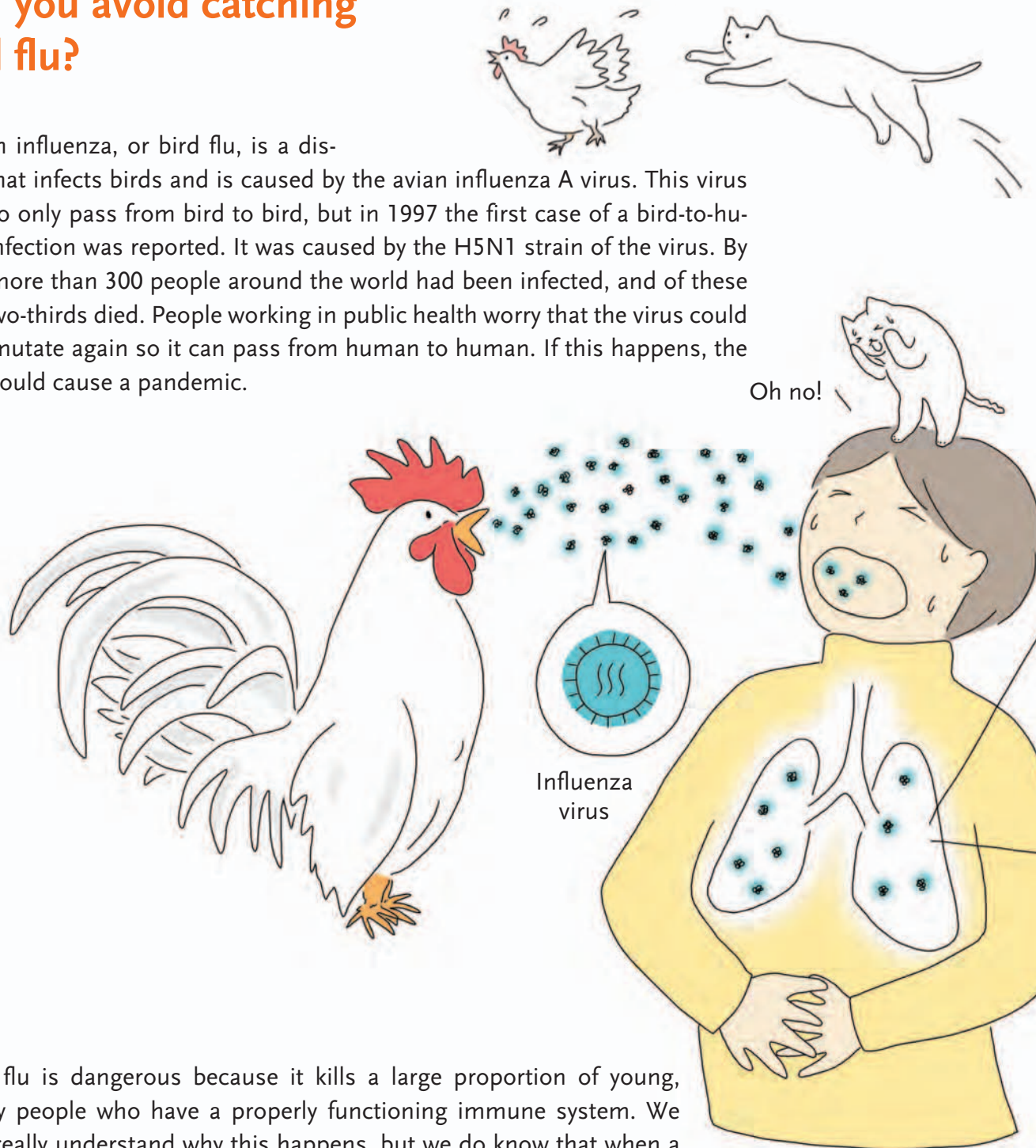
You become infected with all kinds of pathogens.



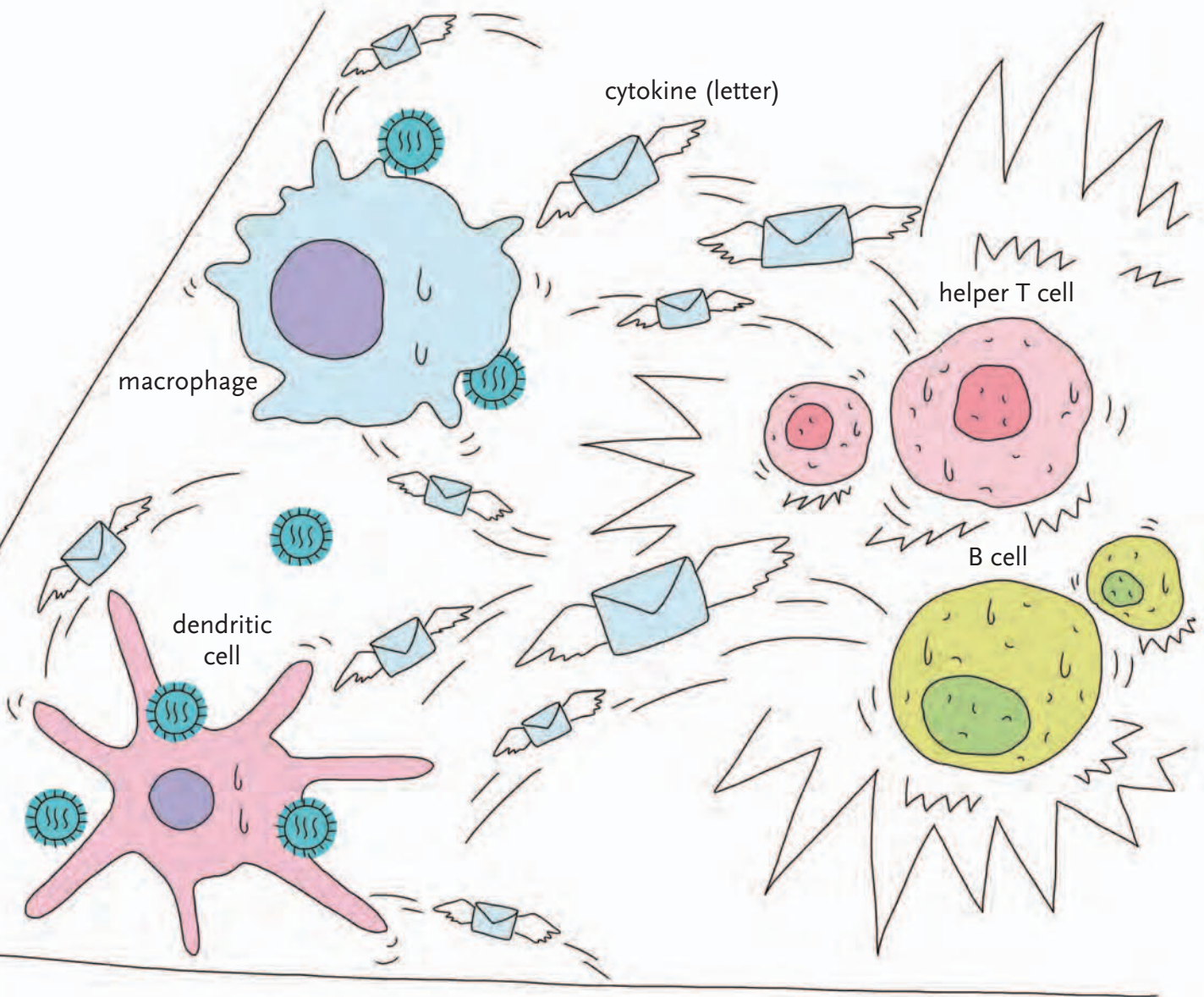
Can AIDS be cured? Unfortunately, there is no treatment yet that can cure the disease entirely. At the moment, people are being treated with a combination of three or four types of drugs. This treatment drastically reduces the amount of virus in a person's body, and has helped reduce the number of people who die from AIDS significantly. But still, people with HIV who live in the developing world cannot afford these drugs.

## Can you avoid catching bird flu?

Avian influenza, or bird flu, is a disease that infects birds and is caused by the avian influenza A virus. This virus used to only pass from bird to bird, but in 1997 the first case of a bird-to-human infection was reported. It was caused by the H5N1 strain of the virus. By 2007 more than 300 people around the world had been infected, and of these over two-thirds died. People working in public health worry that the virus could soon mutate again so it can pass from human to human. If this happens, the virus could cause a pandemic.



Bird flu is dangerous because it kills a large proportion of young, healthy people who have a properly functioning immune system. We don't really understand why this happens, but we do know that when a person catches bird flu, her/his body produces vast amounts of cytokines and that immune cells go on the rampage.



So how can you stop yourself from catching bird flu?

At the moment scientists believe that best means to stop bird flu would be to develop a vaccine. Obviously, the vaccine cannot consist of live avian influenza virus just as it is. So researchers are now working on projects that use parts of the flu virus to make a vaccine. This way your immune system could be introduced to the virus without any danger of your getting sick. Of course the vaccine would have to be tested for safety and efficacy first.

## How much can vaccines do?

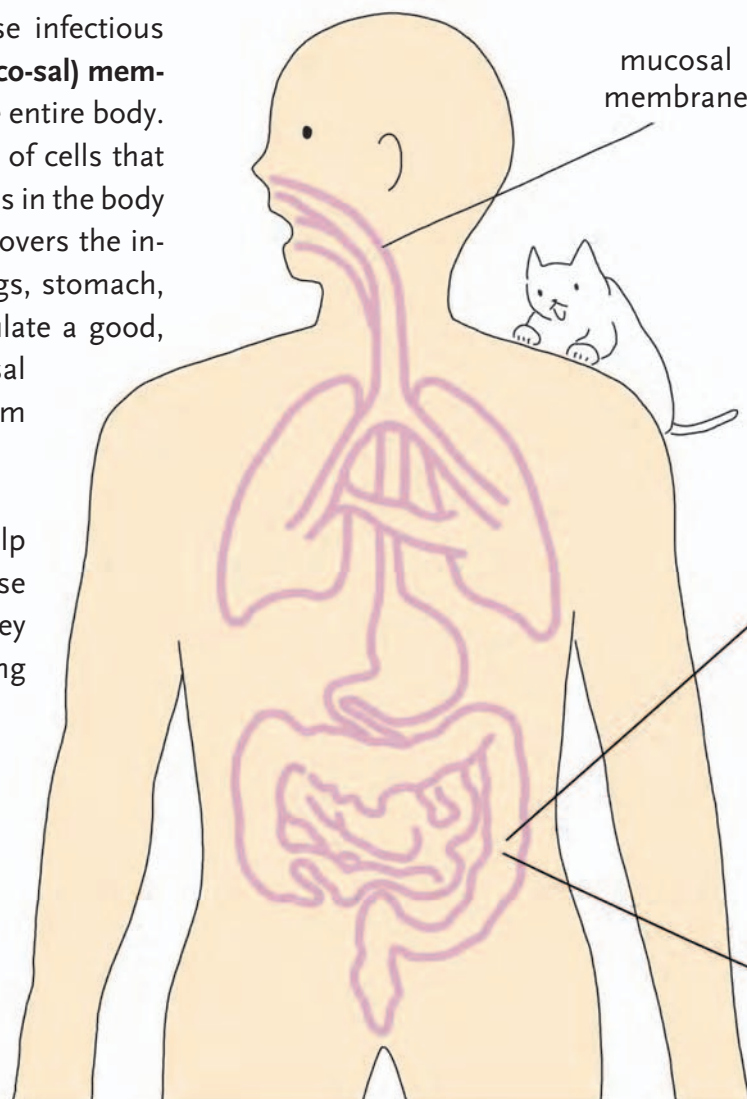


In the first part of this book we heard that vaccines have already been used successfully to protect us from a great many infectious diseases. At the moment, the type of vaccine that Jenner developed is still the most effective way of controlling infectious diseases. But scientists are making progress in developing new types of vaccines that can prevent or even treat infectious diseases.

How can we make vaccines even more effective?

