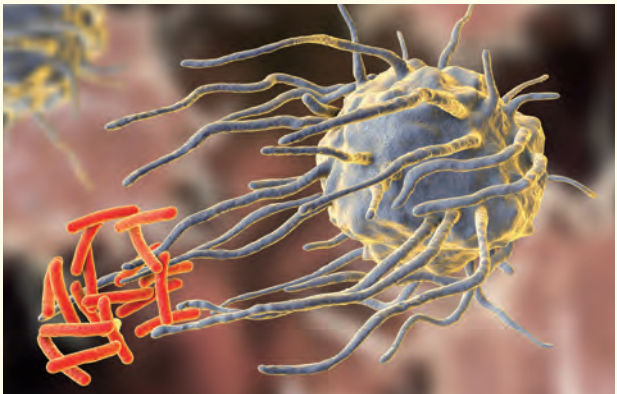
PICOWO-SERIE PART 10

Martine F. Delfos
In collaboration with Juliette van Gijsel

Autoimmune Reactions and the Immune System



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Martine F. Delfos, PhD

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Content

Leonardo da Vinci (1452-1519) on science:

Knowledge which is the issue of experience is termed *mechanical*; that which is born and ends in the mind is termed *scientific*; that which issues from science and ends in manual work is termed *semi-mechanical*. But I consider vain and full of error that science which is not the offspring of experience, mother of all certitude, and which does not result in established experience, that is to say, whose origin, middle and end do not pass through any of the five senses. And if we doubt of everything we perceive by the senses, should we not doubt much more of what is contrary to the senses, such as the existence of God and of the soul, and similar matters constantly under dispute and contention?

And it is truly the case that where reason is lacking it is supplemented by noise, which never happens in matters of certainty. On account of this we will say that where there is noise there is no true science, because truth has one end only, which, when it is made known, eternally silences controversy, and should controversy come to life again, it is lying and confused knowledge which is reborn, and not certainty.

But true science is that which has penetrated into the senses through experience and silenced the tongue of the disputers, and which does not feed those who investigate with dreams, but proceeds from the basis of primary truths and established principles successively and by true sequence to the end…

Da Vinci, L. *Collected Works of Leonardo da Vinci, The Notebooks of Leonardo da Vinci; 9 True science based on the Testimony of the Senses*. p. 10-14; Pergamon Media.

Foreword Dick Swaab

When I was a medical student taking my first steps into the field of brain research, over 50 years ago, psychology and psychiatry were 'brainless'; the practitioners of these disciplines were not interested in the brain and were convinced that patients should receive very personal psychological or psychiatric treatment. They considered scientific research in relation to the disorder or the analytical therapy to be meaningless. In the same period, neuroscience was still 'mindless'. In recent decades, neuroscience has gained momentum, and more and more researchers who used to focus either on the brain or on the environment, or studied either the brain or the mind, are now building bridges between these two worlds.

Martine Delfos is one of those exceptional people who, at a very early stage in her career, successfully started to build bridges between the fields of psychology, medicine and neuroscience. For a long time she was one of the few psychologists truly interested in neurobiology. She is a scientist by trade but corroborates her scientific insights as a clinical psychologist and a therapist. As she says: "A scientist needs to be confronted with his mistakes through real life". Martine contacts me a couple of times a year with in-depth biomedical questions. Her questions always concern a very different topic, are never easy to answer, and are always original and force me to look at a problem in a new way. The latest fruit of her labours is the present volume 10 of her PICOWO-series on 'Autoimmune Reactions and the Immune System.'

The classic concept of the relationship between these two immensely complex systems, Autoimmune and Immune, is that the immune system defends our body against the dangers of the outside world and our brain is protected through the blood-brain-barrier. The autoimmune system was classically considered a mistake of the immune system, attacking the body itself.

However, recent research has shown that the brain and the rest of the body belonging together, effectively share one immune system and autoimmune reactions could sometimes be a protection. Martine Delfos suggests that the autoimmune system could protect the body against malfunctioning of the body and against the effects of viruses.

The brain and the immune system are intimately intertwined in many ways. In the first place, the autonomic nervous system has a firm control of the immune system. A number of principal autonomic neurotransmitters, such as acetylcholine and noradrenaline, are involved in immune regulation in the context of inflammation through various molecular pathways.

Cytokines and interleukins, typical inflammatory mediators – immune mediators, affect many brain functions, as is clear in the case of cytokine-related cancer and even in the case of hypothalamic regulation of reproduction. In addition, it has become clear that neurons, too, are producing these inflammatory mediators themselves.

Complex systems can easily become disrupted, and this holds for both the brain and the immune system, and certainly for their interactions. Recently it has become clear that the immune system too, in its autoimmune function, can attack all types of molecules, cells and synapses in the brain, and cause neuropsychiatric disorders.

It is amazing that my interest in this topic was raised a long time ago by a patient with anorexia nervosa, the same disorder that triggered Martine Delfos' interest, as she says in the epilogue. Anorexia nervosa is one of the most serious psychiatric disorders, with a high suicide risk. For a long time its cause was thought to be purely psychological in nature, and this directed the measures that were taken. For instance, the French parliament drafted legislation which made glorifying anorexia a punishable crime. The bill in question did not just target the skeletally thin models in the fashion world, but also the 'pro-ana' websites that a French minister claimed were disseminating 'messages of death'. Also, the French fashion industry signed a charter in which it undertook to promote healthy body images and to stop using ultra-skinny models. The British doctors' association claimed the existence of a link between abnormally thin models and the onset of eating disorders in others. And in the Netherlands there were newspaper reports of a 16-year-old girl with anorexia weighing only 21 kg being expelled from secondary school. People suddenly seemed to buy into the myth that you can 'catch' anorexia by seeing it, rather in the way that homosexuality was previously regarded – completely erroneously of course – as a contagious condition. However, all the symptoms of anorexia indicate that it is a disease of the hypothalamus and I lean towards the theory that it is an autoimmune process, just as Martine Delfos does and shows in her book. Antibodies directed against chemical messengers in the hypothalamus involved in regulat-

ing eating and metabolism have indeed been found in the blood of anorexia patients. A girl who was treated for her asthma with a corticosteroid spray did so well that she was told she could stop taking it. She subsequently developed anorexia nervosa, as if an immune process causing this disease had been suppressed by the anti-inflammatory asthma spray treatment. Autoimmune neurology is now becoming one of the most exciting and rapidly evolving fields in contemporary neurology. It represents a new subspecialty driven mainly by the discovery of novel neural (neuronal or glial)-specific autoantibodies and their target antigens. Autoimmune neurological disorders may affect every level of the nervous system, from cortex (epilepsy, encephalopathy, dementia) to hypothalamus (narcolepsy) and muscle (myasthenia gravis, autoimmune myositis), and are increasingly recognized as important and often treatable causes of neurological disease. Recently, evidence has been collected that shows that autoimmune processes may also play a role in psychiatric disorders such as schizophrenia, autism and bipolar disorder. Autoimmune neuropsychiatric disorders transcend traditional borders of specialties and will rapidly become more important in the coming years.

The endeavour of Martine Delfos in her book on the immune system is to develop an insightful schema of the immune system with its subsystems, which did not exist to date. And she develops this further, discovering probably the deeper function of the immune system for the body as a whole, not only in fighting, defending and protecting but as the ingenious orchestrating system of the body. She proposes a fourth pathway of complement activation: the melatonin pathway.

I congratulate Martine Delfos and her collaborator Juliette van Gijsel with this timely volume on the many aspects of the pathways involved in the brain-immune interactions in health and disease.

Dick F. Swaab MD PhD
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1 Introduction

If it was not for medical science, I would be a widow. Life and death are the very scope of medicine. Everything starts with birth. The carrying of and giving birth to children has developed and been surrounded by so much knowledge and skill that child death in the second half of the twentieth century is vastly reduced in Western cultures; for the same reason the mortality rate of women in childbirth has also reduced spectacularly (Meslé and Vallin, 1989).

Certainly since the Middle Ages we have covered a lot of (medical) ground, gathered an enormous quantity of knowledge and as a result we have so much knowledge that we reach the point of being able to connect the available knowledge, bring it together. This would foster a deeper insight of the human body and be helpful to develop an overview of the body. The connecting of knowledge is what this book is about.

The human body is a very complex organism which we are only beginning to understand. So much has still to be discovered. In medicine the human body presents quite a challenge, and has done so for centuries. Challenges are there to be met, which medical science did and continues to do.

We continue to discover the body, unravelling it from outside to inside, from visible with the eye to nano-small. With heLa-cells we try to discover bits from the workings within the body and about the interaction of body tissues with the surrounding world. The instruments used to examine the body have also undergone a process of becoming more and more refined. The invention of the microscope is still very useful, but new possibilities such as MRI devices are far beyond the imagination of those who invented the microscope. We often try to understand the human body by examining it through analogies, such as with animals, when we dare not subject the human body to risks that could make people suffer and might even kill them. So we learn from mice and man, struggling patiently to progress in knowledge, which in medicine means a better life for humankind and even means life itself.

Medical science is about the human body and an analogy with geography is relevant. We mapped the world thoroughly and we honour the famous explorers, but nevertheless we sometimes suddenly discover a place in the world, which existence was still unknown to us. This also happens with the body; its enormous diversity has not been totally mapped yet What we can do with the

brain is impressive, but the brain itself has not yet been fully mapped. In 2015 the presence of the *immune system* with vessels and *lymph nodes* in the brain was discovered (Louveau et al., 2015). A totally new area of medical science was disclosed and a deeper insight of the immune system was made possible.

One of the important elements of progress in medical science and of science in general is *discovery*. What it means is that many breakthroughs in (medical) science are discoveries that happen accidentally, opening totally new areas.

Another road to progress is *specialisation* in the functioning and malfunctioning of every part or system of the body. Specialisation is crucial for medical science.

In medical science most of the progress comes mainly from three sources with their multiple specialisations. *First* is the specific knowledge about a part or a system of the body. *Second* the knowledge to assess whether some part or system of the body is malfunctioning or defective, 'broken'. *Third* is how to repair what is not functioning well or no longer functioning well or is even absent. But there are other sources of progress. Naturally, after discovering a part of the body and starting to understand its function and malfunctioning, the next step would be to focus on the prevention of malfunctioning of that part of the body. This presents a *fourth* source still in full development which is *preventive medicine*. Then there is a *fifth* source about the interactions between all parts and systems of the body together, which is slowly developing.

Preventive medicine is still just beginning to advance, because true prevention would need a perspective not only on a part or system but on the organism as a whole, which is not yet within reach but we reach the point of being able to connect existing knowledge, leading to more of an overview.

Of course this is not everything that medicine encompasses, but it makes clear that much in medical science is knowledge about more or less separate parts, organised in medical specialisations. We do not yet know much about the interactions between the parts and systems of the body as a whole. This will be the challenge of this century and probably of the next centuries.

Progress in medical science requires time because precision – a sine qua non in medical science – requires time. When the genes and DNA were discovered it took many decades to map the genome. Medical science is not yet so far advanced that the paradigm of medicine could shift towards the perspective of the body as a whole. We build our insight about the body from knowledge of the different body parts and systems of the body. All those parts are already so many, engendering so much meticulous scientific work that the interactions

between them still are beyond our imagination and mostly beyond our medical endeavour.

