

BACKGROUND INFORMATION

THE IMMUNE SYSTEM AND AUTOIMMUNE DISEASES

The Enemy Within our Bodies

Autoimmune diseases – when the body attacks itself

Acting as a protective shield, our immune system wards off invaders like bacteria and viruses. However, when it turns against the body's own tissue, the consequences are fatal: The result is autoimmune disease such as rheumatoid arthritis or multiple sclerosis.

Our immune system determines whether we stay healthy or get sick. If it is intact and in working order, this defence system activates the various immune cells that can rapidly and effectively overcome any threat from a viral or bacterial attack. Once the disease is overcome, the body pulls back the immune response and the defensive cells almost completely disappear from the circulatory system.

In some cases, however, the cells of our immune system get out of control. They turn against the body itself and begin to destroy healthy tissue. This results in autoimmune disease, which currently affects around four million people in Germany, often causing severe and life-threatening complications. As a rule, these diseases are incurable.

Autoimmune diseases affect about five percent of people living in industrialized nations; over 80 of these "autoaggressive" diseases are now recognized.¹ This family of diseases includes rheumatoid arthritis, as well as multiple sclerosis, psoriasis, and "juvenile" type1 diabetes. Recent research has also shown that autoimmune processes are implicated in cases of arteriosclerosis.²

For unexplained reasons, the incidence of autoimmune diseases worldwide is increasing. In industrialized nations they are the third most common diseases after cardiovascular disease and cancer. They are among the ten most common causes of death in women.³

In principle, autoimmune diseases can affect every organ in the human body, including the central nervous system and heart. Correspondingly,

► **What are Autoimmune Diseases?**

A large group of diseases characterized by an overactive immune system. In cases of autoimmune disease, the immune system is no longer able to differentiate between foreign structures and those of the body itself. The body then attacks its own tissue with immune cells and autoantibodies, which leads to inflammation and disrupted function of the affected organs (hence *auto*, Greek for *self*).

Organ-specific autoimmune diseases, which only affect one or a few organs (e.g. the pancreas in type 1 diabetes, the “juvenile” form of diabetes mellitus), are differentiated from systemic diseases (e.g. collagenoses), which affect the entire body.

the symptoms of these diseases vary greatly depending on which organs or structures in the body are attacked by the immune system, and on how far the disease has progressed. Common to all autoimmune diseases is the fatal malfunctioning of the immune system, which can no longer differentiate between a pathogenic invader and the tissues of its own body. The body becomes its own enemy.



Sebastian Kaulitzki, Fotolia

Typical of “true” arthritis of the joints: pain and swelling in the finger joints.

The joints under fire

This is what leads to the erroneous activation of T-cells in cases of rheumatoid arthritis or “true” arthritis, which affects around 800,000 people in Germany (up to 7 million sufferers in Europe).⁴

⁵ These defensive cells first attack the synovial membranes in the joints. Rheumatoid arthritis usually begins subtly, with swelling, pain, and problems with movement of the small and middle finger joints, as well as with unspecific symptoms like rapid fatigue and general weakness. If the disease is not stopped it leads to complete destruction of the joints. With periodic flare-ups, the disease marches inexorably onward, affecting more and more joints.

Not only bones, cartilage, and joints are affected, however: as the disease progresses, the heart, lungs, and nerve tissues are also attacked and eventually the whole body suffers. At the end of this path lie disability and dependency on long-term care. Afflicted individuals can then no longer care for themselves and become permanently dependent on outside help.

The inflammatory reaction involves a whole series of immune cells and messenger substances, with T-cells playing a special role. They are the ones that are improperly activated when the disease begins, triggering the inflammatory cascade. They trigger the activation of other inflammatory cells like monocytes, B-cells, and macrophages.

Subsequently, antibodies are formed and then inflammation-inducing messenger substances like interleukin-1 and tumour necrosis factor-alpha (TNF-alpha) are released, which augments the inflammation by releasing enzymes that destroy cartilage as well as other signalling molecules.

Like rheumatoid arthritis, the causes of multiple sclerosis, another autoimmune disease, are largely unknown. It is estimated that 2.5 million people are affected by multiple sclerosis



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Rheumatism also affects the heart: rheumatoid arthritis raises the risk of heart attack and stroke.

(MS) worldwide; in Germany, about 2,500 new cases are diagnosed annually, with women affected nearly twice as often as men.⁶

In MS, nerve cells and their sheathing are massively damaged and then destroyed by attacking self-destructive T-cells.^{7 8} As a consequence of the increasing damage, the nerve cells become less and less able to conduct electrical impulses. This leads to difficulty with movement, speech, and concentration, as well as numbness and paralysis.