Most bacteria and viruses that cause infectious diseases enter through **mucosal (mew-co-sal) membranes** and then spread throughout the entire body. The mucosal membrane is a thin layer of cells that covers the inner surface of all the cavities in the body that have contact with the outside. It covers the inside of the mouth, nostrils, gullet, lungs, stomach, intestine and anus. *If you could stimulate a good, strong immune response at the mucosal membrane, you could prevent germs from even entering the body.*

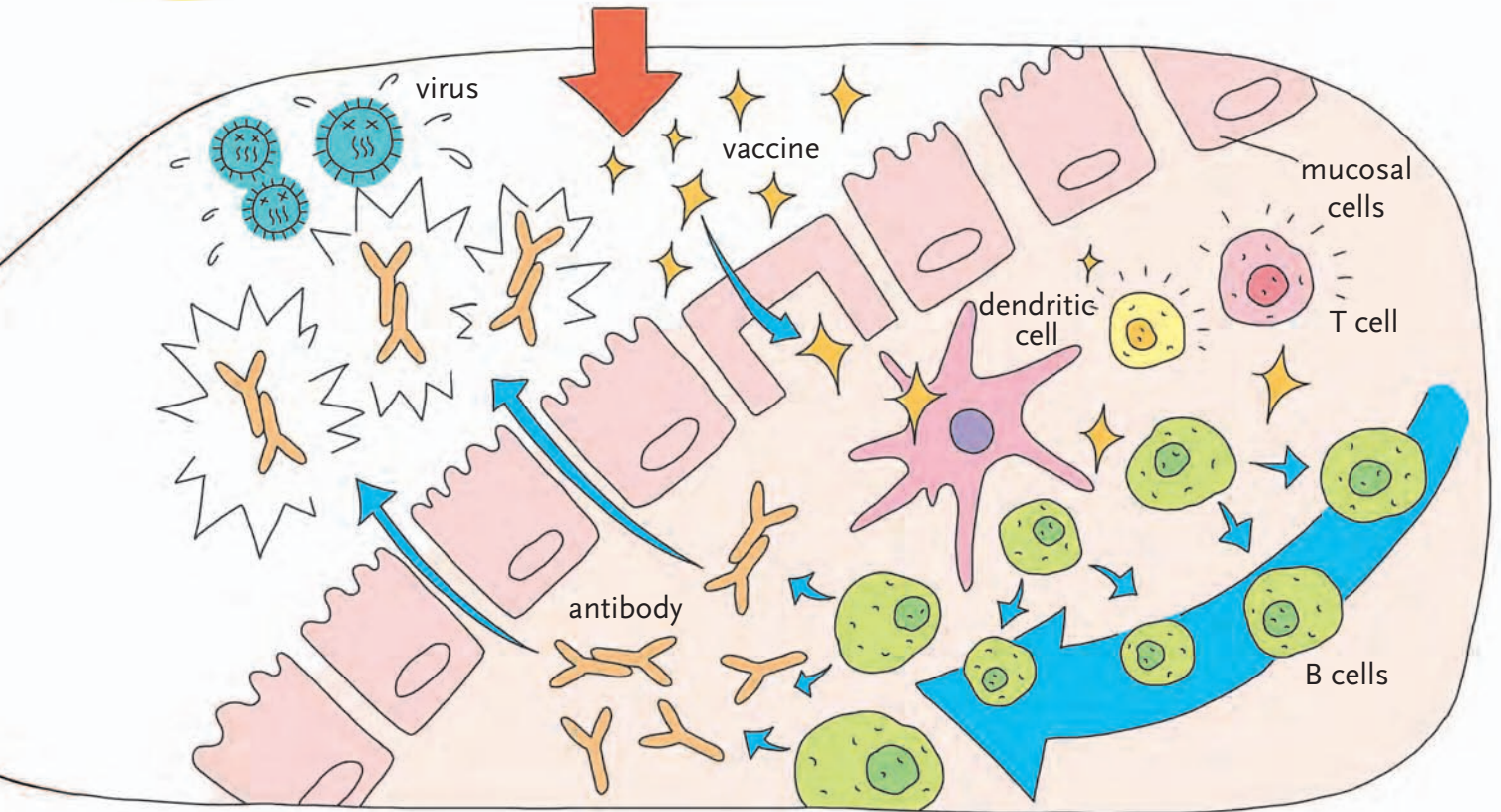
The vaccines we currently use only help the immune system stage a response once the pathogen is inside the body, they cannot prevent pathogens from entering through the mucosal membrane.





What could these new vaccines look like?

At the moment, researchers are developing vaccines that you can eat, drink or inhale. Being vaccinated in this way is less scary than facing a needle and it should improve the mucosal immune response. Results have been promising. Already a flu vaccine you can inhale is available in the US and many mucosal vaccines are in development.

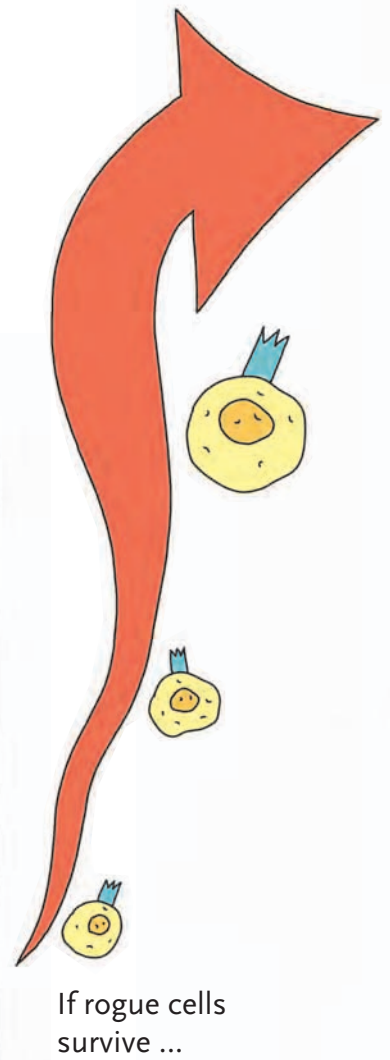
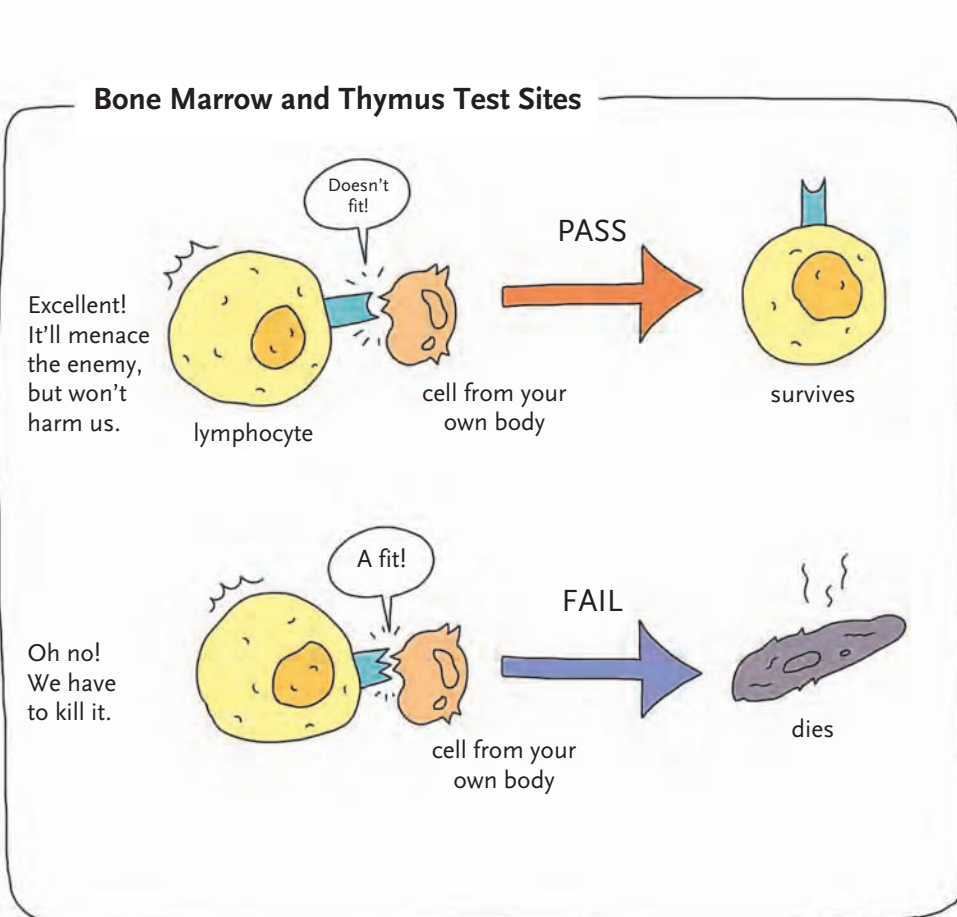
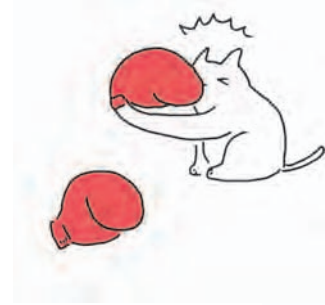


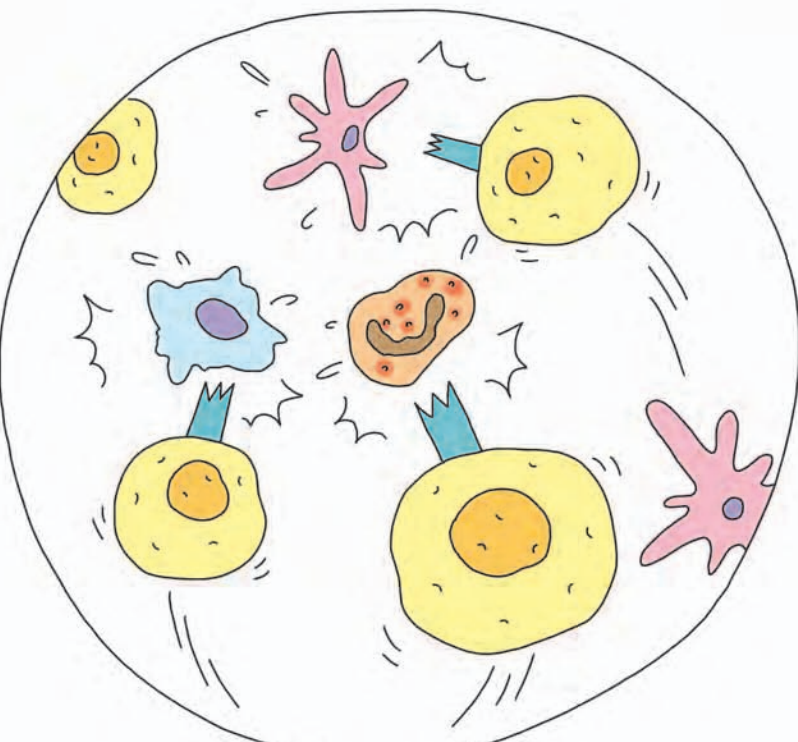
## 2. Autoimmune Diseases

### What is an autoimmune disease?

We know now that immune cells are dependable allies, always at the ready to defend our body from the germs that invade it.