Looking at the perspective of the beginning of mankind the progress in medical science is incredibly impressive, as much about life as about death. The life span has extended with people reaching a higher age because health issues such as hygiene and food, are increasingly being addressed. We further evolved towards extending life through refining the knowledge about repairing malfunctioning parts of the body and facing external threats.

Preventive medicine is great and really life-influencing, but it is structurally counteracted by the course of time which creates time and again new challenges to be faced. We conquered the plague and many other big diseases of the past, but only recently we had to face HIV (Human Immunodeficiency Virus) which we conquered more or less, that is we understand the way it is transmitted and we treat the consequences. The threat of HIV as such – the virus – has not yet been overcome. We are progressing seriously in trying to face cancer, the many cancers the body can yield. We have mapped the genome, which enabled us to make progress in understanding gene mutation, and without doubt this knowledge will create new problems. We can push life to extend it a little bit longer, but we ask ourselves whether this extended life has a quality we should pursue. Naturally, medical ethics has to try to catch up with medical progress.

We know that the body is a whole, functions as a whole, is born as a whole, gets older as a whole and dies as a whole. The person itself is always a whole, never only a body part or a collection of parts and systems, and all parts are interacting together all the time in order to form that whole, just as one gigantic orchestra. Interpretation of a problem in the body not only depends on the function of the concerned part but also on its role in interaction with the rest of the body. The construction of building the overview is in full process.

1.1 Induction and deduction

As Leonardo da Vinci (see p. 8) made very clear we need mind *and* experience through the senses to establish what he calls 'true science'. We have two methodological paths that can help constructing the whole: *induction* and *deduction*. Induction fosters conclusions based on gathered evidence and deduction enables us to connect the already gathered facts which in turn fosters developing theories with testable hypotheses.

The primordial way to gain progress in medical science has always been induction, thus building knowledge from what we see, what we discover and to develop that knowledge further step by step from a *bottom-up process*. To be able to develop an overview one has to switch from induction to deduction and the other way around. Induction is helpful to prove gathered facts. An overview can more easily be gained by deduction, connecting knowledge upon some proven elements – gathered in a bottom-up way – and discover new elements through generating hypotheses, a *top-down process*. Neither pure induction nor pure deduction is possible, they need each other.

The process of *induction* is building from facts to a conclusion and further on to a theory. But that would not really be a theory, because induction is based on facts and this does not easily progress into a theory which by definition is based not only on facts but on logical interactions with logical hypotheses. Gathering facts is fundamental for induction and the inductive process is necessary for deduction. The problem is you never know when you have gathered all the necessary facts that lead to sound conclusions. Every conclusion is as broad as the collection of facts allows it to be. Support for a conclusion is gained by repeatedly gathering the same facts, which we call *replication* in research.

In this context it is interesting to note what Leonardo da Vinci said about replication. He dissected some ten bodies to be able to find the course of a vein, and explained: *it was necessary to proceed with several bodies by degrees, until I came to an end and had a complete knowledge; this I repeated twice, to learn the differences* (The Collected Works of Leonardo da Vinci, *Anatomy*, page 2-4 of 8', p. xi. 4-6). He started by working hard to attain *knowledge*, insight, understanding and he used *replication* to find the *differences*, not to find the *similarities*. It is by deeply understanding, by true knowledge that we can discover what the – more superficial – differences are.

In the process of replication a conclusion can be falsified by new facts that were not present among the already existing facts the conclusion was based upon. Because of the new facts the conclusion has to be adapted and thus insight grows into knowledge. We speak of *evidence-based* as the process by which we attain certainty from gathering facts and replication of the facts. In this way we have evidence from several inductive processes of one element which plays a role in different parts of the body. We do not attain certainty this way, because for that we would need the different parts to be embedded in a fitting theory.

Let us take a hormone as an example; at a later stage we will explore this further with the hormone melatonin. A hormone has a scientific starting point

in its *discovery*. The discovered hormone has been found in a certain *context* where it can be shown to play a *role*. By induction with gathering similar facts in that same context a conclusion can be formed about the role of that hormone in a certain context. Through this conclusion the role of that hormone is then attributed to that context. Later another context could be found where the hormone also plays a role and so the process of discovery goes on. The facts of induction are unilateral: they have been proven to exist. Each inductive process can lead to a specific *conclusion*. With respect to one hormone many conclusions can exist before we can begin to form an overview, a theory, in which case we need deduction.

The process of *deduction* is building a theory from different already established facts which seem to be related in one way or another, without yet understanding how. The theory is a general picture that encompasses many more facts than those on which it is based, a very broad spectrum of facts with specific interrelations. These facts and interrelations between facts follow from the theory if the theory is valid. The theory therefore generates *hypotheses* which can be tested. The hypotheses concern facts and also the interrelations of facts, which results in the proven interrelation becoming a new fact. The elements in deduction are multilateral, some are proven facts, others have not yet been proven. Some of the facts have already been discovered and proven without being placed in a general picture; some 'facts' are not known yet but are to be expected from the theory and could be found, because through the theory we know what we are looking for and thus these elements could be proven by searching for them, instead of finding them by accident while gathering other facts; and some facts could never happen according to the theory.

The process of deduction needs at least some already established facts which seem in one way or the other related to each other. In the example of the hormone, the relation is in the fact that in the different established contexts it is effectively the same hormone, as we will see with melatonin.

Happé (1994) states that a good *theory* should meet the following criteria:

1. It should present predictions that can be tested.
2. It should go beyond existing proof and go beyond simple description.
3. It should be specific and at the same time fit into what we already know in general.

In medical science the results of the inductive process starting with a discovery are without doubt impressive and together with tentative deductive processes

they contributed to the progress of medicine. Because of the enormous inductive body of knowledge in medicine deductive processes are certainly in order. This is what this book will do with the immune system: using the known inductive knowledge and try to broaden the insight by deduction to present an overview. After centuries of gathering knowledge we approach a paradigm shift from specialisation of elements of the body to interrelations of elements of the body.

1.2 The organisation of medical science

It is not always easy to place new knowledge into already existing knowledge. To place new knowledge in the right way you need a profound knowledge about the already existing knowledge, which is enhanced through *specialisation*. You also need an overview and some insight into the whole with its interconnections and interactions.

To enable the huge body of knowledge on parts of the body to develop, the medical profession at the scientific level as well as at the practical level is organised in *specialisations*. The knowledge about the body is organised in levels; this organisation is reflected in the organisation of the textbooks. The *first* level is that of the *organs*. The knowledge, research and specialisations are primarily about organs. The *second* level is that of the functions of the body organised into specific *systems*, such as the *blood system*, i.e. to make organs work; the *muscle system*, i.e. to make an action of the body possible; the *respiratory system*, i.e. to take out of the environment what the body needs, such as oxygen; the *metabolism system*, i.e. to process food.

All these organs and systems make the body capable of living and of performing many tasks. The organism itself also provides the system to let the organism *die*, which in detail is the *apoptosis*, cell-death. To protect the organism, there is a higher order system, connected to everything in the organism, which is the *immune system*.

The result of this enormous quantity captured in specialisations is that medical science is still quite specialised and this comes with a huge progress in the details, but also with lagging behind in what function a part has for the body as a whole. This is the point where deduction can help develop overviews and theories.

Some of the systems of the body more explicitly call for an encompassing view on the body. The immune system is one of the encompassing systems. How truly encompassing it is, became clear after the discovery of a immune vessel in the brain in 2015 (Louveau et al., 2015). This is a moment where a new fact – an immune system in the brain – has to be placed into an already existing theory of the immune system.

It is by connecting known facts and new facts that we can discover why this new element could remain undiscovered for centuries. This is where we need the interlacing process of induction and deduction to connect different elements. This could bring new insights that could foster a broader perspective.

1.3 The perspective of medical specialisation: four examples to illustrate new connections

Research shows progress each year, but we can still be taken by surprise when a new element is discovered and we are mystified and confused as to how it could have been missed. This happened in 2015, when a new vessel in the brain was discovered, until then unnoticed.

Science News published in January 2016 reprinted materials provided by the University of Virginia Health System, about an only newly discovered vessel:

> *In a stunning discovery that overturns decades of textbook teaching, researchers at the University of Virginia School of Medicine have determined that the brain is directly connected to the immune system by vessels previously thought not to exist. That such vessels could have escaped detection when the lymphatic system has been so thoroughly mapped throughout the body is surprising on its own.*

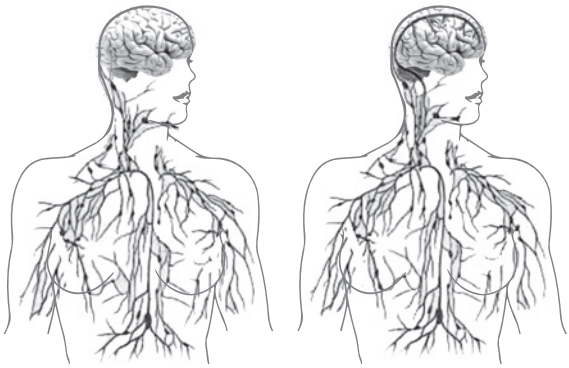


Illustration 1: *The recently discovered vessel in the brain, which proves to be a part of the immune system. Left: how the lymphatic system was visualised in textbooks until this discovery in 2015, and on the right how it should have been* (UVA-University of Virginia School of Medicine, 2015).

Indeed how could this vessel have been missed? The explanation can be found in the perspective on the immune system of that moment. The theory on the immune system was not yet broad enough to include the brain. A new element, such as this vessel, can broaden our insight. It was difficult to find the *meningeal lymphatic vessels* belonging to the immune system, simply because we did not conceive a role for the immune system in the brain.

> *'As to how the brain's lymphatic vessels managed to escape notice all this time, Jony Kipnis described them as "very well hidden" and noted that they follow a major blood vessel down into the sinuses, an area difficult to image. "It's so close to the blood vessel, you just miss it," he said. "If you don't know what you're after, you just miss it"* (University of Virginia Health System, 2015).

It is not so easy to map everything. Let's illustrate this by going back to Leonardo da Vinci (1452-1519), the brilliant mind, the *uomo universale*, the first to try to map the body by making very precise drawings. He needed several dead bodies, at a time that there were no refrigerators, to discover one element, to understand it and for instance to be able to make the drawing of a particular vein.

> *'...I have dissected more than ten human bodies, destroying all the other members, and removing the very minutest particles of the flesh by which these veins are surrounded, without causing them to bleed, excepting the insensible bleeding of the capillary veins; and as one single body would not last so long, since it was necessary to proceed with several bodies by degrees, until I came to an end and had a complete knowledge; this I repeated twice, to learn the differences* (The Collected Works of Leonardo Da Vinci, Anatomy, page 2-4 of 8', p. xi. 4-6).