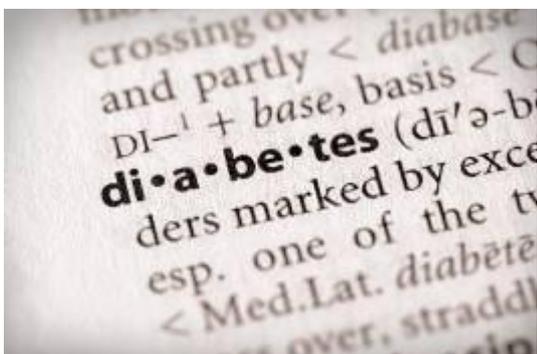
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Autoantibodies play a central role in autoimmune diseases.

MS usually begins in early adulthood between the ages of 20 and 40. Patients often feel a tingling sensation in their arms and legs, stumble more often, or have difficulty with their vision. This disease also progresses in stages. In severe cases, patients later suffer from severe disability; some must use a wheelchair. In multiple sclerosis, the autoreactive T-cells appear to be particularly aggressive in that they equally attack several different structures on the nerve cells. This was recently demonstrated by an international research team.⁹ They discovered something else as well: In

contrast to what was previously assumed, multiple sclerosis also involves interaction between autoaggressive T-cells and corresponding antibody-producing B-cells. It is the resulting host of B-cells whose antibody attacks trigger the full-blown disease.¹⁰

Mark Poprocki, Fotolia



Diabetes can also result from a malfunctioning immune system.

In type 1, or “juvenile”, diabetes, the body forms antibodies against its own structures. These antibodies are directed against the insulin-producing islet cells in the pancreas.

In Western Europe, about 0.3 percent of the population have type 1 diabetes. If these individuals are not treated properly, they may suffer loss of vision or disruption of the blood supply to the kidneys, leading ultimately to kidney failure. Another complication is

“diabetic foot”. Poor circulation results in poorly healing wounds and ulcers on the feet, which may eventually require amputation.

In addition to the personal suffering of the patients, the societal costs of treatment, rehabilitation, and early retirement due to autoimmune diseases are immense. Chronic inflammatory rheumatic diseases, with rheumatoid arthritis (RA) in the lead, are the most expensive diseases in all of medicine. In Germany alone, the expenses for the treatment of RA patients are estimated at 20 to 25 billion Euros.

A glimpse at the statistics shows that RA patients use health care services significantly more often than others. They visit their general practitioner at least twice as frequently and have three times as many appoint-

ments with specialists.¹¹ Direct expenses for visits to doctors, medication, hospital stays, and rehabilitation only make up one third of the total cost of the disease; two thirds are due to sick days and inability to work because of the disease. In the EU, inflammatory

► **Horror autotoxicus:**

From a historical point of view, the concept of autoimmune disease can be traced back to the German Nobel laureate Paul Ehrlich. At the end of the 19th century, he used the term *horror autotoxicus*, the fear of self-destruction, to indicate that the body’s immune system normally only attacks structures foreign to the body, leaving the body’s own tissue alone.

Paul Ehrlich injected the blood of a sheep into a goat. As a result, antibodies appeared in the blood of the goat, which were directed against the red blood cells of the sheep. Paul Ehrlich observed the same phenomenon when he injected the goat with blood of a different goat instead of the blood of a sheep. If he injected an animal with some of its own blood, this reaction did not occur and the blood cells were not destroyed.

diseases of the musculoskeletal system, such as rheumatoid arthritis, are the number one cause of early retirement, disability payments, and loss of employment.¹²

The social and economic consequences for the individual are drastic even in the first years of the disease. Within seven years, up to 40 percent of patients are no longer able to work in their profession.¹³ According to the WHO, this percentage rises significantly as rheumatoid arthritis progresses: ten years after onset of the disease, nearly 60 percent of RA patients are no longer able to work.¹⁴

Cause unknown

The causes for the different autoimmune diseases are as varied as their symptoms. Relatively little is known about the underlying mechanisms of the various diseases. However, at the centre of all of these disease processes lie the autoantibodies produced by the B-cells and the T-cells, which control the immune reaction through various signalling substances.