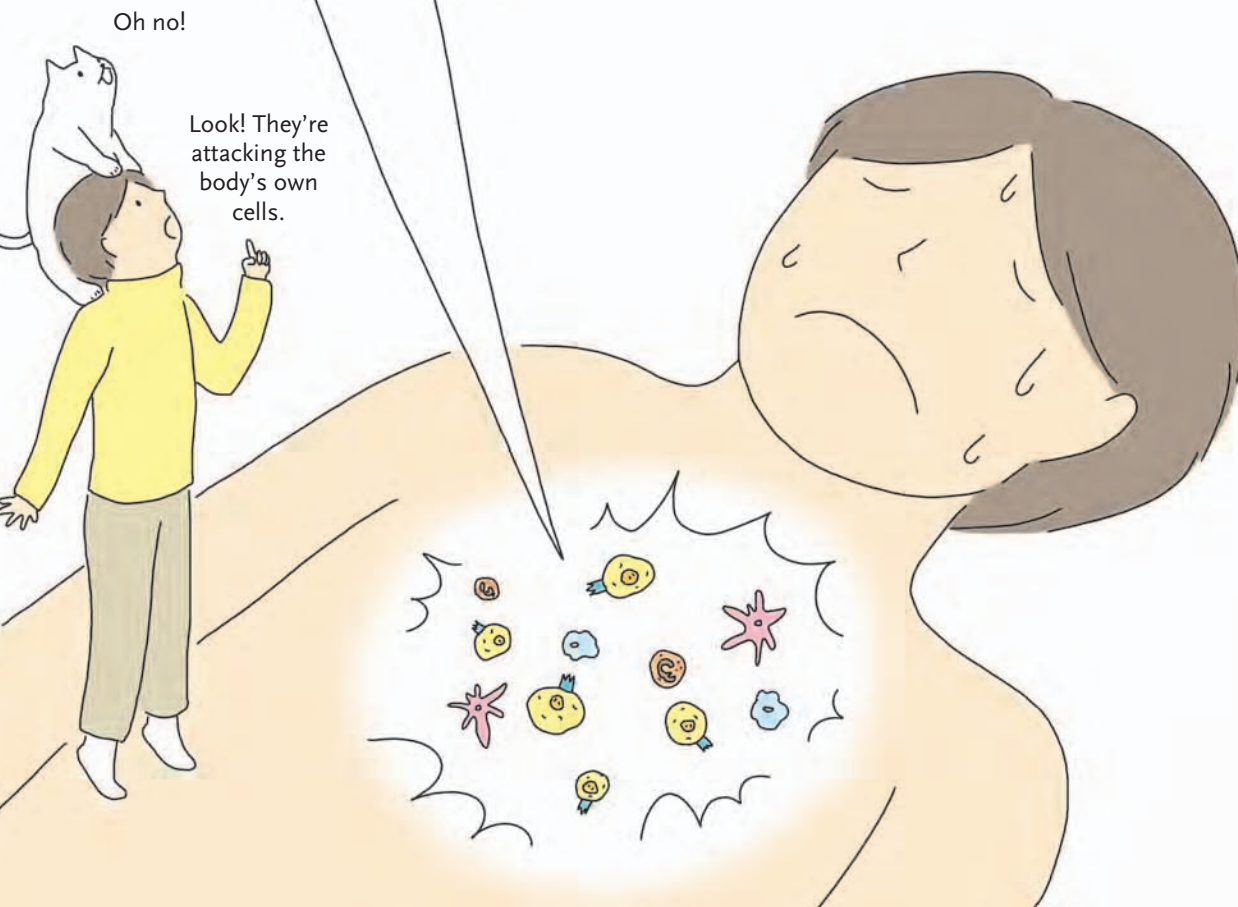
Before the cells get to work they are tested in the bone marrow and thymus, where they are made. The cells need to distinguish between the body (**self**), and potential invaders if they are to be our true friends. An immune cell that attacks the body is a danger and has to be destroyed. Sometimes, however, these rogue cells manage to survive.



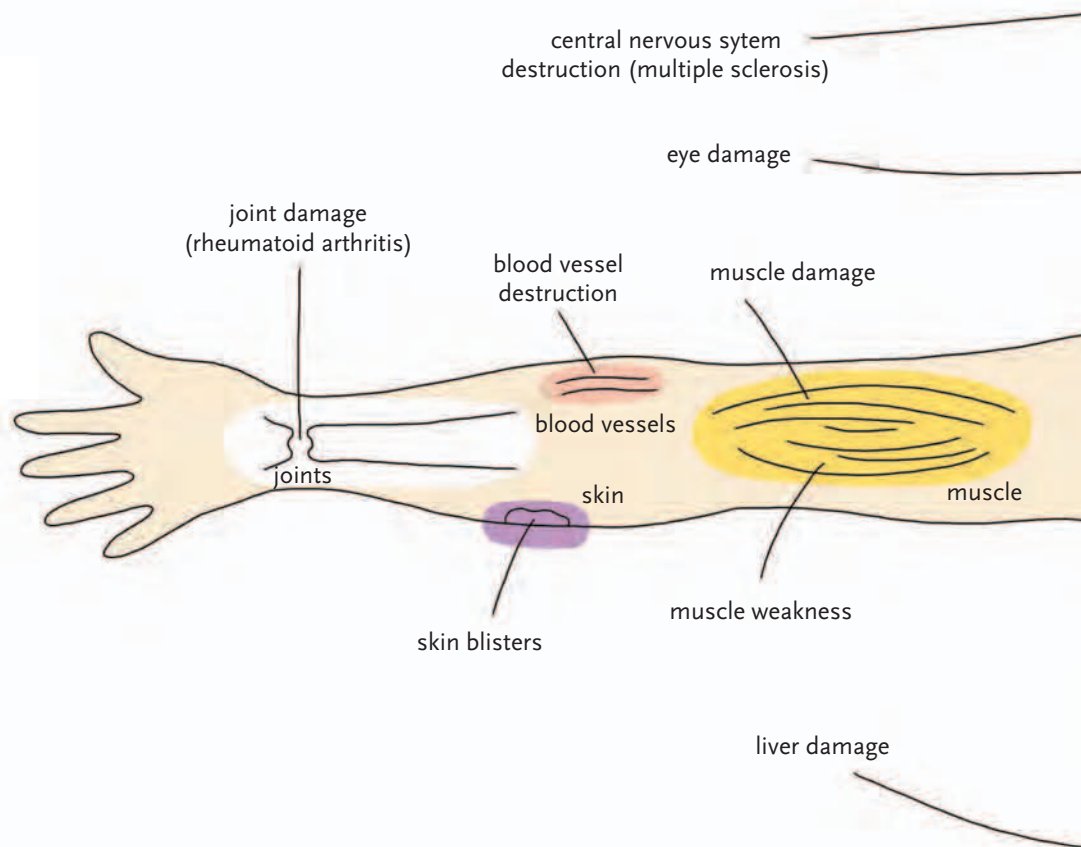


All is not lost, however, because of the self-tolerance mechanisms built into the immune system that we told you about in Part I. These safeguards stop immune cells from attacking the body or things that are of no harm to us, like food. Normally these mechanisms also take care of any escaped rogue cells and keep us safe.

However, if this ability to tolerate self breaks down, the body ends up under attack as the immune system mistakes the body's cells for enemies. This condition is called autoimmunity or **autoimmune disease**. Exactly why this happens is not well understood.



# What kinds of autoimmune disease are there?



There are a great number of autoimmune diseases, and they can occur in any part of your body. Let's take a look at a few.

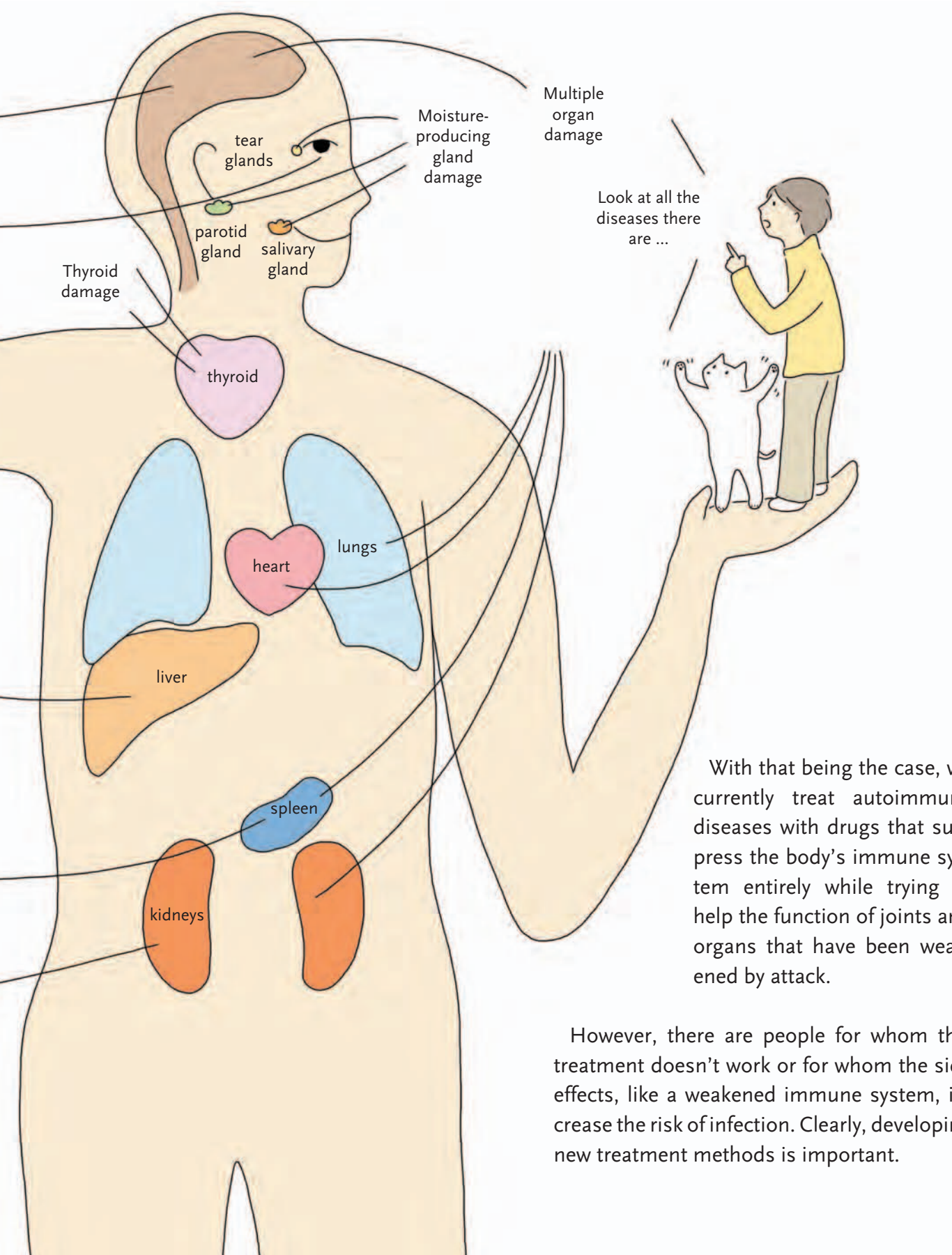
Every cell of the body contains a structure called a nucleus in which all your genes are packed. If you get a disease called Systemic Lupus Erythematosus (SLE), your immune cells make antibodies that attack the nucleus and this causes inflammation all over your body. Other autoimmune diseases attack your joints, like rheumatoid arthritis, or your brain and spinal cord, like multiple sclerosis.

The symptoms of each autoimmune disease and how it develops differs from person to person. We do not clearly understand why the body begins to attack itself.

pancreas islet damage (type I diabetes)