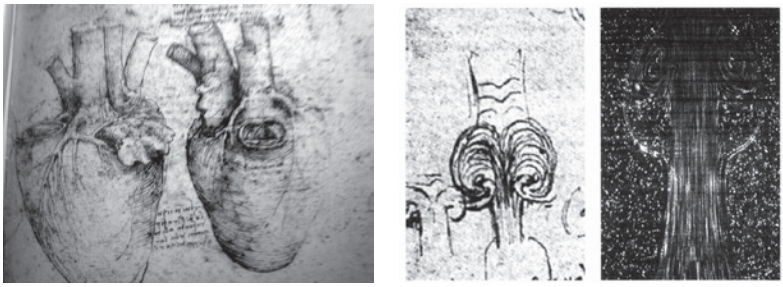


Illustration 2: *The genius of Leonardo da Vinci. The picture on the left is a drawing of the heart by Leonardo da Vinci. The picture in the middle is a drawing of what Leonardo da Vinci discovered about the bloodstream in the heart. To the right is a photo of the discovery by a scientist 500 years later, Gharib, who followed the guidelines of Da Vinci's notes on his experiments about this bloodstream in the heart. Da Vinci was proved right 500 years after his death* (Klein, 2008, p. 170-171).

We not only missed the vessels but also the *lymph nodes* that are deeply embedded in the brain. Once the vessels are discovered one can search for the lymph nodes.

But is this explanation sufficient to understand why the vessel was not discovered, to say that it was a difficult search, or could there be reasons why it took time for researchers to look for the elements of the immune system in the brain? As Jony Kipnis said: *"If you don't know what you're after, you just miss it."* This eloquent sentence of Jony Kipnis shows that finding something can follow two roads: first is the *discovery* because you find something by accident; second is looking for something because you have the insight, the overview through a *theory* that presupposes and engenders discoveries not yet made and thus you can go looking for it, which at the same time is proof for the insight to be correct or not.

Trying to find by deduction *how* the vessel could be missed can help us broaden the theory on the immune system. Could the vessel in the brain have been missed because an overview, an encompassing insight on the immune system where the brain would fit in was absent and because the immune system was built only on what had already been discovered outside the brain, by induction? The answer is yes; the very perspective on the immune system at that moment – 2015 – excluded the brain.

The specialisation of medical science makes knowledge of the functions remain in savant islands of knowledge. When you start connecting different parts you find the relations and the 'missing links'. Because it is a whole body, you know by definition that everything is linked to everything. Within a specialisation, at the border of the knowledge is the connection to another specialisation. When the paradigm changes from specialisation to *specialisations and connections*, a broader view will emerge. This means that the elements of the body can be placed more in their total interaction or in their total concept.

To understand this better and illustrate it, let us consider some scientific puzzles which specialisation creates by examining some of the composing pieces that created the puzzle. We will present four examples. The *first* example is the puzzle of the discovered vessel of the immune system in the brain; the *second* one is the puzzle of side-effects in medication; the *third* one is the puzzle of the functions of different subsystems of the immune system; and the *fourth* is the puzzle of the introduction of a new element in already established elements of the immune system, the autoimmune reaction.

1.3.1 First example: the discovered vessel

Deduction is not about finding answers but about asking the right questions.

First question: How can a vessel have been missed when in reality within the body it is an extension of other vessels of the immune system already discovered?

Element 1: the immune system. The immune system has been conceived from induction as a body system that *fights* against *intruders*. The intruders being: *viruses*, *bacteria*, *parasites* and *fungi* (vbpf). This theory on the immune system is based on the discovery *that* the body fights against vbpf, then cast into a conclusion after much evidence gathered in a specific context, that it is the body fighting against vbpf. A first finding (also in medicine) often leads to the frame, in this case the conceptual frame: *the function of the immune system is to fight against intruders*.

Element 2: the brain. The vbpf are the core element of the concept of the immune system. These vbpf are considered not to be able to pass the *blood-brain-barrier* (BBB). Between the circulation in the brain and the systemic circulation in the body there is the BBB, discovered some hundred years ago (Mizee & De Vries, 2013). Because of the BBB the brain is considered as not having to fight the vbpf, because the brain would normally not encounter them. This idea is respected, even when sometimes these intruders do pass through the BBB. The conceptual frame of the brain with respect to vbpf would then be that the brain is *protected* from intruders by the BBB, and thus protected from having to fight the vbpf. This would mean that no immune system would be needed in the brain and as a result we would not look for an immune system in the brain. From this conceptual frame a trespassing intruder (v, b, p or f) would be considered a *mistake* or an *error* of the BBB-function, and in continuation of that this would be considered an *immature BBB*, a *damaged* BBB or a *disease* of the BBB.

However, we have room for progress because the understanding of the BBB is still far from complete (Mizee & De Vries, 2013). Obermeier and colleagues stipulate for instance that causes and consequences of BBB breakdown are diverse, and comprehensive knowledge about all its manifold pathways is still pending to a great extent (Obermeier et al., 2016). The BBB is considered to be an interface between the brain and the rest of the body (Obermeier et al., 2016). Of course it is even more important to signal now that the BBB is not only a barrier protecting the brain because, it is more, and in 2015 the presence of the immune system in the brain was discovered, meaning that the immune system in the brain can effectively fight the vbpf entering the brain.

Conclusion: On the basis of these two elements (1+2) and using deduction from the existing conceptual framework/theory of the immune system, would lead to the following conclusion: *the brain is not part of the immune system because the brain is protected from the fight against vbpf by the BBB and this leads to no function for the immune system in the brain.*

The discovery that sometimes intruders (vbpf) pass the BBB did not trigger an adaptation of the conceptual framework of the immune system. The reason is probably that the new element – intruders passing the BBB – is not a completely new element. With an existing explanation, an incident would not always trigger broader thinking, instead another already known frame would

be used: that is the frame of 'error' or 'disease'. Medicine – as all science – needs out-of-the-box thinking or otherwise a new discovery risks being placed in an old, too narrow framework, and out-of-the-box thinking is most easily triggered by a completely new, strange element. Otherwise an innovation will fail because it will be discarded as a fault or a mistake. This is what happened with the immune system, the basic thinking frame of the immune system remained: *fight against vpbf*.

When the paradigm is specialisation, mapping the immune system in this case ends at the level of the brain. This is what we see in Illustration 1, left drawing. This is the way the immune system, the lymphatic system, has been represented in the textbooks till 2016: it ends at the level of the brain. The lymphatic vessels and lymph nodes were found in the face and in the neck, but the vessels and lymph nodes were not searched for in the brain. Only recently lymph nodes were discovered in the brain (Louveau et al., 2015) and this is surprising when we see the presicion mapping of the immune system, for instance in the ear.

How strongly the paradigm of specialisation influences medical science can already be understood by the fact that the newly discovered vessel in the brain is of course since always an extension of vessels of the lymphatic system outside the brain. The vessels in the textbooks and in the conception of the immune system ended literally and figuratively with an open end.

Even though there is a vessel that continues from beneath into the brain or one could say from above into the body, from the perspective of the immune system (*fight against vbpf*) and the BBB (*vbpf is stopped from intruding the brain*) the part of that vessel that is in the brain becomes simply *unnoticed* when mapping the immune system. However, as the brain is a basic controlling element of the body, probably the lymphatic system could well be steered from the brain down instead of the other way around.

This is what connecting existing knowledge can do: connecting the element of the utmost importance of the brain to the findings on the immune system elsewhere in the body, we would then consider an immune system in the brain to be of utmost importance and we would have been looking for it.

It is the perspective on the immune system supported by the BBB on the one hand and the brain not being totally mapped yet on the other hand that leads to not noticing the vessel and not looking for the lymphatic system in the

brain. As a result representing the lymphatic system of the immune system by a drawing thus mistakenly stops at the level of the brain.

Second question: How could this vessel have been 'missed' by brain surgeons for instance, people directly working and operating in the brain?

The answer can be found through the same basic idea, the perspective of *specialisation*. The brain surgeon is focused on operating in the brain, that is on what we already know and has already been mapped in the brain. However, the brain is not yet fully mapped. Surgeons know there runs a vein there, and quite a large one, the *superior sagittal sinus* (SSS), so how could brain surgeons miss the vessel? The *meningeal lymphatic vessel* that was discovered is aligned to this SSS vein. Brain surgeons are instructed to leave the SSS aside. Piercing that vein is too dangerous because it could provoke a brain-wide central haemorrhage leading directly to death. So, brain surgeons are trained to leave that vein aside and they stay as far from it as possible and do not include it in their work because of the risk of opening it and then causing death. As a result, together with the vein, the aligned (lymphatic) vessel is also left aside. Here again a specialised perspective puts the vessel out of the picture, outside the domain of brain surgeons. In fact, there is a continuous awareness in brain surgeons of the necessity to leave the vein (and thus the aligned lymphatic vessel) aside.

This is why we did not look for lymphatic vessels in the brain, and this is how they can remain unnoticed, and not be discovered. If you are focussed on the immune system, you do not pay attention to the brain, was the idea. If you are operating within the brain, you have to take care not to damage the sinuses, and certainly the SSS, so the aligned lymphatic vessel is included in disregarding the SSS-vein.

The discovery of this 'new' vessel, proving to be a lymphatic vessel, makes us aware that we could perhaps develop a deeper understanding of the immune system. We need another perspective that goes further than the perspective on the immune system as a *fighting* system. Connecting the brain to the immune system is a progress that has been made possible by the discovery of a lymphatic vessel in the brain.

1.3.2 Second example: melatonin, the side-effects of medication

The perspective of specialisation can create problems, not only with the immune system but with any system. Also an intervention aimed at a part of the body could have consequences for the body as a whole. Taking medication

is such an intervention, and taking medication often goes along with *side-effects*. Such an effect is called a side-effect with respect to the subject of the medication, for instance 'sleep'. This conclusion of being a 'side-effect' however is only valid within the specialisation perspective. Considering another part or system of the body where the 'side-effect' appears, it would perhaps be called a 'main effect' there.

Medication is often the chemical reproduction of a hormone or another substance of the body. When a *correlation* is found between a substance and a medical problem, causal thinking is not far away, even when we know that a statistical *correlation* says nothing about a *causal* relationship, only that two elements are occurring together for one reason or the other. We sometimes – too easily – think that the one causes the other. For instance a shortage or an abundance of a substance compared to what we know from research to be the average situation, leads to the idea to decrease or increase the substance by administration of medication, which is a causal interpretation. The focus is on the specific relation, and not on the different relations with other parts of the body. An imbalance in one place (considered a problem) could mean a stabilisation of the body as a whole (considered a blessing), for instance.

Administrating the new substance is aimed at a specific problem. But hormones and other substances of the body rarely, and probably never, play only one unique role. This means that using a body substance – such as a hormone – for a specific goal, an influence on other parts and systems of the body can be expected. As with so much in (medical) science, many things have yet to be discovered, as is the case about the hormonal system. An intervention somewhere, could and probably will, have effects and counter effects elsewhere in the body and in every aspect and every interaction where it could play a role.

We use the hormone *melatonin* (N-acetyl-5-methoxytryptamine, MEL) as a second example of a complication that could be engendered by the perspective of specialisation. MEL proves to be an extremely important hormone and is also connected to the immune system, as we will see. MEL was discovered in 1958 by Aaron Lerner (1920-2007) (López-Muñoz, 2016) when he examined affective and sleep disorders in people with psychiatric disorders, and discovered melatonin to play a role in these sleep disorders.