Antibodies are large protein molecules whose job is to rapidly identify and quickly fight off viruses, bacteria, and other attackers. They are the source of our body's "immunity" against pathogens. In autoimmune diseases, however, these antibodies are also directed against tissues of the body itself; they are then referred to as autoantibodies (*auto* is Greek for self, own). However some good does come with the bad, because these antibodies are often also used to diagnose the various autoimmune diseases.

This is the case for rheumatoid arthritis. The detection of ACPAs (ACPA stands for anti-citrullinated protein/peptide antibody) has become a standard procedure in the diagnosis of RA.^{15 16} The use of ACPAs allows physicians to predict the progression of the disease,^{17 18} and some of these autoantibodies also seem to be a good and objective measurement of disease activity and the effectiveness of treatment for rheumatoid arthritis.^{19 20}

If these early results from international studies are borne out, this would be a significant step forward for the diagnosis and treatment of rheumatoid arthritis, which is the most common autoimmune disease overall and affects nearly one percent of the world's population.

It is known that certain ACPAs are directly involved in the development of rheumatoid arthritis, in that they bind to components of the body's own articular cartilage.^{9 21} This attracts scavenger cells, which release inflammatory signal substances like tumour necrosis

factor-alpha and interleukins, as well as joint-degrading enzymes like elastase and other proteases. This causes a flare up of inflammation, which the body can no longer control. The result is fatal: the joints are eventually destroyed.

Genetic predisposition

It is now accepted that those affected by these diseases must be genetically predisposed toward them. Many autoimmune diseases occur more frequently within families, and in some families there is an increased tendency toward autoimmune diseases.²² For some autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis, the genetic component of the disease has already been scientifically verified.^{23 24 25}

In addition, environmental factors like eating habits and lifestyle always contribute to this predisposition to promote the development of an autoimmune disease. This means that not every “genetically burdened” individual is certain to become ill. As well as predisposition, there is generally a trigger. For

► The Immune System – a Glossary:

Autoimmune diseases are diseases in which the immune system erroneously attacks its own body.

Autoantibody: Due to a failure of the control system, the immune system considers the body’s own structures to be “foreign” and attempts to eliminate them by using antibodies. These antibodies are called autoantibodies (*auto* is Greek for self).

B-cells or **B-lymphocytes** are special defensive cells in our bodies. They are formed in the bone marrow and can produce antibodies once they become **plasma cells**.

Macrophages: These are the body’s “scavenger cells”. They clear and destroy cell debris. By presenting the cell fragments on their own surface, they activate other immune cells in the body.

Monocytes remove bacteria.

Proteases like elastase are protein-degrading enzymes. They may participate in the destruction of joints in rheumatoid arthritis, as well as other diseases.

TNF-alpha, tumour necrosis factor-alpha: Together with **interleukin-1**, it is one of the primary inflammatory signalling substances in the body. It promotes the release of numerous other messenger substances.

T-cells: Actually T-lymphocytes. These cells mature in the thymus, hence their name. They recognize antigens that are presented to them by other immune system cells.

Cytokines are inflammatory signalling substances, like the interleukins, and are released in immune reactions. They often have an inflammatory effect.

example, smoking increases the risk of developing rheumatoid arthritis when there is a familial predisposition toward the disease.²⁶ In addition, smoking RA patients require appreciably more medication, which increases the risk of side-effects.²⁷

Autoimmune disease causes the body to lose its capacity for immune tolerance, which makes it possible for a healthy body to differentiate between “foreign” substances and the body itself. Clearly, in these diseases the autoreactive cells, which are always also found

in healthy individuals, are excessively activated. Or they escape from the control of the immune system.^{28 29}

Finally, scientists have hypothesized that pathogens may be the culprits that lead the immune system astray. Attacks by bacteria and viruses activate the immune system and autoreactive immune cells through specific molecular structures called antigens. If these structures too closely resemble those of the body, it can no longer differentiate between the foreign bodies and itself. The body's own tissues are then targeted by the destructive



moonrun, Fotolia

Smoking raises the disease activity in patients with rheumatism.

immune response.

One very vivid example of how a normal and appropriate immune reaction can derail and render a normally harmless infection into a catastrophe for the body is rheumatic fever. In this disease – which is also an autoimmune disease – a bacterial streptococcal infection* leads first to tonsillitis, with a sore throat, or common scarlet fever.