kidney failure





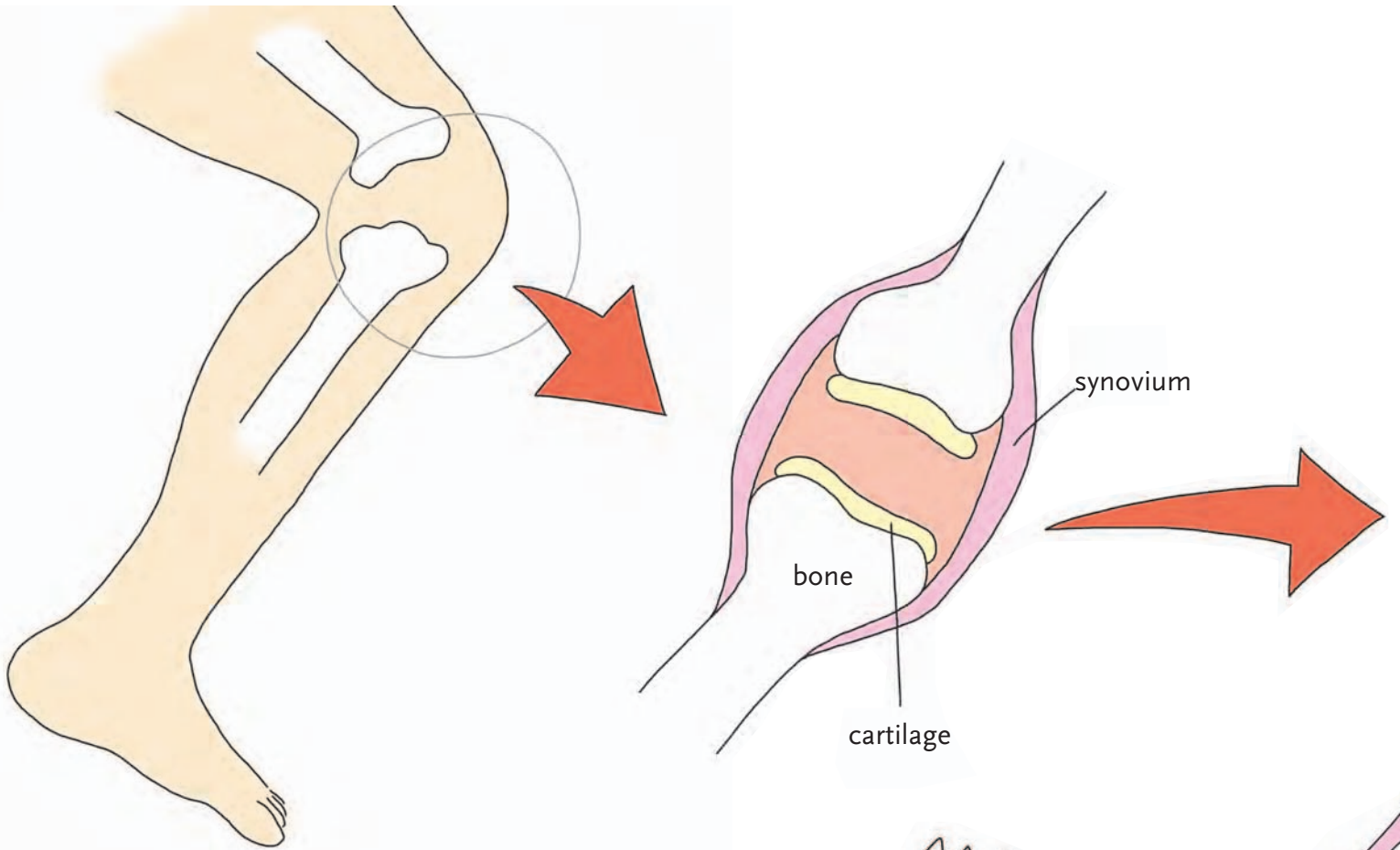
Moisture-producing gland damage

Look at all the diseases there are ...

Multiple organ damage

With that being the case, we currently treat autoimmune diseases with drugs that suppress the body's immune system entirely while trying to help the function of joints and organs that have been weakened by attack.

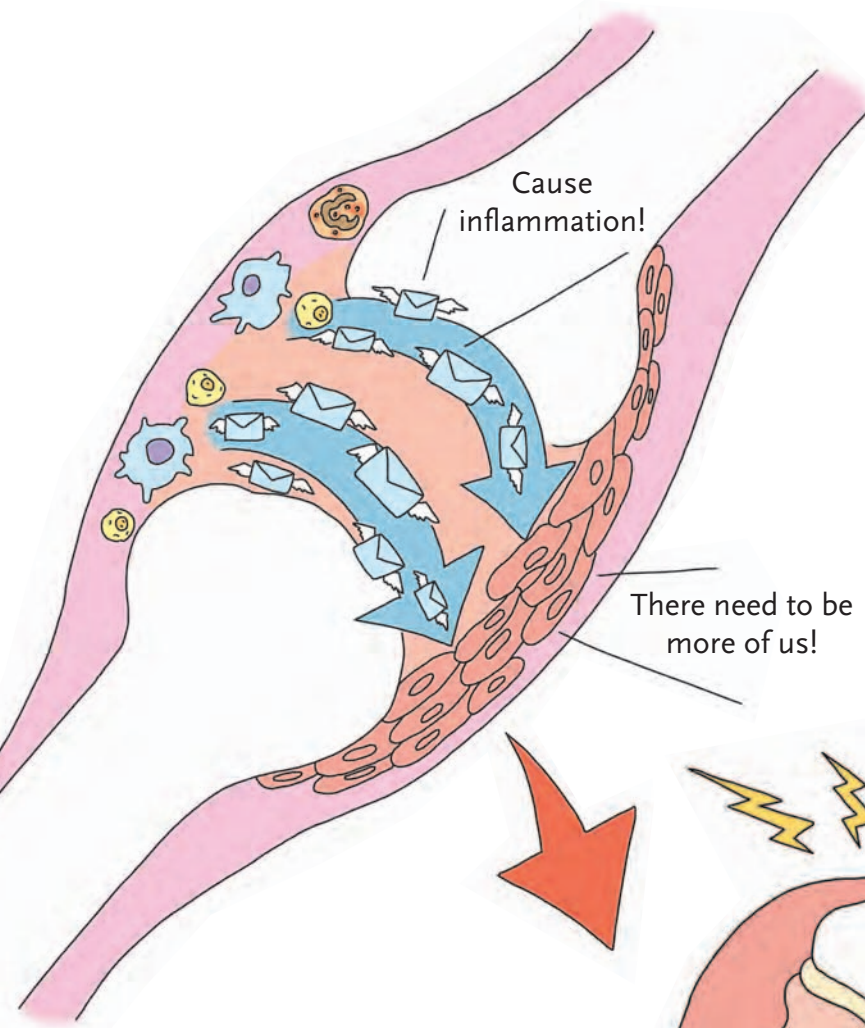
However, there are people for whom this treatment doesn't work or for whom the side effects, like a weakened immune system, increase the risk of infection. Clearly, developing new treatment methods is important.



## Rheumatoid arthritis and its treatment

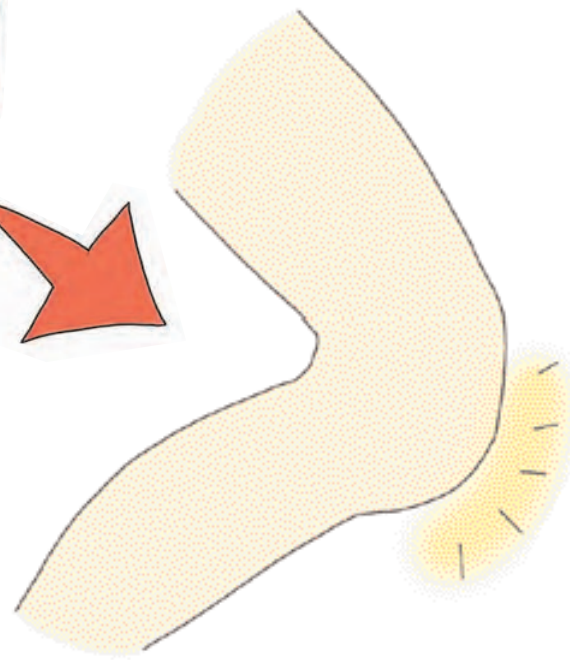
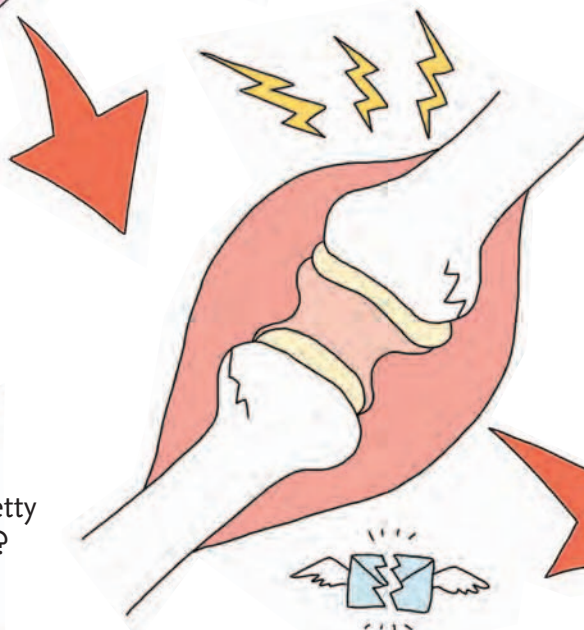
Rheumatoid arthritis is an autoimmune disease that makes the joints around the body ache, and if it is left untreated, it ends up destroying them. If a joint becomes infected, immune cells collect around it and produce a stream of cytokines with the order “Cause inflammation!” The swollen, red and throbbing joint that results is painful, but it is the result of a necessary response to an infection. If this attack, however, is directed against the joint itself, things become serious.

The synovium (si-no-vi-um) is a membrane that protects joints. If its cells receive cytokine messages with the order to cause inflammation, they spin into action making more copies. As the cells continue to multiply, the synovium begins to grow, and instead of protecting a joint, it starts to destroy the bone and cartilage, causing damage to the joint.



Based on their understanding of how the mechanism behind arthritis works, scientists have developed a new treatment, called **anti-cytokine therapy**, which stops the cytokines that cause inflammation from functioning.

In fact anti-cytokine therapy is already in use and has proved far more effective than any of the treatment methods that have been used until now.



### 3. Allergies are also Immune Reactions

## What is an allergy?



When spring arrives, do you start sneezing non-stop? And do your eyes get itchy? When you eat an egg do you break out in hives?

When you go hiking do your hands get itchy as soon as you touch the grass or trees? For the most part, these reactions are immune responses and are better known as allergies.

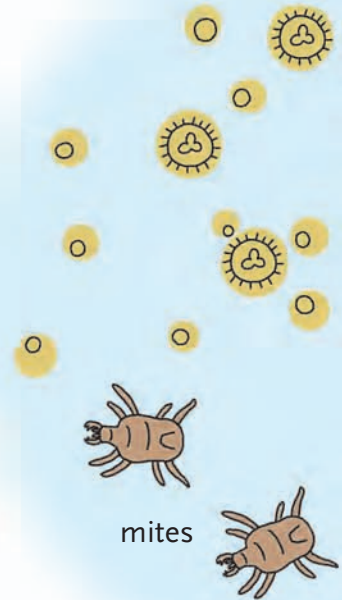
Things that cause allergies, like pollen, dust mites and food, are known as allergens. And when your immune cells launch an attack against things that are not generally harmful, you get an allergy.

Most allergies are caused by a group of immune cells called mast cells. Mast cells contain lots of chemicals that cause sneezing and inflammation. People with allergies have an antibody called IgE (I-G-E) stuck to the surface of their mast cells. When IgE comes across an allergen, the mast cell thinks that it has come across an enemy and in a flash it spews out all the chemicals it contains. The inflammation this action causes makes your skin turn red and itchy.

Other immune cells quickly come onto the scene, and, because they then fire off weapons normally meant for germs, your body hurts instead.

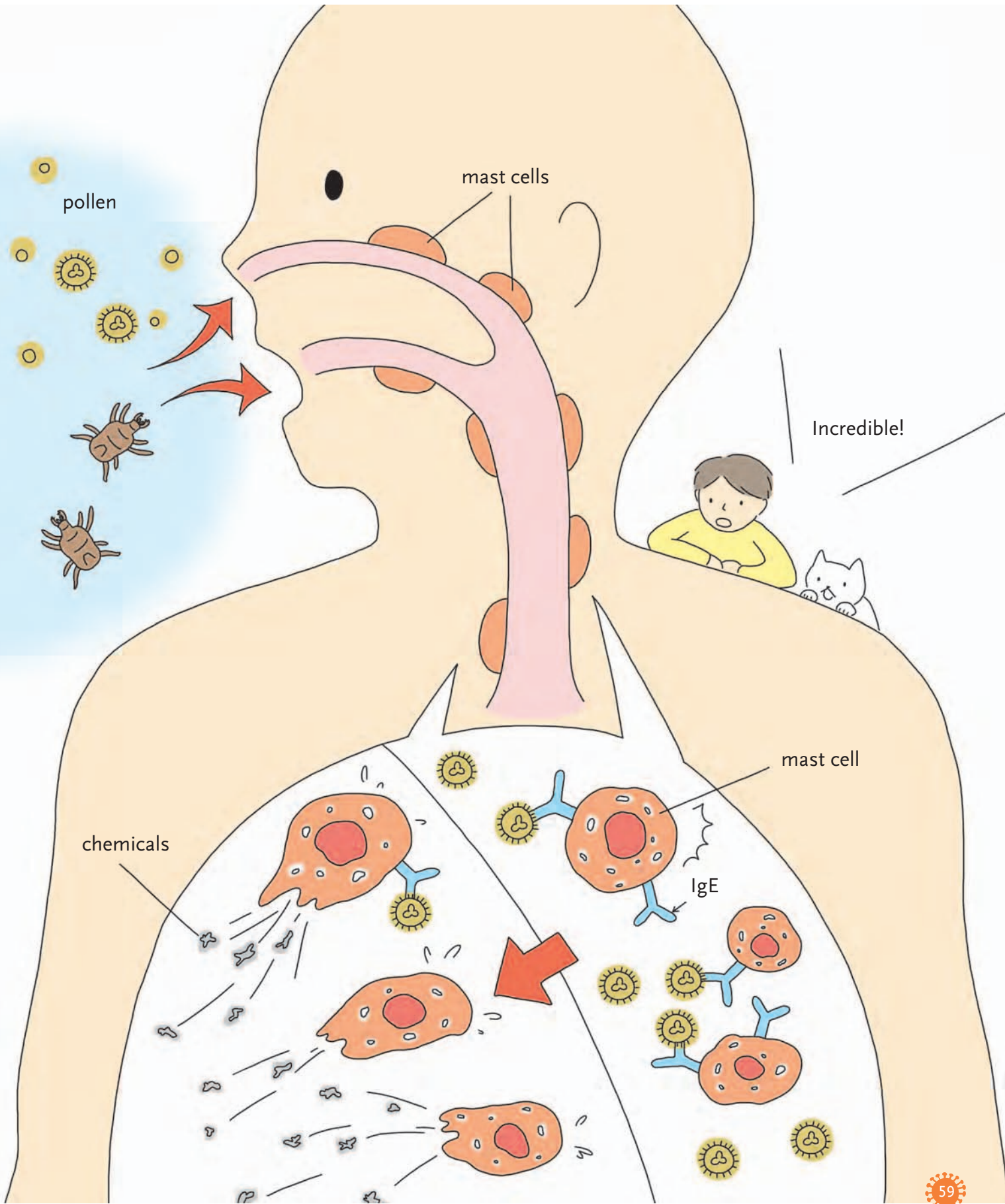
This is what you call an allergy.