Melatonin is *a*, or better is *the*, *pineal hormone* that regulates among others circadian rhythms. Its synthesis and secretion comes mainly from the pineal gland during the night, with a peak between 2:00 and 4:00 am (Brzezinski, 1997). It is also produced in cells of the immune system and in the brain

(Ramos et al., 2016). In the immune system it has a stimulating effect and a potent anti-inflammatory function (Terzi et al., 2016). It also has a regulating effect on the brain immune system (Ohgidani et al., 2016).

Melatonin was first discovered through its role in sleep and after research it was concluded to be a chronobiotic molecule associated to circadian rhythm and sleep. In the meantime it is widely accepted as a medication in case of sleep disorders in children, adolescents and adults and for counteracting jetlag. But it has many other functions that have been discovered beyond this first discovery which was considered to be the typical, 'classical' role of melatonin. However, this role is only considered 'classical' because sleep was the *first* role of melatonin to be discovered, that does not mean, however, that it is necessarily the most important role, and it certainly is not. In other specialisations melatonin was also discovered to play an important role, such as in *reproduction*.

We will speak about three basic fields of importance with respect to melatonin, although there are many more, in order to try to make connections between areas of knowledge.

Element 1: Melatonin and sleep. Melatonin plays a role in the sleep, regulating the sleep metabolism, and is synthesized in the suprachiasmatic nucleus of the anterior pituitary gland. MEL is also produced in the cells of the immune system and the brain. Melatonin is either stimulated or inhibited by the pineal gland. Its release into the circulation is stimulated by the onset of darkness, followed by a progressive decrease in blood levels with the onset of dawn (Opie et al., 2016). Chronodisruption is associated with alterations of the immune system (Acuña-Castroviejo et al., 2017).

Melatonin can have a beneficial effect on sleep quality (Fernando & Rombauts, 2014). Melatonin is widely used to counter transatlantic travel jetlag and insomnia. Dysregulations of sleep through jetlag and night shifts provoke an imbalance in the sense of a shortage of melatonin production (Brown et al., 2009; Sack, 2009; Srinivasan, et al. 2008; Herxheimer, 2014). However, the *timing* of administration of melatonin proves to be more important than the dose (Sack, 2009). Melatonin can have unwanted sedative effects (Srinivasan et al., 2008). There are many factors that play a role in jetlag. The melatonin imbalance and shortage is only one of them, the time-light exposure is also very important (Brown et al., 2009). The many adverse effects have not been well researched yet (Herxheimer, 2014). Night shifts have more or less the same effects as a jet lag, but are more structural in character (Rüdiger, 2004).

Conclusion 1: Melatonin has an important role in regulating sleep. Much research has been done on sleep disorders and the problem of jetlag. The effects are not always clear and there are also many adverse effects.

Element 2: Melatonin and reproduction. Melatonin plays an important role in procreation. It also appears to regulate reproductive seasonal variation in many animal species. Melatonin exerts a role on the maintenance of a proper follicular function, and is thus important for ovulation and progesterone production (Maganhin et al., 2013).

Melatonin has been used to foster reproduction. One of the reasons for using Melatonin to foster reproduction is that it has a strong antioxidant capacity, and oxidant stress plays a role in infertility. Because of its potent antioxidant capacity (Shiroma et al., 2016), melatonin is considered for treatment of infertility in men (Rad et al., 2013). A low melatonin level could be involved in infertility (Rad et al., 2015). Melatonin also could play a role to protect the ovarian graft activity in transplantation (Shiroma et al., 2016). Being limited to patients with a low fertilization rate in the first cycle (<60%), the fertilization rate dramatically increased after melatonin treatment (35.1 versus 68.2%). The rate of good quality embryos also increased after melatonin treatment (48.0 versus 65.6%) (Nishihara et al., 2014). Melatonin is also likely to improve oocyte and embryo quality in women undergoing IVF (In Vitro Fertilization) or IcSI (*Intracytoplasmic Sperm Insemination*) (Batioglu et al., 2012; Kim et al., 2013). Melatonin can play a favourable role in PCOS (*Polycystic ovarian syndrome*) and can lead to complete follicular maturation and ovulation (Jain et al., 2013).

Conclusion 2: Melatonin proves to be an important hormone for the reproductive task. Much research, however, is about reproductive *problems*. It certainly already proved helpful in infertility problems and in regulating safe development of both oocyte and embryo.

Element 3: Melatonin as a central protective, life supporting hormone. Melatonin is found in humans, animals, plants and even in unicellular organisms. The secretion always depends upon light and dark signals and it is the key circadian hormone (Kloss et al., 2015). MEL plays a role in preventing *apoptosis* that is preventing the death of a cell. These functions show how fundamental this hormone is, it is understandable that it would be present in unicellular organisms, certainly where the one cell has to be protected from cell-death.

Descartes (1596-1650), the French philosopher, was one of the first to understand the importance of the pineal gland, and called it the 'the seat of the soul' (Descartes, 1637). He thought that the *interaction* of body and soul, life and death, took place in the pineal gland. Going further in this line of thinking, we would now say that the pineal hormone melatonin is effectively an important *interactive* element for sleep and cognition, for life and death. Descartes was close to the truth, even if he had to deal with concepts such as the soul, which was current in those times; but he felt the pineal gland to be of utmost importance, and he was effectively proved right.

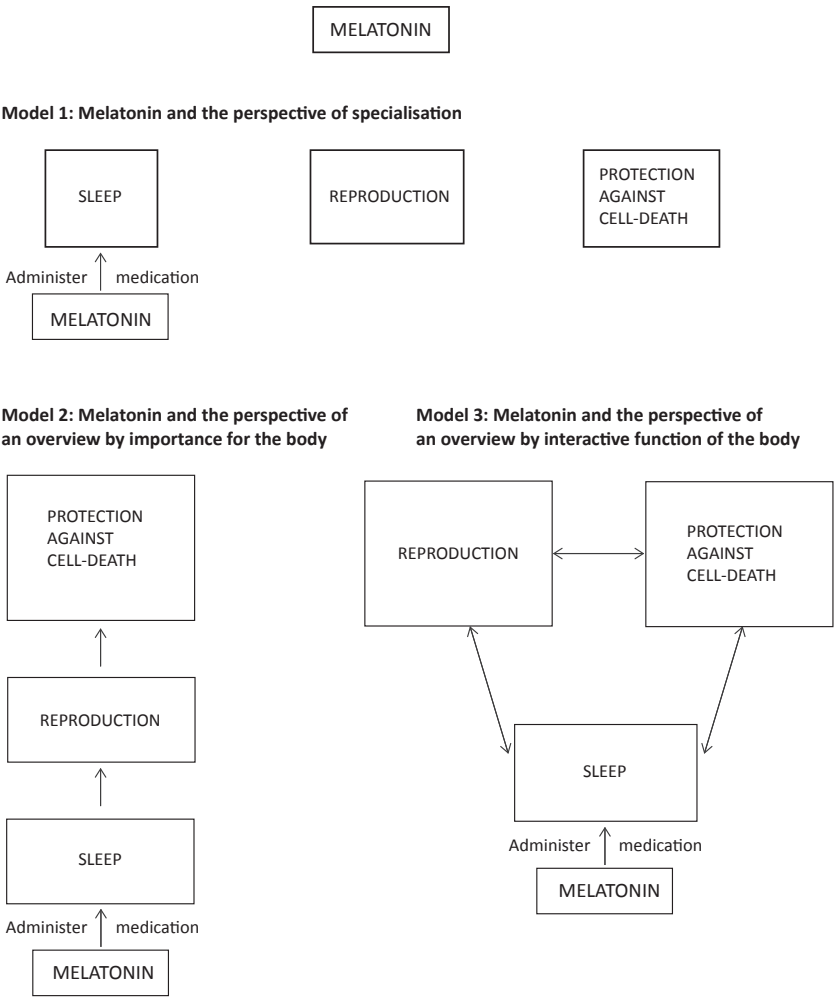
Conclusion 3: *Melatonin is a fundamental hormone, protecting the organism, fighting decline and making survival possible.*

Melatonin has *at least* three important areas: *sleep*, *reproduction* and *protection against cell death*. In Schema 1 we show three conceptual models for melatonin. The first (Model 1) shows the specialisation perspective and second (Model 2) an overview according to its importance for the body as a whole based on the importance of different elements, and the third (Model 3) represents the conceived real interactive functioning of the body.

In Model 1 we see three areas of importance for melatonin existing alongside, belonging to three totally different specialisations. When melatonin is administered from the perspective of the first model, we increase melatonin where it seems lacking: sleep. Because we do not conceive the other areas as being connected to sleep, we do not think about reactions in the other areas (i.e. *reproduction* and *protection against cell death*). We just observe side-effects when administering MEL. When we take other fields into account, these side-effects could perhaps be connected to those other fields where melatonin plays a role. A different line of thinking arises when we build not from specialisation but from an overview and take into account the warning of Leonardo da Vinci (motto, p. 8): *… true science …proceeds from the basis of primary truths and established principles successively and by true sequence to the end;…*

In Model 2 we then go one step further. The first step was that melatonin and sleep are correlated. The second step is melatonin is also correlated with reproduction and thirdly with protection against cell-death. We could then think out what the importance of these three fields could be with respect to the body as a *primary truth* and could come up with a hierarchy of 1 Protection against cell-death, 2 Reproduction and 3 Sleep.

In Model 3 of Schema 1 we can go another step further and use an 'established truth' as Leonardo da Vinci calls it, which is that these three fields and many more fields in the body would act in mutual interaction. Thus creating a wide range of hypotheses such as: sleep and reproduction are correlated; sleep and death are correlated, and of course many more areas in the body.



Schema 1: *Three possible models to represent the effect of administrating melatonin medication* (Delfos)

When we administer melatonin from the Model 1 perspective, we expect that the imbalance in sleep will be restored by melatonin. Whereas when we admin-

ister melatonin for sleep from the perspective of Model 2 we would expect it to have effect on reproduction and possibly on protection against cell death. In the case that we administer melatonin from the perspective of Model 3 we would expect that the sleep problem could be associated to activities in reproduction and activities in protection against cell death. For instance we would expect that the melatonin is produced and used where it is most needed and nevertheless or even because of that produces an imbalance in sleep. We would be more reluctant to use melatonin for sleep, because of the possible side-effects in the areas *reproduction* and *protection against cell death* which are more important areas than sleep; we would know that when administrating melatonin we could be facing important issues. We probably would expect that administering melatonin would not have so much of an enduring effect on sleep, because of the other areas of importance. It is also not amazing then, that the organism would counteract the – externally administered – melatonin; the effect would then not be as successful in promoting sleep as we would expect from the perspective of Model 1.

Conclusion: There are more areas where MEL has influence, but just from these three elements together (*sleep, reproduction, protection*) it can be seen that melatonin has a very refined, important and encompassing role in the body as a whole. It regulates *among others* sleep, it regulates reproduction, keeps reproduction in good health and is fundamentally protecting the body at a essential level for survival: protecting against cell death. Because of its multiple roles, using it as a medication would logically engender many possible adverse reactions, which are not always noticeable however. Melatonin would need to be very precisely attuned to all the parts of the body in mutual interaction. Using melatonin in one part or system of the body will presumably have effects on other parts. Melatonin teaches us, that infractions on the light/dark signals are of utmost importance, of basic importance for the organism. Instead of resorting to medication and using melatonin, it could be wiser perhaps to restore the light/dark cycle in people. This is what hospitals have started doing with premature babies: foster a normal light/dark cycle in neonates who already have to develop everything as their body has not sufficiently matured before birth. This could also mean stimulating a healthy day-night rhythm in people, which normally means decreasing stress, less night-shifts but also less nocturnal gaming in adolescents.