If the infection is not completely cured, it can develop into the dreaded rheumatic fever weeks after the infection and long after the acute symptoms have disappeared. Because of their similarity to

the bacterial antigens, the body then directs its immune response toward the body's own structures.³⁰ The result is reddening of the skin or the inflammation of multiple joints, known as polyarthritis. As a result of this autoaggressive reaction against the body itself, there may be dangerous inflammation of the kidneys or heart valves with lasting effects.³¹ Thanks to antibiotics, rheumatic fever has now become rare in industrialized nations; however in threshold or developing countries it remains common. Even in the rural areas of some industrialized nations it is not uncommon.^{32 33}

Women affected more often

Most autoimmune diseases affect women significantly more often than men. One reason for this could be the different hormonal configuration in women. Hormonal fluctuations

* Streptococci, a genus of bacteria

may also play a role. For example, pregnancy can trigger an autoimmune disease or increase the gravity of an existing condition.

However, sometimes the reverse is true. Rheumatoid arthritis may improve during pregnancy, at least temporarily.³⁴ One of the reasons for this may be that the immune system generally significantly curbs its responses during pregnancy so that the unborn child, which is potentially “foreign”, does not become a target of the mother’s immune response. Consequentially, symptoms of RA return six to twelve weeks after birth. Such observations are clear indications that hormonal changes, the body’s constitution, or unusual immunological circumstances do have an influence on autoimmune diseases or may promote their development.

New treatments offer hope

Just as varied as the causes, symptoms, and clinical pictures of autoimmune diseases are the approaches to their treatment. Current treatments are often aimed at slowing progression of the disease as much as possible and alleviating acute symptoms. For many

autoimmune diseases, the current state of the art medications are immunosuppressives, including methotrexate, which is used for rheumatoid arthritis or psoriasis, or cortisone compounds. These medications mitigate the effects of the autoaggressive attacks on the body’s own tissues by reducing the activity of the immune system as a whole. This may cause the “good” parts of the immune system, which normally keep viruses, bacteria, or cancer cells in check, to be suppressed as well, making the patient more susceptible to the day-to-day attacks of pathogens.



Hannes Eichinger, Fotolia

A question of hormones: rheumatoid arthritis can temporarily improve during a pregnancy.

The latest research is thus aimed at the development of targeted drugs and techniques that only disable the overactive parts of the diseased immune system while leaving our body’s defences against bacteria, viruses, etc. intact. The autoimmune disease must be brought to a standstill, but not at the cost of the power and adaptability of the immune system. To this end, researchers are using tailored protein molecules known as biologicals. These

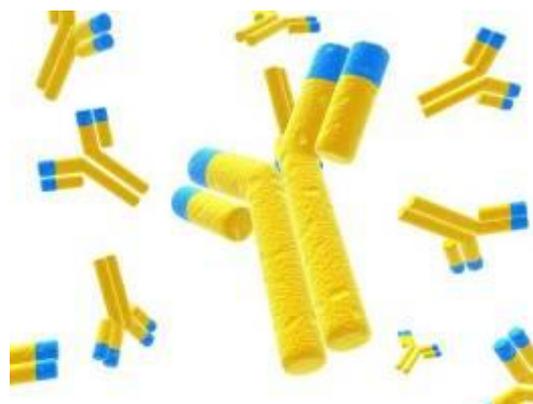
very specifically attack the disease processes by binding to specific tissues in the body and disabling parts of the immune system.

In this way, tumour necrosis factor-alpha can be bound by synthetically produced antibodies or soluble receptor molecules in such a way that it can no longer transmit its message to the immune cells. In a similar way, various interleukins, the messengers of the immune system, can be neutralized, interrupting the fatal immune cascade.

However, even the biologicals are not yet able to remove the source of the autoimmune disease.

The hope is that this goal will be met with new approaches like stem cell therapy or immune tolerance therapy. These techniques, which are currently the subject of intensive research in laboratories, promise to reprogram the malfunctioning

immune system. They should make it possible for a short period of medical treatment to not just bring the disease to a standstill, but to bring about a permanent cure. However, that is currently (still) science fiction.



Sebastian Kaulitzki, Fotolia

Modern treatments use synthetically produced antibodies.

Links:

www.rheuma-liga.de – Bulletin 6.12: Pregnancy [Merkblatt 6.12: Schwangerschaft]. German. – [LinkOut](#)
www.dmsg.de – German Multiple Sclerosis Association [Deutsche Multiple Sklerose Gesellschaft]. German.
www.autoimmun.org – German Society for Autoimmune Diseases. German.
www.drfz.de – German Arthritis Research Centre Berlin [Deutsches Rheuma-Forschungszentrum Berlin].

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