allergens

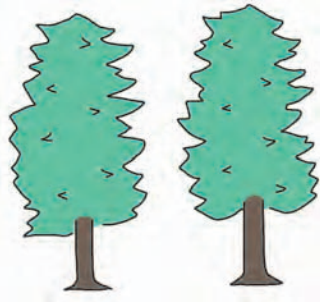


mites





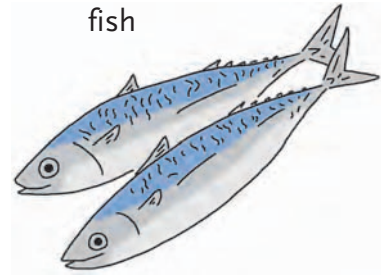
pollen



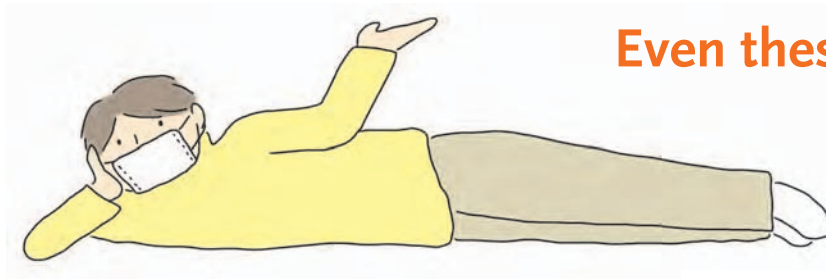
shellfish



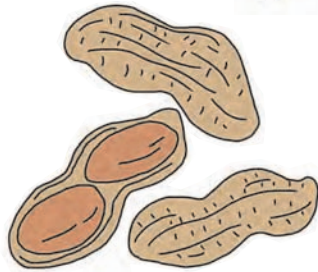
fish



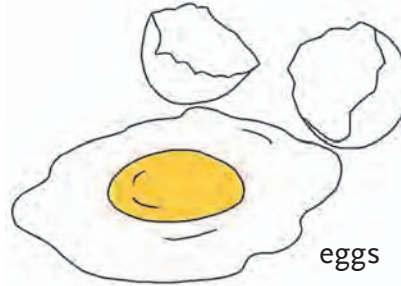
grains



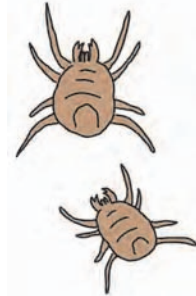
Even these items



peanuts



eggs



mites

What kinds of things are people allergic to?

The most common allergy known is probably hay fever caused by pollen from certain trees such as birch. Other common allergies are eczema, which makes your skin red and itchy, asthma, which makes you cough all the time, and food allergies.

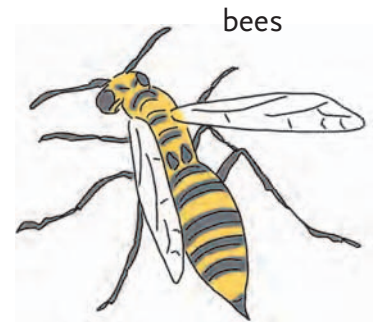
People can also be allergic to things like animal hair, dust mites, bee stings, or the metal from which jewellery is made. Even contact lenses or medicines like penicillin can cause an allergy.



animal hair

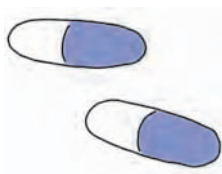
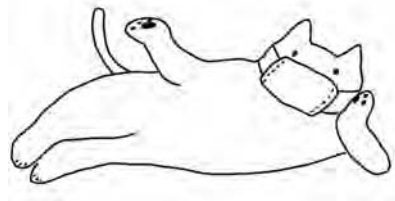


metals

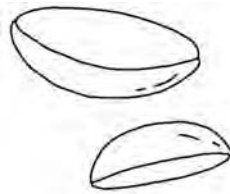


bees

## can cause allergies



penicillin



contact lenses



birch

You need to be particularly careful about things like nuts, bee stings and penicillin as they can cause an intense allergic reaction involving the whole body. This reaction is known as anaphylactic shock. The best way to protect yourself against allergic reactions like this from occurring, is to stop these allergens from entering your body.

Allergies can occur as soon as allergens enter your body (immediate-type reactions) or slightly later (delayed-type reactions).

For each type of reaction, the immune cell that plays the major role in the response differs, as does the mechanism used. Learning more about how these mechanisms differ is vital in order to develop therapies for treating allergies.

## How does asthma develop



Let's take a closer look at a common allergy among kids – asthma.

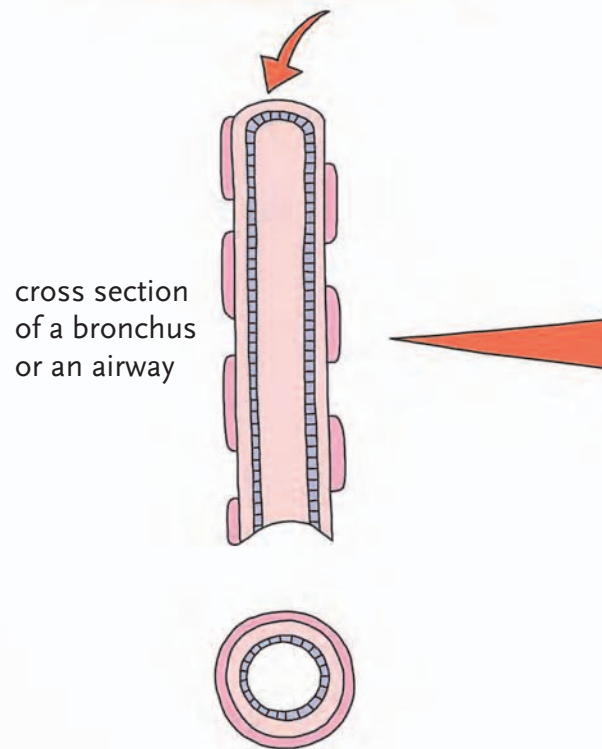
Asthma has many causes, but the most common is a reaction to dust mites. We doubt you've ever seen a mite, but if you were to use a microscope and take a good look at your mattress or the carpet at home ... bingo! You'd find thousands of them. That's right. There are allergens close to you, everywhere.



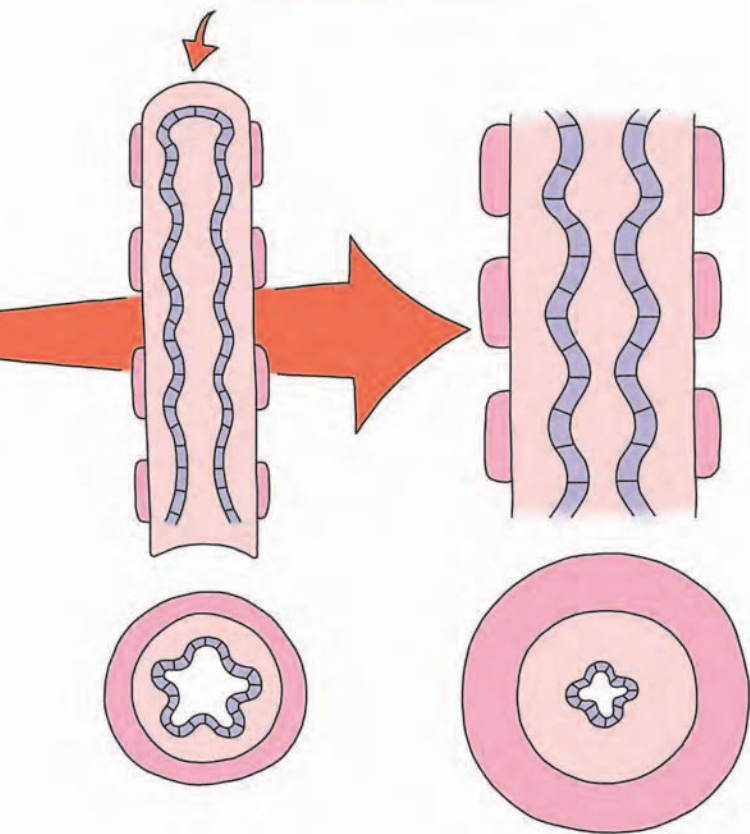
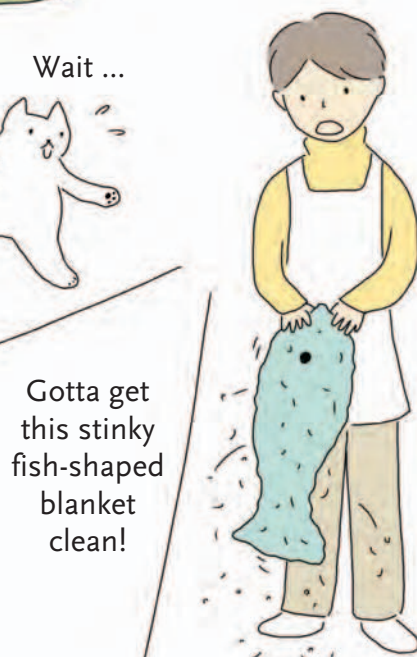
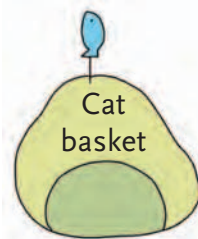
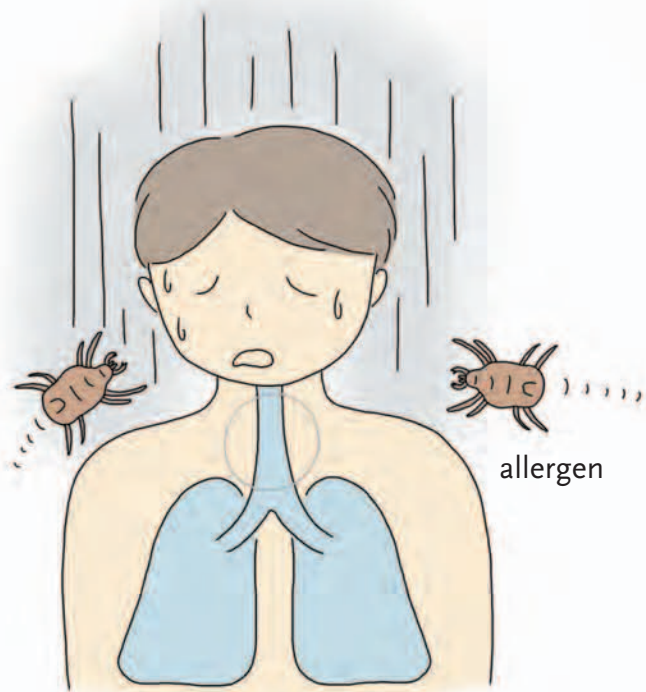
Now, if you had an allergic reaction from breathing in mites, everything would be fine as soon as you got a breath of mite-free, fresh air. What would happen, though, if you kept on breathing in air filled with mites?