Connecting knowledge of different areas could bring about a better overview of the functions of the body. This could have a deeper insight into the side-effects of medication and in the end probably a preventive effect with respect to side-effects.

1.3.3 Third example: connecting nomenclature elements to facilitate theory building

Everything we discover in science has to be given a name: the *nomenclature*. The circumstances of a discovery and our perspective influences the name we give to newly discovered elements. With specialisation there is less connection with the whole concept of the body, and as a result there is sometimes less internal logic in the nomenclature with other elements of the body. This happened with some of the nomenclature of the immune system.

One of the first subsystems of the immune system that was discovered – a pathway of activation of the complement system – was called the *classical pathway*, simply because it was the first pathway to be discovered. A problem arose when a second pathway was discovered, named *alternative pathway*, which accidently proved to be more basic than the first one, in fact deserving the classification 'classical'. In a specialised perspective the name is sometimes not paid enough attention to, because from the thinking frame specialisation it stands more or less on its own. The name of this pathway was never changed afterwards.

As Sompayrac (2016, p. 14) puts it clearly: *Although in evolutionary terms, the alternative pathway certainly evolved before the classical pathway, immunologists call the antibody-dependent activation "classical" simply because it happened to be discovered first.*

Words as 'classic' and 'alternative' have connotations in logical reasoning that influences thinking and thus also scientific thinking and theory building.

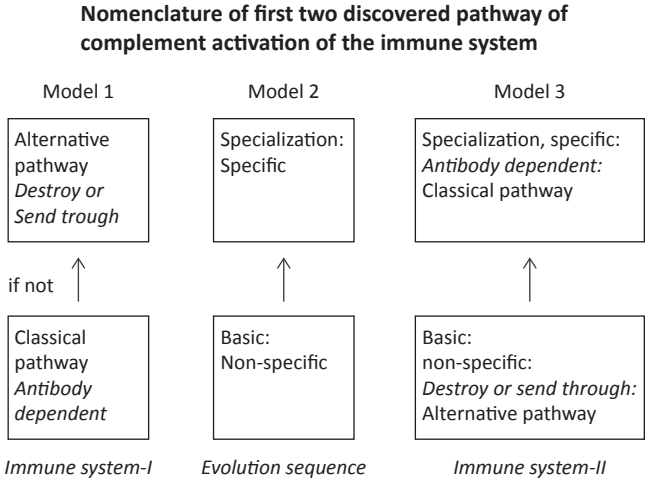
This way, through the names, the insight in the organisation of the elements of a system is not always logical. In Schema 2 we show the confusion the nomenclature of the first pathways incited.

In Model 1 (*Immune system-I*) we visualise what would happen if we would follow the *meaning* of the words 'classical' and 'alternative'. The sequence of the two pathways would then be first the classical pathway and if that does not work ('if not' in Model 1) the alternative pathway would come into action. Notwithstanding the logic the words suggest, this is not how the immune system works; it is actually the other way around. The 'alternative' pathway is the

basic system, the first in line in the fight against vbpf and also the oldest from the evolutionary point of view. It is this basic system that activates the so-called 'classical' pathway to come into action with its broad and specific elements (antibodies) to 'fight' each pathogenic element that needs to be addressed. The classical pathway is the 'refined, antibody-dependent' pathway, and the alternative pathway is the 'basic, destroy-or-send-through' pathway. The two functions are put below the name of the pathway in Model 1, *Immune system I*.

In Model 2 (*Evolution sequence*) we follow the evolutionary and developmental sequence, which is from 'non-specific' to 'specific', which is an evolutionary 'established truth' (see Leonardo da Vinci, p. 8).

When this evolutionary sequence is applied to the two pathways of the immune system this would mean that the 'destroy-or-send-through' (called 'alternative') would be considered basic and non-specific. This pathway is effectively proven to be first in evolution. The 'antibody dependent' (called 'classical') would be considered specialisation and specific and has effectively been proven to be second in evolution. This sequence results in a order with first the alternative pathway and then the classical pathway. This is shown in Model 3 (*Immune system-II*) with the sequence of first the alternative pathway and then the classical pathway. This is effectively how it works within the immune system of the body and this is also in accordance with their evolutionary development: first the alternative pathway, then the classical pathway.



Schema 2: *Models for understanding two pathways of complement activation of the immune system* (Delfos)

The nomenclature of these two pathways is functional: *classical* versus *alternative*. When a third pathway was found another nomenclature *characteristic* was used instead of *function* it was given the *name of the substance*: the *Lectin pathway*. The three pathways, however, have the same role in the immune system that is of activating the complement. Connecting the three pathways in the sense and meaning of the nomenclature would foster insight and facilitate theory building because of their natural coherence in language. The second part of the name does this: pathway; the first part (classical /alternative /Lectin) does not.

In a paradigm of specialisation, all discoveries are considered more or less equal, adding up to the knowledge bank and building a theoretical framework that starts from that first element onwards, but is not yet a theory because that would imply interrelations and internal logic. When building theories the steps also need to be logical in their interconnection and interaction, which is one of the pillars of a theory; non-logical, non-connected names hamper thinking and hinder making logical steps and thus theories.

Both names – 'second' and 'alternative' – are indebted to the idea that in the hierarchy of the whole system they are not the first and are not the basic pathway. But this is the hierarchy of *discovery*, not the hierarchy of *function* of the part in the whole system. Shifting from one thinking frame (*discovery*) to another (*function*) can then lead to wrong conclusions when the names can create confusion. This is certainly the case when the framework 'discovery' is not important and the other framework 'function' is preponderant, as it is in medical science. This is what happens with the pathways of the *complement system* of the immune system: antibody-dependent has been called the *classical pathway of complement activation*, suggesting being basic, ergo at the heart of the system, which is not the case. In the evolutionary sequence we saw that the so-called 'classical' pathway evolved from the so-called 'alternative' pathway.

The words 'pathway of the complement activation' in the names of the subsystems suggests – correctly – a certain relationship between the pathways. At the level of the specific nomenclature the two names (classical and alternative) counteract the logic in interrelationship between the two pathways thereby stimulating specialisation instead of interaction and theory-building.

We tried to solve the arising theoretical problem by using a conceptual framework: the evolution framework in Model 2 of Schema 2, thus shifting from a hierarchy of *discovering* to a hierarchy of *conceptual thinking*, which is closer to theory building. In evolution elements and systems evolve from

non-specific to *specific*, which is more refined and more adapted to challenging changing new situations.

With reference to the immune system, the idea is to fight, so the first action in line – general, non-specific, basic, classical –, would be '*destroy or send through for further action.*' Next would be specific, the second in line: '*antibodies for specific threats*'. The *alternative pathway* is *non-specific*, its role toward vbpf is: *destroy or send through* and would deserve the name 'classical.' The *classical pathway,* however, is *specific*, its role toward vbpf is: develop specific antibodies for specific threats and would deserve a name such as *second pathway*. As a third pathway was found the whole nomenclature should reflect its function in a logical, coherent and consistent way. At the beginning of discoveries the logic of interrelations is weak, and we have to be alert to have logic follow progress (*established principles successively and by true sequence to the end*, Leonardo da Vinci, p. 8) and adjust names to complete this in order to facilitate theory building.

Conclusion: The classical pathway of complement activation is specific and second in line of defence; it should be called the *antibody dependent pathway* of complement activation. The alternative pathway of complement activation is non-specific and could be called the *selection pathway*. It becomes even clearer how important nomenclature is, when we realise there is a third pathway – which by name does not refer to the other two – the *Lectin pathway* of complement activation. Already writing it down, and probably for the reader too, we have to pay extra attention not to get confused and make a mistake, because the words easily guide us the wrong way when speaking about the system of pathways as a whole. All three pathways function to activate the complement system. In the body however the organisation is there: the *alternative pathway* is first to act; the *lectin pathway* is second to act and the *classical pathway* is third to act (Parham, 2015).

Notwithstanding the confusion the nomenclature engenders, we will use the habitual names – because it is not up to us to decide about nomenclature – adding the number to refer to the logical hierarchy in action, which would be 1 for the alternative pathway and 2 for the Lectin pathway and 3 for the classical pathway.

But what to do when a fourth pathway is discovered which would prove to be the first to act?

1.3.4 Fourth example: expanding the theoretical scope by accepting incomprehension

The immune system is conceived as the system fighting against intruders (vbpf), and its sole function would seem to be *fighting*. The BBB is considered to protect the brain against vbpf and although we know sometimes vbpf pass that barrier, until 2015 the immune system was supposed to stop at the level of the brain. We now know the immune system is present in the brain.

If the immune system is considered to fight against intruders, what would be the function of the newly discovered lymphatic vessel in the brain then, would that only be for the few vbpf crossing the blood-brain-barrier? That does not seem probable. And what else would the immune system be fighting against in the brain then?

In addition to fighting intruders, the healthy bodily tissues can also be 'attacked'. The antibodies that are produced quite often are antibodies to own bodily tissues. This attack against healthy bodily tissues was a new element that came up in the field of immunity. How should such a new element be placed in an already existing conceptual frame of the immune system? To place it we have to take into account two elements: 'own healthy bodily tissues' and 'damaging/killing own healthy bodily tissues'. The element of 'own bodily tissues' was translated into 'auto', so this was called 'autoimmunity'. Continuing the idea of the immune system as 'fighting' one would tend to place this new element of attack against 'own healthy bodily tissues' through the already known concepts as 'error' or 'mistake', just as was the case with the vbpf passing the BBB and entering the brain.

Because the own body tissues are not vbpf, these antibodies against own healthy bodily tissues could easily be understood as 'mistakes' or 'errors' of the immune system. From the perspective of *fighting* this action of the immune system would be considered: *wrong fight* and *wrong enemy*. The fight against the own body would be considered as Don Quixote's fight against the windmills.

This action of fighting against healthy bodily tissues, called *autoimmunity,* was considered *pathogenetic* and a *derangement* of the immune system. Talal phrases the autoimmune problem as follows: *As a phenomenon in immunobiology, autoimmunity affords an opportunity to study the normal regulation of the immune response through examination of one of its major derangements* (Talal, 1980, p. 220).

Continuing this line of thought of the *mistake* and the *error*, the outcome of autoimmunity has been named autoimmune *diseases*.

Mistakes of course are possible, but not so probable at this large scale as the autoimmune diseases. Our thinking could also go in the direction that we do not understand the immune system enough to understand what is happening with this totally new element where healthy tissues are attacked instead of pathogens. It calls for out-of-the-box thinking. One step further (out-of-the-box) is that the concept of the immune system should be expanded to include the *autoimmunity*, just as the immune system had to be expanded to include the *brain*. In that case the new element could help broaden the concept of the immune system.