Well, your airway would remain irritated as the immune cells that caused the inflammation continued to linger. Over time the shape of the airway would begin to change and the passages through which air flows would become narrower and narrower.

The technical term for this change in shape is **remodelling**. Once your airway remodels it is very difficult to return it to its normal shape. For that reason treatment is very complicated.







How your airways remodel

That is why it is critical to prevent re-modelling from happening. There are excellent drugs around to treat allergies called steroids. If you are allergic to dust mites, your doctor might treat you with these drugs. At the same time, she/he would probably advise you to get rid of any carpets or get a hypoallergenic mattress so that you reduce your exposure to mites.

## Can you cure hay fever?



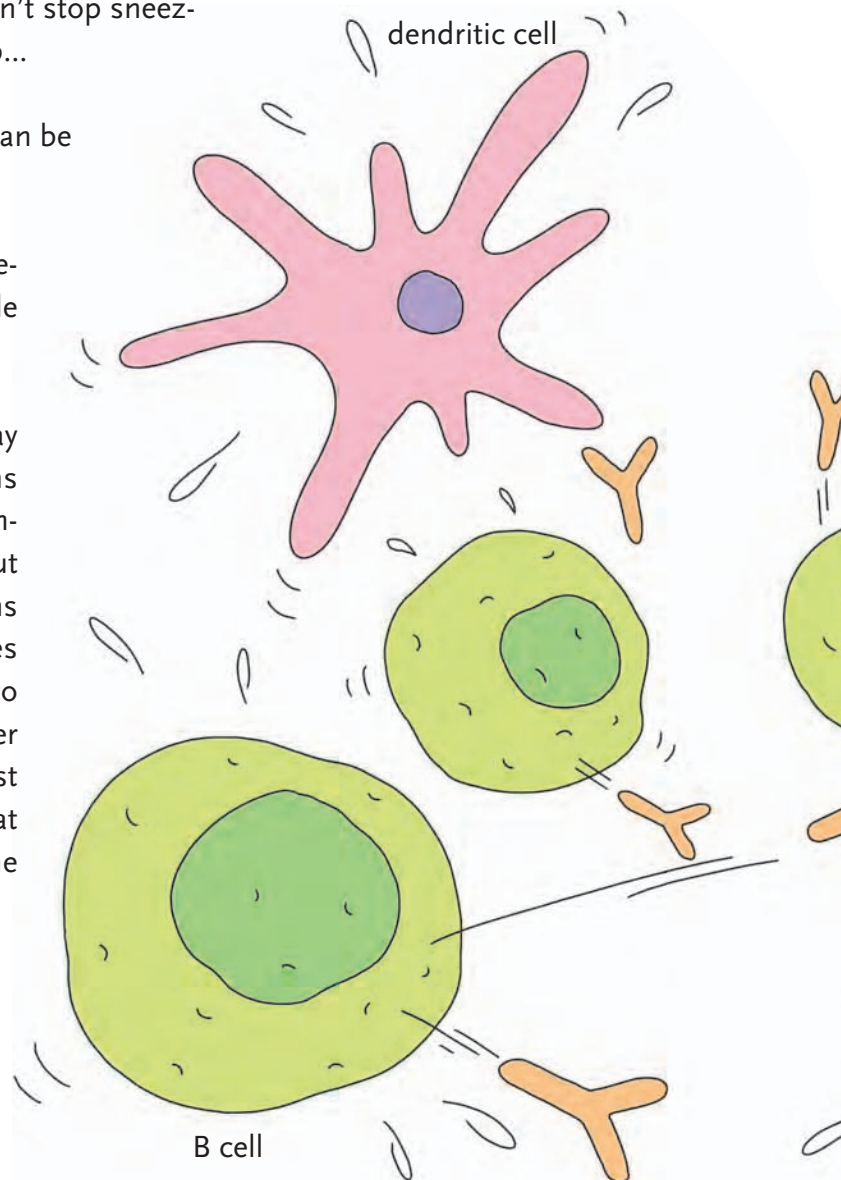
In spring flowers begin to bloom, your spirits begin to soar, and you feel in the mood to get out and about. And yet, as soon as you head outdoors, you can't stop sneezing and your nose starts running non-stop...

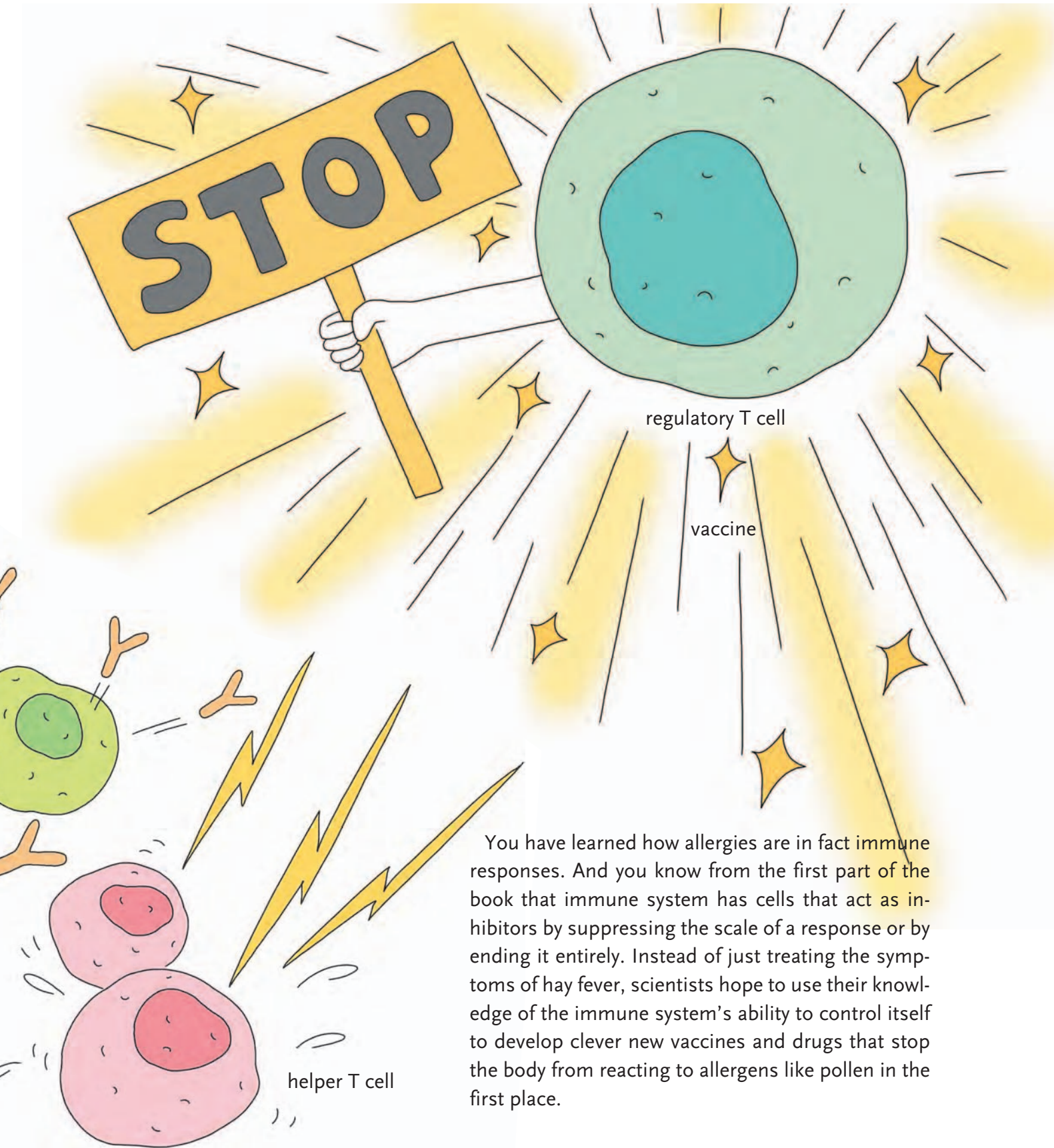
Not much fun, is it? Surely, something can be done about allergies caused by pollen?

In the world of immunology, many researchers are busy looking to help people who suffer from hay fever.

Until now, the drugs used to treat hay fever have focused on relieving symptoms by stopping mast cells from releasing chemicals. But let's take a moment to think about what that could mean. As the seasons change, the type of pollen in the air changes too. And generally people who are allergic to one type of pollen become allergic to other types of pollen over time. So treating just the symptoms of hay fever would mean that you could end up having to take medicine for about half of the year.

Can anything else be done instead?

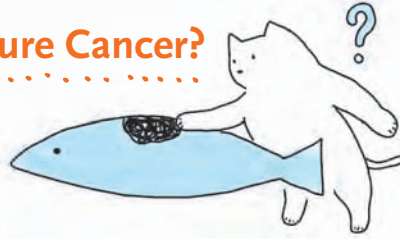




You have learned how allergies are in fact immune responses. And you know from the first part of the book that immune system has cells that act as inhibitors by suppressing the scale of a response or by ending it entirely. Instead of just treating the symptoms of hay fever, scientists hope to use their knowledge of the immune system's ability to control itself to develop clever new vaccines and drugs that stop the body from reacting to allergens like pollen in the first place.

## 4. Can Immunology be Used to Cure Cancer?

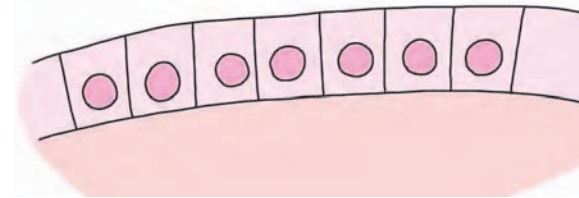
### What is cancer?



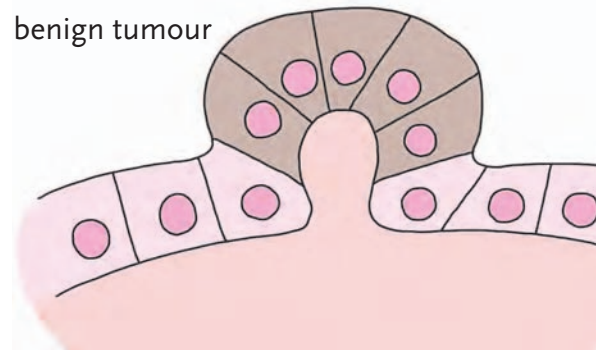
Normally each cell of the body communicates with its neighbours about whether to rest, multiply, work, or die, and in this way the cells collectively form healthy tissue.

Sometimes, however, a cell's genes get damaged and it can no longer make normal proteins. As a result, the cell isn't able to communicate with its neighbours properly. If this cell begins to multiply, it causes that part of the tissue where it is to grow into what we call a tumour. At this stage the tumour is benign, and will do you no harm.

normal tissue

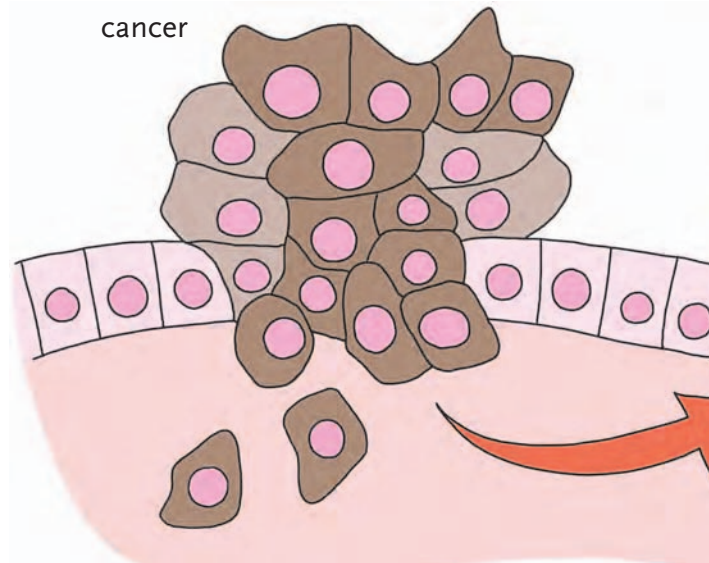


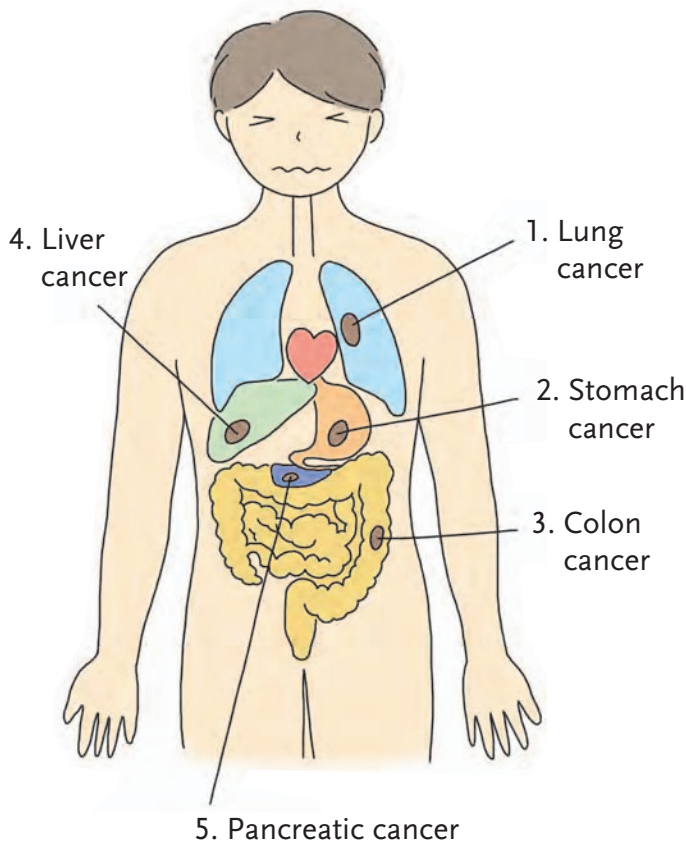
benign tumour



However, damaged cells can behave more roguishly. These rogue cells not only form tumours where they are, but they also invade surrounding tissues or they use the body's fluids to migrate to other parts of the body where they multiply to form new tumours (metastasis). These tumours are called cancer, and the cells that create them are dangerous because they can rob you of your life.

cancer





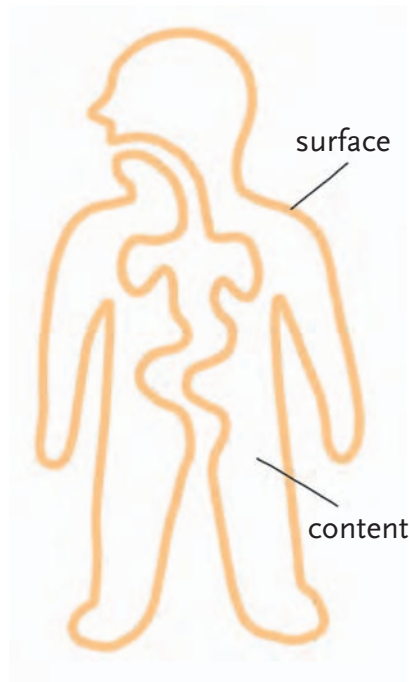
Cancer can occur in any tissue. The most common cancer in humans worldwide is lung cancer, followed by stomach, colon, liver and breast cancer.

People all around the world hope that researchers will one day be able to develop a cure for cancer.

## What kind of cancers are there?

Our body can be divided into what is considered the **surface** and what is considered the **content**. Although digestive organs like the stomach and intestine are inside the body, they are still considered a surface. Cancers formed from such 'surface' tissues are called carcinomas. Other cancers have different names depending on where they develop in the body. For example, cancer of the bones and muscles is called a sarcoma and cancer of the lymphocytes is called a lymphoma.

All these cancers invade tissue or spread through the body in similar ways but cancers formed from surface tissue (carcinomas) are more common and they occur more often in old people.



## How the immune system works against cancer



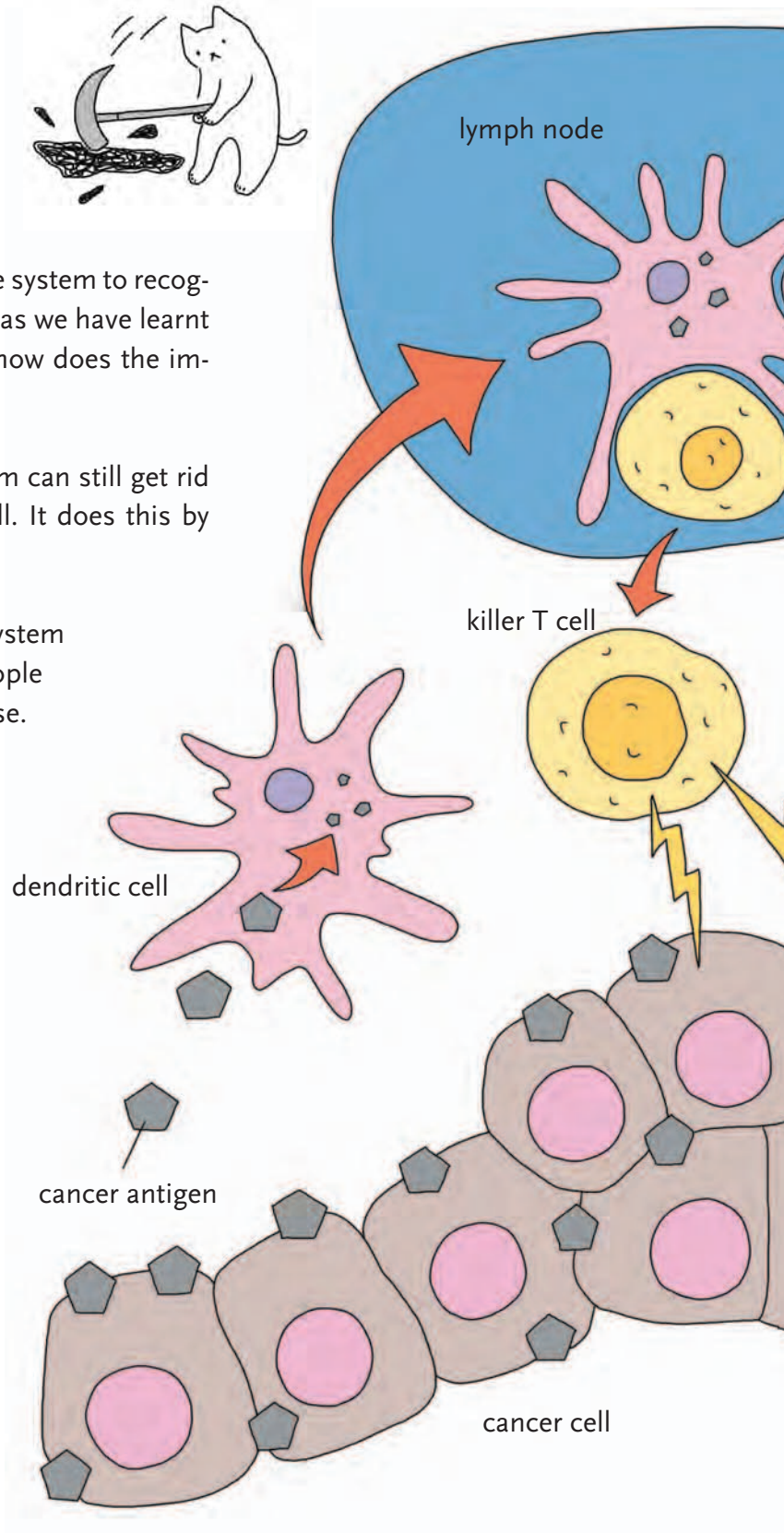
We know that the body uses the immune system to recognise what is foreign to it and expel it. But as we have learnt here, cancers are a part of the body. So how does the immune system deal with cancer?

If a cancer develops, the immune system can still get rid of it as long as the cancer remains small. It does this by means of **immunological surveillance**.

Let's take a look at how the immune system works, and learn why it can't guard people completely from getting ill with the disease.

As we explained a little earlier, cancer cells are a part of you but they behave differently from your other cells. They often produce damaged proteins or proteins not produced by other cells.

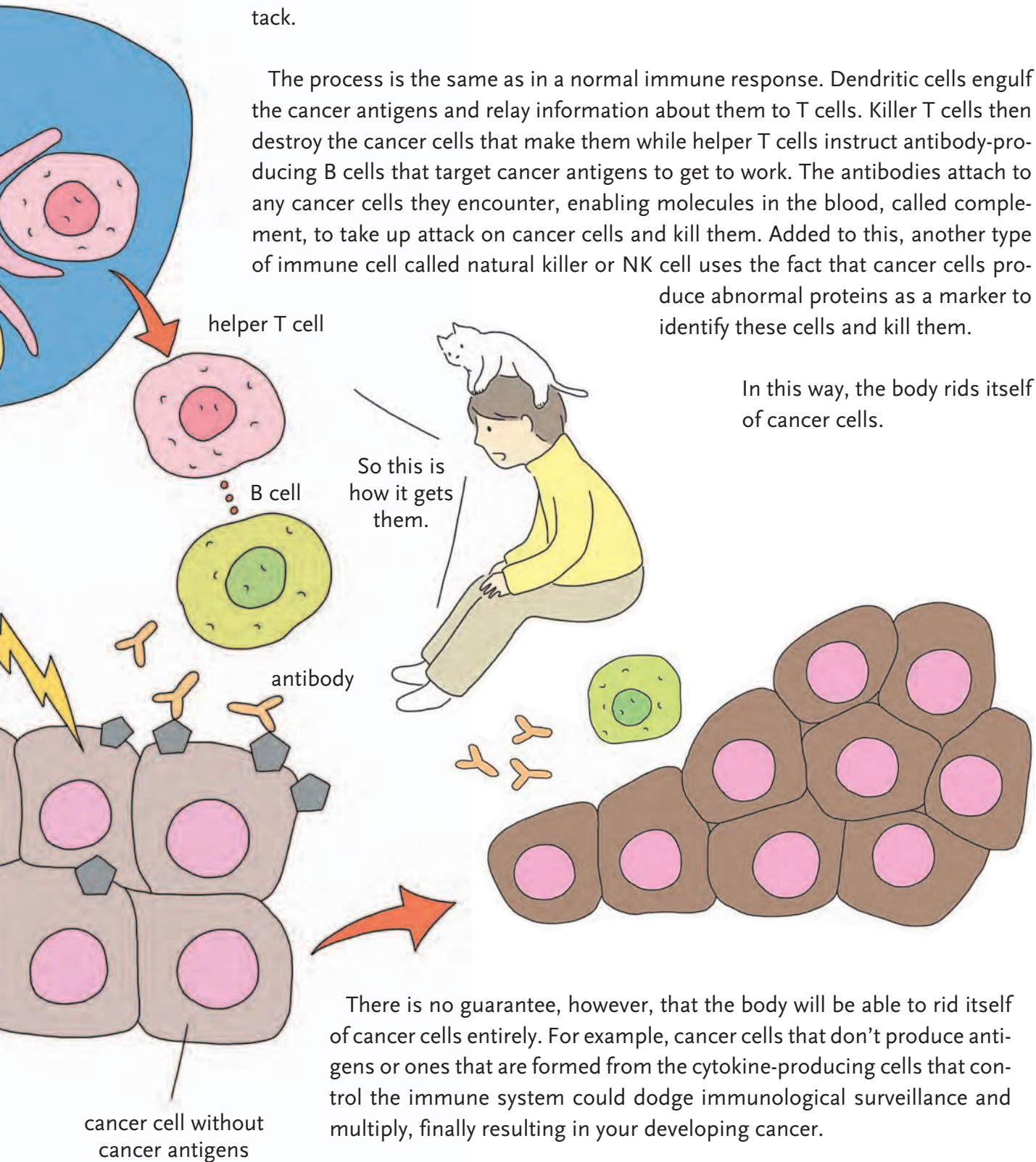
It is these proteins, often called tumour-associated or cancer antigens, that the immune system targets.