The name *disease* steers thinking and research in a certain way: disease-wrong-mistake-error. Although it seems logical to speak of disease where healthy tissue is attacked, a broader view could perhaps shed some new light on the concept of the immune system. Therefore we need the nomenclature to follow the idea that we do not know yet, that we do not understand yet, that is about *incomprehension* and not yet name the activity in the way it fits the already established concept of the immune system: *autoimmune* yes, but *disease* no.

The concept of autoimmune *reactions* of the body instead of the more narrow autoimmune *disease* could include a broader view on the immune system. In the conception of the immune system as fighting against intruders a direct connection is established between the intruder and the action, and is also limited to that connection. When we consider the connection between 'healthy tissues' and 'attack' this connection does not seem logical. We could never explain the autoimmune reaction within the limited frame of 'fight healthy tissue'. We would need to broaden the view to the context in which this 'fight' takes place: if not vbpf, what then?

A change in name influences thinking, in case of autoimmune *reactions* the question could come up: *Why does the body have autoimmune reactions?* In the case of autoimmune *diseases* the question that would come up could be *How come this organ is attacked by an autoimmune disease?* The last would narrow thinking, because it starts from a judgement about the action.

The next chapter is a brief and general description of the immune system resulting in a schema of the immune system.

2 The immune system

Probably the most ingenious, intriguing and complex system of the body is the *immune system*. The immune system makes us look at the whole body and at the body as a whole, even more so now that we know the brain is involved in the immune system. The immune system plays a role in early-life programming of later-life brain and behavior (Bilbo et al., 2009).

In the body the *organs* are described by their *components*. Body *systems* are characterised by their *function*. The immune system is also characterised by its function. To understand the immune system, and certainly the body as a whole, it makes a difference how this function is defined. We described that the function of the immune system is considered to be *fighting against intruders* (the vbpf / the pathogen).

Parham (2015) opens his book on the immune system with the following definition: *Immunology is the study of the physiological mechanism that humans and other animals use to defend their bodies from invasion by all sorts of other organisms. The origins of the subject lie in the practice of medicine and in historical observations that people who survived the ravages of epidemic disease were untouched when faced with that same disease again – they had become* ***immune*** *to the specific infection*.

So, the immune system is about *defence*, and it is named after the spectacular result of people becoming *immune* to an infection after having faced the disease before.

The immune fight is a fierce fight between a very large organism, the human being, and microorganisms invading the human body and multiplying at an incredible rate compared to their host, the human body. The reason why foreign bodies enter the human body to begin with is for gaining access to the rich resources that the human body provides.

The framework of the process of the immune system is clear: *fighting against microorganisms invading the body, through which the body becomes immune for a new attack*. The – ingenious – preventive medical intervention for a life-threatening disease that could arise from this idea became *vaccination*. This is an exposure to the disease, without the risk of fully catching the disease, but with the result that the immune system is activated and prepares the tags and antibodies to fight that specific disease. The first to discover this

was Edward Jenner in the 1790s when he managed to immunize a little boy for smallpox through vaccination with smallpox (Sompayrac, 2016).

It becomes even clearer that the immune system is about the whole body when we realise that the first and primordial protection of the immune system, and *first line of defence*, consists of the 'envelope of the body' that is the skin and the mucosal tissues (Helbert, 2017, p. 138-149). The first action of the immune system and *second line of defence* is to be prepared for foreign intruding bodies (vbpf) penetrating the protective *epithelial body tissues* – the skin and mucosal surfaces and also respiratory system and gastrointestal tracts (eg pH of the stomach) – receiving them by facing them immediately with the *innate immunity* also called the *innate immune system* (Helbert, 2017, p. 1-6). It has mechanisms that are fast and fixed in their mode of action and very effective in destroying intruders and thus stopping most infections at an early stage. The innate immune system aims at destroying the vbpf directly (kill through the Natural Killer cells, NK cells) or sending through information for further action to the *adaptive immune system*, which cooperates with the innate immune system. For this cooperation the immune cells of the adaptive immune system hook up with the complement components of the innate immune system (Parham, 2015, p. 329). The innate immune system can detect common and uncommon invaders; it collects and integrates information about an invader which will not be destroyed directly. This information provides the *third line in defence*, the *adaptive immune system,* with the necessary information and activates this adaptive system. The innate immune system also detects danger signals sent by dying cells.

2.1 Connecting the innate and the adaptive systems

The immune system consists of two basic subsystems: the *innate immune system* and the *adaptive immune system*, the nomenclature being consistent with the nature and evolution of the systems. 'Innate' was the first one to appear in evolution and 'adaptive' was the second in line. From an evolutionary perspective, the innate immune system (non-specific) is most ancient and the adaptive immune system (specific) evolved after and from the innate immune system. This also becomes clear in the fact that the innate immune system is found in invertebrates and vertebrates, and the adaptive immune system only in vertebrates. The innate is the first to appear in evolution (600 million years ago); the

adaptive immune system some 200 million years later (400 million years ago) (Parham, 2015).

The interaction between innate immune system and adaptive immune system is natural because the adaptive immune system builds on the work of the innate immune system (Nairn & Helbert, 2003, p. 3). The interaction and working together of both systems becomes immediately clear in one of the first actions of the adaptive immune system: to 'hook up' with the innate immune system in case of infection.

The specialisation of medical science generated two specialisations of the immune system – the one 'innate', the other 'adaptive'. Both specialisations developed their own methods and concepts independently, in the beginning without mutual scientific interaction, because they were not aware of the two systems interacting with each other in the body. This went on for nearly two centuries. These two specialisations gained of lot of knowledge and insight in their specific area, for innate it was the subject *inflammation* – the *innate immune system* was formerly even often called *inflammation –;* and for adaptive it was the wealth of the diversity of *antibodies* (Helbert, 2017, p. 1-6).

This division of innate and adaptive immunity continued despite increasing evidence for connections between the two systems. The most important of these connections was the universal observation that an inflammatory response is a necessary prelude for making good antibodies. Although implemented in practice, this well-known fact was not present in the thinking of most immunologists. An example of this phenomenon of the working together of the two systems is that the classical pathway of complement activation, in which antibody was the innovation of adaptive immunity hooked up with the pre-existing complement components of the innate immune system. The innate immunity evolved further once the adaptive immunity had appeared and developed; this could be called *coevolution* (Parham, 2015, p. 329).

The idea that they both (*innate immune system* and *adaptive immune system*) have the same general function (*action against intruders*) and the same activation system (*the complement system*) and proof that there was interaction between the two in the body, only came to the scientific awareness in the 1990s. This was the time to connect the two specialisations.

The specialisations engendered a lot of knowledge, but it is quite a task to bring those two bodies of knowledge together, because they developed their own concepts and methodologies and different nomenclature rules. After some 25 years at the beginning of the twenty-first century to make this connection is still quite an endeavour.

In textbooks we see problems arising from a rather young connection, for instance in the struggle with definitions where different systems carry the same name and same systems carry different names. For instance two concepts carrying the same system name 'immunity' are totally different concepts with respect to the process of the immune system. The *innate* concepts from the specialisation 'innate' are defined as the *mechanisms* or *processes*, such as *innate immunity*, and the concepts from the specialisation 'adaptive' are defined in terms of their *outcome of a process*, such as the *adaptive immunity* shown in Outline 1. In this Outline we show four examples from four textbooks (one of them a new edition – *Helbert* – of a former one – *Nairn & Helbert*) to illustrate the problem of the terminology. The first (Nairn & Helbert, 2002) is a book published shortly after the two specialisations began to work together; the second (Parham, 2015) is a textbook on the immune system published 25 years after the two specialisations began working together; the third (Sompayrac, 2016) is a modern book to help students understand the immune system, and the fourth is a new edition of Nairn and Helbert by Helbert (2017). All four books struggle with the concepts around 'innate' and 'adaptive.' We looked at the entries of 'innate' and 'adaptive' in the *index* and in an eventual *glossary*, where definitions are in order, see Outline 1.

The entries on 'innate' and 'adaptive' in the index of the book shortly after the start of the two specialisations working together are multiple: more names for one concept, and no glossary definitions, see the first row Nairn & Helbert. In Outline 1 it becomes clear that the innate system and the adaptive system, notwithstanding that they are mentioned in the textbooks, do not always come up in the glossary, where a definition is needed and expected (first and third row). This is most probably due to the confusion when two specialisations with their own development and concepts are in the process of being brought together. The most recent book in Outline 1 is the third edition of Nairn and Helbert by Helbert (2017) which shows a glossary with *adaptive immune system response* and *innate immune system response*, that is the respons but not a description of the systems as such.

Outline 1: *The naming/nomenclature of innate and adaptive in three textbooks on immunology*

Textbook	Innate		Adaptive	
Nairn & Helbert, 2002). In index, no glossary.	One entry in index: Innate immunity/immune response (natural/non-adaptive).	No glossary, so no definition.	One entry in index: Adaptive immunity/ acquired immunity.	No glossary, so no definition.
Parham, 2015. In glossary, definitions + index.	In index: innate immunity.	In glossary: *Innate immunity*: the host defence mechanisms that act from the start of an infection and does not adapt to a particular pathogen or generate immunological memory.	In index: adaptive immunity.	In glossary: *Adaptive immunity*: the state of resistance to infection that is produced by the adaptive immune response. *Acquired immunity*: alternative term for adaptive immunity; pathogen-specific immunity acquired as a consequence of infection or vaccination.
Sompayrac, 2016. In index, no definitions in the glossary.	In the text and index: innate immunity system.	No mention of innate immunity or innate immunity system in the existing glossary.	In the index and text: adaptive immune system.	No mention of adaptive immunity or adaptive immune system in the existing glossary.
Helbert, 2017 (third edition of Nairn & Helbert, 2002). No index in digital edition. Entry in glossary.	No index in the digital edition.	Glossary: Innate (non-adaptive) immune system response. The older part of the immune system, which responds rapidly to infection but with exactly the same response each time.	No index in the digital edition.	Glossary: Adaptive (acquired) immune system response. Part of the immune system in which genetic recombination is used to recognize specific molecules. Slow to respond, but produces lasting memory.

The differing definitions and concepts are not yet connected, and as a result different elements have not yet got their clearly defined place and role in the immune system as a whole. This is why in the textbooks we find no model or schema of the total immune system with the innate and the adaptive system. There are schemas or models of parts of the immune system, for instance models of the pathways with their activation of the complement and the following cascade of the complement. In schemas and models elements are placed in their mutual relationship and thus the overall processes become clear. To understand and explain the system, but also to develop theory it is necessary and even of utmost importance to place elements in a schema or a model.

To be able to connect and place the elements it was necessary to scrutinise the available information and try to find a solution to the – only superficially – contradictory material by finding out what is already evidence-based about them. It took an effort to reorganise the names in the correct sense so that subsystems at the same level and with basically the same function could be placed in a logical way, in fact the most important was to make the connection between the two specialisations 'innate' and 'adaptive.'

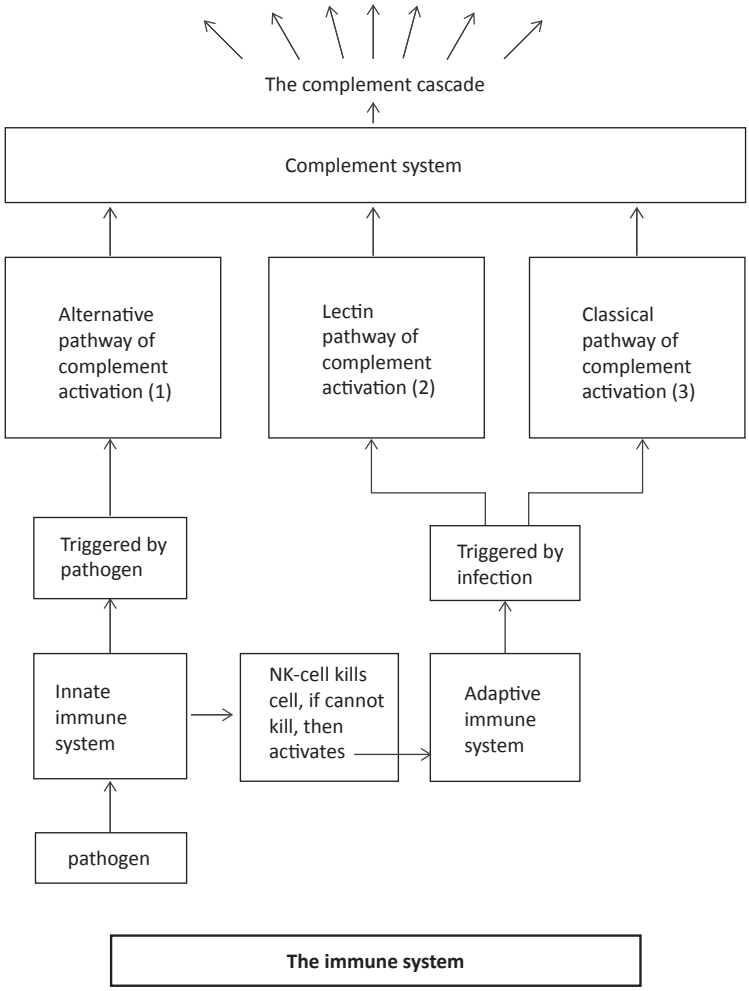
Many terms are used, but often in textbooks and articles they speak about the *innate immune system* and the *adaptive immune system*, when they speak about the process, not the outcome, both terms are at the same organising level. In a schema we need the process, not the outcome. And these two systems are the basic ones, the bottom line of the immune system activity. So, we chose to use the terminology at the same level of meaning: the *innate immune system* and the *adaptive immune system* (definitions in the glossary, see Appendix I). Through this process we arrived at a schema of the immune system shown as Schema 3, page 45.

2.2 The schematic representation of the immune system

Because new microorganisms evolved, interaction and cooperation of the *innate immune system* and *adaptive immune system* in the human body became primordial in order to defend the organism against intruders. The innate immune system builds on the ancient already existing microorganisms; the adaptive system keeps evolving within the human body because the human body has to face new microorganisms throughout life. For instance migration to new areas for a human being comes with new dangers. The two immune

system systems (innate and adaptive) have to interact and cooperate with each other in order to face the dangers.

On the basis of connecting 'innate' with 'adaptive' and putting these two in place with the three pathways and the complement with its cascade, we were able to construct the schema of the immune system as shown in Schema 3.



Schema 3: *Schematic representation of the immune system in case of a pathogen* (Delfos)

When a pathogen has penetrated the skin or mucosal surfaces this triggers the immune system through the *innate immune system*. When the pathogen cannot be killed an infection can arise and the innate immune system decides whether there is a role for the *adaptive immune system*, which then hooks up

with the innate immune system (Helbert, 2017, p. 7-13). Both the innate immune system and the adaptive immune system have their pathways to activate the complement system which leads to the complement cascade with its NK-cells, the killer cells which kill cells infected by pathogens (1-alternative pathway, innate), the opsonization of a cell to prepare to be killed (2 the Lectin pathway, adaptive) and the many antibodies (3 classical pathway, adaptive) with specifically adjusted attack cells (Helbert, 2017, p. 138-149).

The *immune system* starts by being triggered by a *pathogen*. When it detects that it can *kill the pathogen* through *NK-cells* it *activates* the *complement system* through the *alternative pathway* to *destroy the pathogen* (vbpf). If it *cannot destroy* the pathogen and *inflammation* occurs it *activates* the *complement system* through the *Lectin pathway* by *informing the adaptive immune* system by mannose-binding lectin (MBL) activity on the surface of many common pathogens. The adaptive immune system thus *hooks* up with the innate immune system to activate the *complement system* with B- and T-cells through the *classical pathw*ay.

2.3 The pathways of complement activation

From the actions of the innate and the adaptive immune systems three pathways can be stimulated to activate the *complement system*. The three pathways that can activate the complement system are: (1) the *alternative pathway of complement activation* (antibody-independent); (2) the *lectin pathway of complement activation* (mannose-binding) and (3) the *classical pathway of complement activation* (antibody-dependent) (Helbert, 2017, p. 138-149).

The part of the immune system that can identify and attack a pathogen is the *innate immune system.* When the innate immune system has detected a pathogen and has the possibility to kill this pathogen, this triggers the first pathway (1, *alternative pathway*) to destroy the pathogen by part of the cascade of the complement; its role is *killing the pathogen*. This pathway does not involve antibodies. It is the most ancient pathway and is characterised by the *NK-cells,* the *Natural Killer-cells*. NK-cells are the basis of the innate immune system and thus these cells of the immune system are most ancient in origin. The NK-cell is capable of killing/destroying cells that have been penetrated by

pathogens. They are relatively simple cells; they are the only lymphocytes that do not rearrange receptor genes (Helbert, 2017, p. 162-171).

The *failure to kill* by the innate immune system was probably caused by evolution because new microorganisms evolved which the NK-cells could not handle and therefore a more specific response was called for (Helbert, 2017, p. 14-17). This evolved as the *adaptive immune system*, which can adapt to protect the body against almost any invader. The adaptive immune system comes into action through the innate immune system when the innate immune system cannot kill the cell containing the pathogen, and thus cannot stop the infection.

Where in the innate immune system the detection of a pathogen is the trigger for action, the ongoing infection is a trigger for the adaptive immune system. The adaptive system is therefore slower, it has to build on the information of the innate immune system, tag the pathogen and stimulate production of the right antibody. The adaptive immune system is capable of stopping nearly all infections that outrun the innate immune system, and the innate immune system itself is capable of stopping nearly all pathogens (Helbert, 2017, p. 7-13).

Failure to develop a successful response can arise from inherited deficiencies in the immune system or from the pathogen's ability to escape, avoid or subvert the immune response.

The pathways that are more associated to the adaptive – selective – immune system are the *lectin pathway of complement activation* and the *classical pathway of complement activation*. There are three groups of molecules that specifically recognize foreign antigen (another term for the intruders, term used for the target of antibodies or T-cells): the first two groups are the cell-surface receptors found on B- and T-cells, the third group the MHC (Major Histocompatibility Complex) genes.

The adaptive system is triggered by the infection and activates its two pathways (2, *lectin* and 3, *classical*).

The second pathway (2, *Lectin pathway*) is opsonizing pathogens, preparing them for uptake; its role is *opsonization of pathogens* and the third (3, *classical pathway*) is specifically reacting to specific pathogens by means of specific antibodies; their role is *recruitment of inflammatory cells*.

As a result of the actions of the three pathways there is the *complement cascade,* which comes to terms with the pathogens by destroying them or putting them in quarantine in order to free the body from infection and immunizing the body – whenever possible – against repetition of an attack of the pathogens.

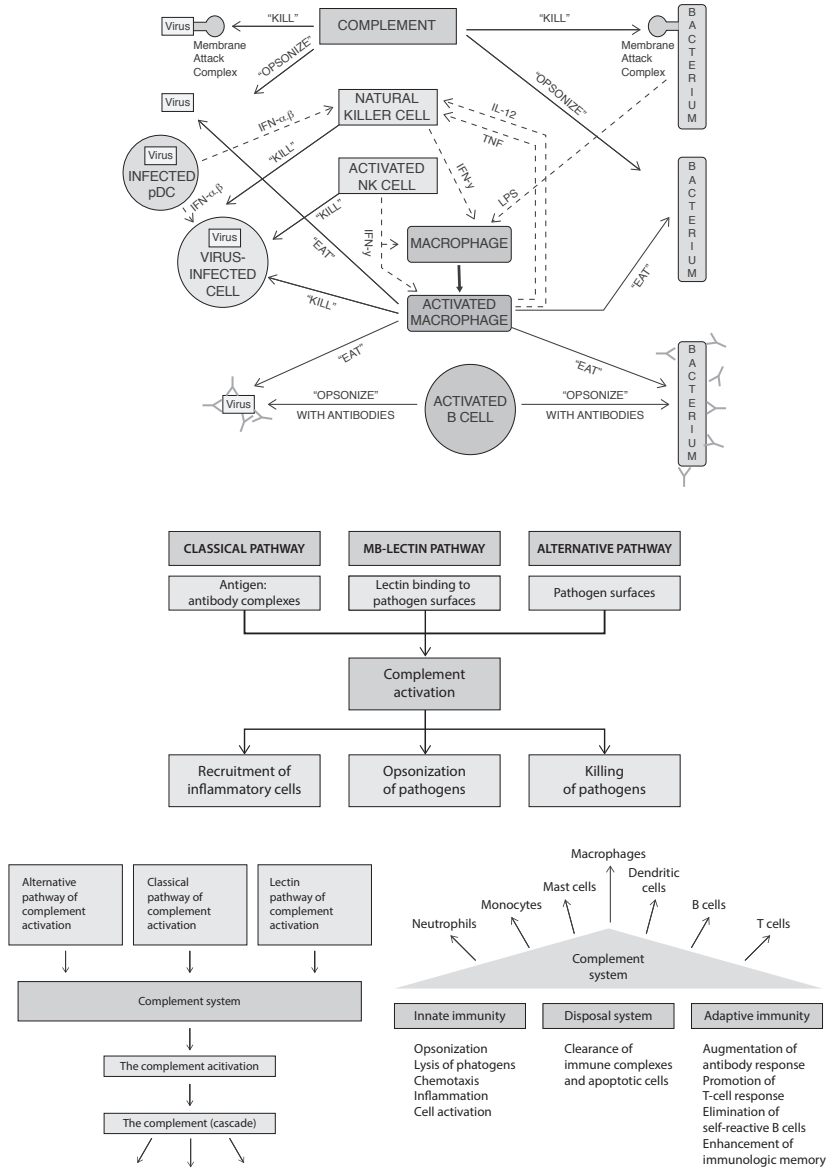
2.4 Schematic representation of the complement and the pathways

In Schema 3 on page 45, the immune system is schematised in its reaction to a pathogen. This schema is built upon the perspective of the immune system as fighting against intruders, on the knowledge of two basic subsystems and on the knowledge of three pathways. It is organised according to the compiled and researched knowledge on the (sub) systems of the immune system.

The immune system showed in Schema 3 works bottom-up beginning by where it all starts: a pathogen having penetrated the *first line of the defence*, the skin and mucosal surfaces. In fact this is not really the first line of defence, because the skin is, as we will see in paragraph 3.1.

The innate system is triggered by the pathogen as a *second line of defence* and in a *third line of defence* activates the adaptive system to the direct action against intruders. The complement system is activated to perform these tasks through three pathways and as a result the complement cascade opens up with all the elements (cells) of the cascade.