As soon as the immune system detects cancer antigens, its cells launch an attack.

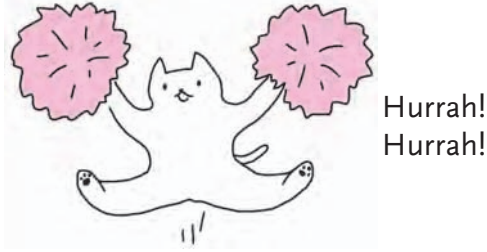
The process is the same as in a normal immune response. Dendritic cells engulf the cancer antigens and relay information about them to T cells. Killer T cells then destroy the cancer cells that make them while helper T cells instruct antibody-producing B cells that target cancer antigens to get to work. The antibodies attach to any cancer cells they encounter, enabling molecules in the blood, called complement, to take up attack on cancer cells and kill them. Added to this, another type of immune cell called natural killer or NK cell uses the fact that cancer cells produce abnormal proteins as a marker to identify these cells and kill them.

In this way, the body rids itself of cancer cells.



## Treating Cancer with Immunotherapy

Even the cancer cells that manage to avoid the body's immunological surveillance and multiply possess some sort of antigens. Evoking an immune response against these antigens could provide a means to cure cancer. This is exactly the goal of various clinical trials that are taking place now.

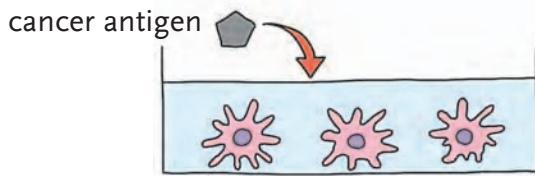


### Cancer Vaccine Therapy

Treatment with a combination of cancer antigens and agents that stimulate the immune system holds some promise as vaccines against cancer.

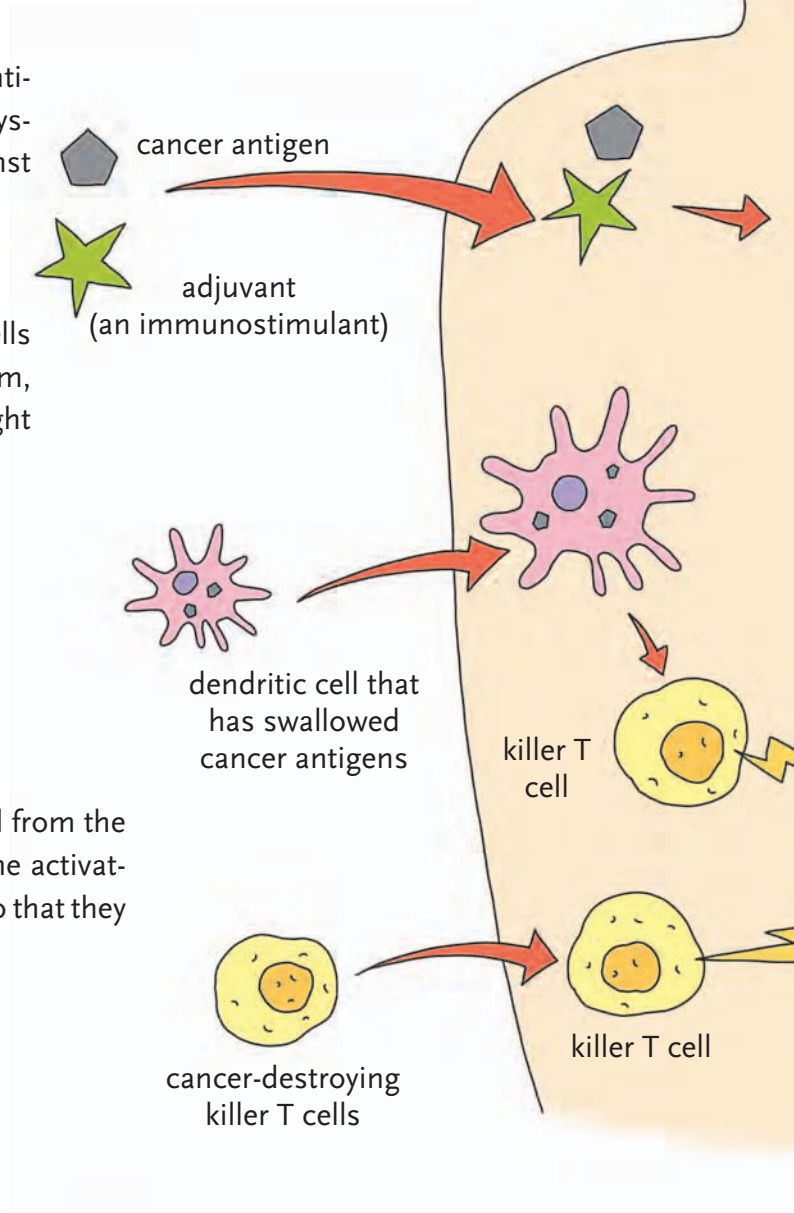
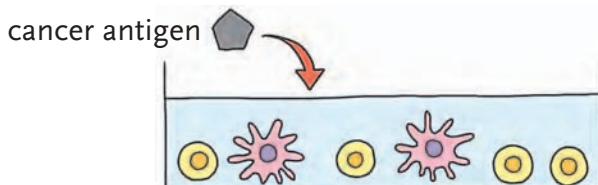
### Dendritic Cell Therapy

This method involves taking dendritic cells from the body, incorporating antigens into them, and then reintroducing them to the body to fight the cancer.

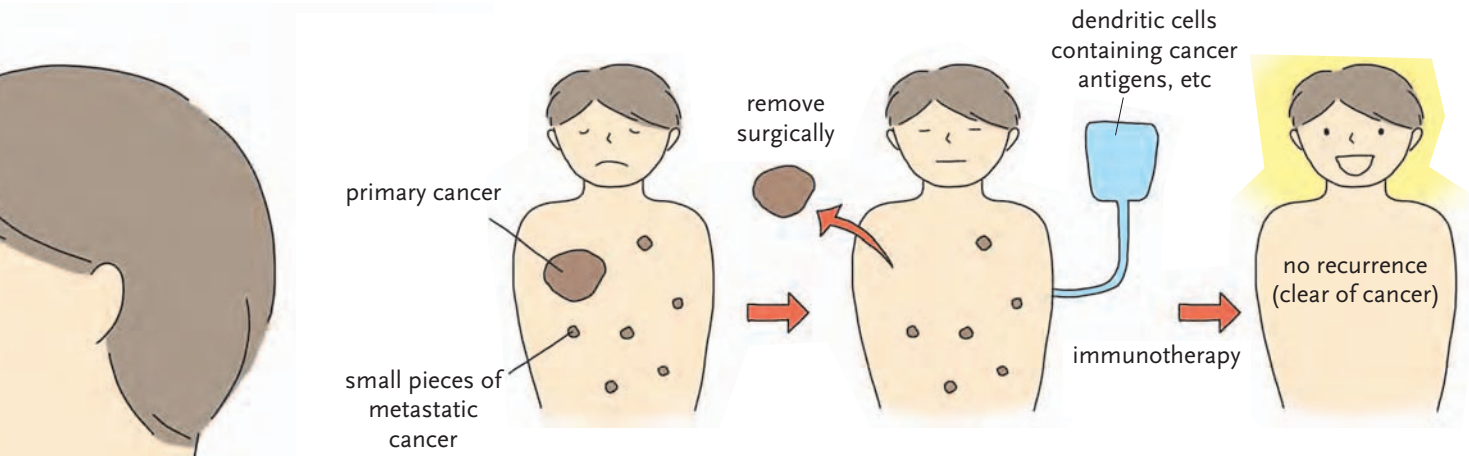


### T Cell Therapy

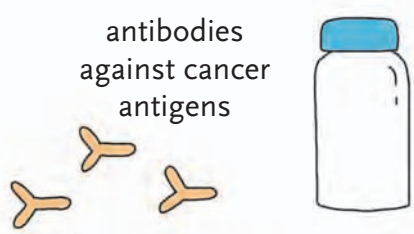
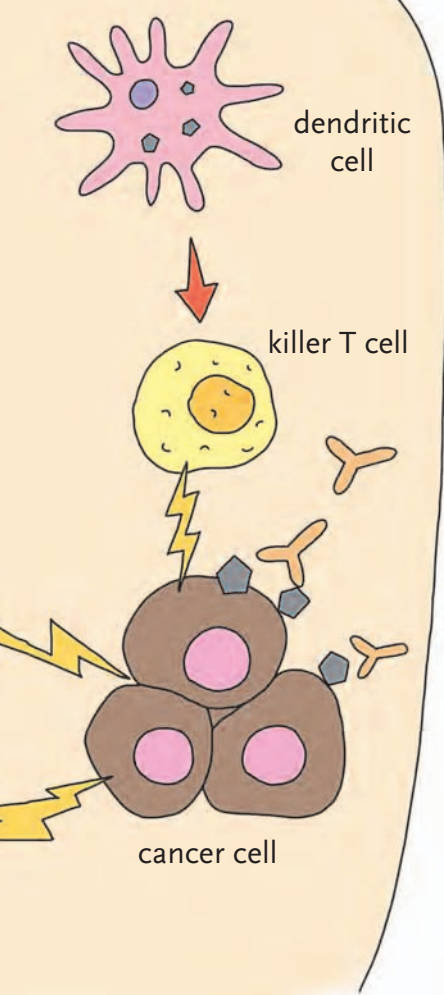
Killer T cells and dendritic cells are removed from the body and stimulated with cancer antigens. The activated killer T cells are then returned to the body so that they can attack the cancer.







Immunotherapy alone is not capable of destroying large cancers. These cancers need to be removed surgically first and then immunotherapy can be used to mop up any small pieces of metastatic cancer that remain. Used in this manner, the treatment promises to be an effective way of preventing cancers from recurring.



### Antibody Therapy

Antibody therapy involves treatment with antibodies that target cancer antigens.

Most immunotherapies are still at the experimental stage. Some types, however, such as antibody therapies for particular types of cancer, have already been put to practical use.

In the past, nothing could be done for patients whose cancer had spread around the body. However, immunotherapy holds the potential to help.

We believe the future holds a great deal of promise.



## Afterword to the Japanese Edition

This book forms a part of the Japanese Society for Immunology's outreach activities. We created it because we believe that our society should offer everyone, from primary school children to adults, a book that gives them easy access to the world of immunology. By combining a rigorous content with an approachable format, the aim was to give you a little taste of the subject in the hope that it would awaken your interest to explore it further.

The project began with the creation of exhibition panels and guide books for the *Meneki Fushigi Mirai* public outreach event organised by the Society last year. Putting together such a book for the general public is a rather new endeavour for us, but as we now have become a specialised non-profit organisation, building understanding and disseminating information has taken on a greater significance. In this sense, the publication of this book could be viewed as a test of how organisations like ours can find an appropriate role for themselves in today's world. We believe that such outreach activities also offer researchers a good opportunity to re-examine their public roles, too. If the publication of this book brings some benefit to society and our members and, by extension, helps to further the progress of immunology or the Society, then I would be very glad.

I would like to offer my heartfelt thanks to all members of the Japanese Society for Immunology beginning with the President, Dr Masayuki Miyasaka, for his kind guidance and support from the very inception of the project. Also, to Dr Hiroshi Kiyono, for his hard work in getting this project off the ground. And to the joint authors of this book, Dr Hiroshi Kawamoto, chair of the education promotion committee, and Dr Toshiaki Ohteki, Dr Noriko Sorimachi, Dr Shinsuke Taki, and Dr Sachiko Miyake, of the Committee on Public Affairs, for their dedicated work in deciding on the content, format and text of this book. In addition, I am very grateful to Ms Shinobu Yamashita of the Yodosha editing department for her patient handling of our continuous negotiations and Ms Tomoko Ishikawa, our illustrator, for her gracious response to our many detailed requests.

April 2008

*Japanese Society for Immunology*  
*Dr Yousuke Takahama*



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