Until this book no total schematic representation of the immune system existed where the innate and adaptive immune systems were inserted. The models that one can find in the textbooks are the complement with its cascade of cells, see Schema 4 left image, where the model starts on top with the complement and thereunder the cascade with its cells. In the second image of Schema 4 an example of models with the three pathways, the complement activation and their three actions: recruitment of inflammatory cells, opsonization of pathogens and killing pathogens. The third image of Schema 4 shows part of the schema of the immune system of Schema 3, but then upside down to facilitate comparison with the usual way the immune system is visualised, such as the left and second image of Schema 4. In Schema 3 however, the schema is built from where it begins, that is from the *bottom up* to the end with the complement cascade. A schema that shows the whole process should be built bottom-up; this is how Schema 3 was constructed. The fourth image of Schema 4 is the complement system with its cells, and thereunder three systems presented partly by their cells, partly as functions. The innate and adaptive immunity and the disposal system are placed with their functions and cells. The body of knowledge comprehends the cells and their actions; this is why the schemas are cells and functions. The representation in Schema 4 left, second and fourth are at cell-level instead of system-level as in the third image.



Schema 4: *Schemas of (parts) of the immune system. From left to right: first: usual visualisation of the immune system in textbooks where normally only the complement and the cascade are shown***;** *second: the three pathways, the complement activation and their roles; third: part of the schema from Schema 3 with the three pathways, complement activation and cascade, but then upside-down* (Delfos)*; from the fourth: the complement cascade without the three pathways and with three systems: innate, disposal and adaptive.*

A comprehensive schema of the immune system would have to integrate the different subsystems of the immune system, in relation to each other without all the details of the many cells involved, which we see in the cascade.

Schema 3 shows the schematic representation from what we know to be the ongoing perspective on the immune system. The systems are represented in their mutual relation.

The discovery in 2015 of the immune system in the brain enables us to extend the perspective on the immune system.

3 A broader perspective on the immune system

There are medicals problems we cannot solve without a perspective on the whole body. And this certainly holds true for the immune system, because it works for every cell of the body. This total perspective was ultimately opened up when the lymphatic system in the brain was discovered in 2015 (Louveau et al., 2015).

The formerly supposed non-involvement of the brain in the immune system places the brain in a subordinate position, which would be improbable because the brain is considered the major steering element of the body. As Dick Swaab puts it: *We are our brains* (Swaab, 2015).

We mentioned before that defining the immune system only as *fighting* would be insufficient. If we broaden its perspective, it would have to be a function for the whole body, including the brain, and of course the broader perspective should include the action of fighting against intruders, but also attacking own healthy tissue.

3.1 From fighting to protecting

Fighting against intruders is without any doubt a role of the immune system, but is it the only role? The start in broadening the framework of the immune system is to shift from *fighting* to *protecting*. This does not seem a big step, but it broadens the perspective with unexpected possibilities.

That protection is a concept which would encompass the immune system becomes clear when we observe the actions of the immune system. The immune system becomes active when the vbpf enter the body, but is already active in preventing the vbpf from entering the body. The function of the immune system could be called *protection* of the body against intruders such as vbpf, because the *first line of defence* is the body-envelope of the skin with mucosal tissues whose goal is to prevent the vbpf entering the body, which is clearly a *protective* function and not a *fighting* one because no harm is done to the pathogen by keeping it outside the body. The concept of protection is

broader than fighting, because fighting is only one of the strategies of protection. It allows for a broader perspective on the immune system.

If the conceptual framework of the immune system would be about protection then naturally the brain should be included, because the brain is too important not to be protected, and the formerly unnoticed vessel in the brain from the unnoticed lymphatic system in the brain would be expected instead of undiscovered. In the brain, because of its paramount function, we would then expect an intricate and vast *meningeal lymphatic system* with many lymphatic vessels and lymph nodes. The BBB would not be the way the brain can be excluded from the immune system, but an extra protection for the brain, because of its importance.

To illustrate what broadening the perspective of the immune system in the brain could yield, let us examine the idea of the lymph nodes in the brain. In order to do so it would be logical to begin by applying the knowledge of lymph nodes in the body to the lymph nodes of the brain. The lymph nodes in the brain could be swollen by tumour material and immune cells travelling to the nodes, just as is the case in the rest of the body. If we were unaware that there are possibly swollen lymph nodes in the brain, these nodes could be perhaps – mistakenly – considered 'simple' brain tumours. If we do not realise these swollen elements are lymph nodes instead of tumours we would operate on them with the skill and knowledge belonging to operating on tumours without the knowledge of operating on lymph nodes. If we know that a tumour could be a lymph node, we would operate with the skill and knowledge about lymph nodes and would be careful when operating on a lymph node in the brain to examine the lymphatic system of the brain and try not to damage this lymphatic system too much, because damaging the brain is very hazardous for the body as a whole.

Going further on the idea of *protection* we could say that the vbpf are called *intruders* because the immune system is considered to be a fighting system, since this function was the first to be discovered. But vbpf are not always intruders, many bacteria for instance are beneficial for the human body.

When we take the role of fighting by the immune system seriously and place this in the context of protection we would realise that to fight you not only have to select your target, but you also need knowledge about everything that is not a target, because there you would have to withhold from fighting. Here the immense wealth of the immune system begins to show itself.

The discrimination of *self* from *non-self* tissue has to be an essential and primary function of the immune system (Talal, 1980).

In fact this action of identifying cells should be recognised as a basic function of the immune system and should be part of the immune schema with a specific role: *identification* of cells.

To begin with, to recognise a pathogen (non-self), you must know what a non-pathogen is. This could be non-self but also self. The *thymus* is therefore an important organ for the immune system because this is what the thymus does and what the immune system needs: discrimination between self and non-self cells; familiar and non-familiar. Because of that, the thymus has been called the *biological self* (Hamilton & Timmons, 1990; Damasio, 1999). According to Damasio (1994), the thymus gland can be considered as part of the complex 'biological self', the 'proto self', which exists as a continuously active neural structure in the brain and is constantly fed by information from the organs. The thymus gland as a source of the development of the immune system and as an 'investigator' of familiarity of cells could be seen as the first building block of the biological-psychological-neural self. The thymus gland is fully developed at birth, and by one year after birth it begins to degenerate, and this goes on throughout life, without impairing its functioning. The last part of the sentence – 'without impairing its functioning' – does make us wonder if 'degenerate' is the right word to use in this context. Maybe this word came up because it explains a loss, the loss of volume. But this 'loss' is not necessarily a degeneration. Perhaps it is a maturation process. The process of *maturation* of the brain means a process of an increase and then a decrease of cells; this is a process of deleting cells that are not functioning well or are not adequate in connecting with other cells and also creating new adequate cells. This process of maturation is progressing towards a more effective brain. The change of the thymus could perhaps mean a thymus developing into a more effective thymus instead of a degeneration of the thymus.

The lifelong importance of the thymus becomes clear when we realise that the thymus is the place where the T-cells of the immune system are developed, after being produced in the bone marrow. The T-cell is important for the *adaptive immune system* (Parham, 2015).

The concept of discrimination of *self* versus *non-self* is not refined enough. Within 'self' and within 'non-self' discrimination is also necessary. Within non-self the discrimination between beneficial for the body or harming to the body system is necessary. For instance the oxygen we take out of the surroundings is

non-self but beneficial as are many bacteria for instance. The concept 'pathogen' and 'intruder' does not match totally the concept of non-self.

The immune system cannot be considered as a system that only *fights* against intruders, because these 'intruders' are not always considered dangerous or damaging 'intruders', they can be very welcome. Bacteria are not always considered bad. On the contrary, they can be useful for the body. So the immune system, starting with the innate immune system, must from the beginning discriminate between good and bad 'intruders', and put more broadly: between good and bad 'non-self'. The *fighting* perspective of the immune system is in fact restricted to bad non-self, which would represent only part of the actions of the immune system.

Which bacteria are necessary for the body and which ones are not, is not always the same for everyone. Many intruders of the body have the same effect on nearly everyone, but some need to be screened for that specific body at that moment. It is the task of the immune system to discriminate among them. It is not the same even for the same body on a lifelong basis, it changes with the change of the body needing things it did not need before and the other way around, and also the travel of a person to different regions requires adaptation to the situation in a new region. The immune system has to discriminate taking into account the *situation* of the body at *that* place at *that* moment.

If we take *protection* as the perspective on the immune system we have to broaden the idea of a simple connection between an intruder and the reaction of the immune system. The demands of the body for protection change throughout life. Also the way the body is developing within its surroundings has an influence on the needs of protection by the immune system.

The innate system of the immune system recognises that some foreign elements have simply to be authorised to get through without being killed by NK-cells or being processed by the adaptive immune system. Thus, again the immune system is a protecting system because it authorises good non-self (for instance some bacteria) to enter the body. This is not new knowledge, just *connecting* that knowledge to the knowledge about the immune system.

The activity of the immune system needs to be regulated for a very broad spectrum of activities. For example a fetus brings foreign but healthy non-self DNA-tissue from the father in the body of the mother. This tissue has to be accepted by the immune system, otherwise procreation would not be possible.

The innate system has to be able to *discriminate* within 'foreign, non-self' between *healthy* and *not-healthy*, between *harming* and *not harming*. This

identification would lead to the next steps with respect to 'foreign healthy' choosing between *needs to be destroyed* or *should not be destroyed*.

The innate and adaptive immune systems have to be *restricted* and *restrained* with respect to attack and have to develop specific tolerance. Gantt and colleagues reviewed the research on suppressing the innate and adaptive systems. Myeloid-derived suppressor cells (MDSC) are a heterogeneous population of granulocyticormonocytic cells that suppress innate as well as adaptive immune responses (Gantt et al., 2014). *Suppressing* too is a protective action. A well-known example is the reaction to the fetus.

3.2 Suppressing in order to procreate

A well-researched example of attacking healthy tissue is the fight between the pregnant woman and her fetus. In order to suppress allogeneic responses and pathologic inflammation due to antigenic differences between the fetus and its mother, the feto-maternal environment evolved to be *immunosuppressive*. The MDSC promotes *feto-maternal tolerance*. How ingeniously and intricately the immune system must work becomes clear by the fact that the immunosuppressive action necessary for the maternal environment to develop a fetus into a child that can be born, also engenders an increased *susceptibility to infections* in the mother during the postpartum situation, but it also helps prevent *postpartum inflammation* in the mother. This shows how very subtle the balance between the mother and the fetus is. MDSC mediated reduction in levels during pregnancy and the perinatal period is not just a by-product of T-cell *immunosuppression*, but potentially a primitive part of the innate immune system (Ismail, 2017). The fetus is antigenically different from its mother, and is thus analogous to a semi-allogeneic *transplant*, with the risk of immunologic rejection (Gantt et al., 2014). The immunological relationship between the mother and the fetus is a bi-directional communication determined on the one hand by fetal antigen presentation and on the other hand by recognition of and reaction to these antigens by the maternal immune system (Szekeres, 2002). The fetus inherits 50% of its genes from the father, thus half of fetally derived antigens are of paternal origin, and the mother's immune system would be hostile to this. There is ample evidence now that pregnancy is recognised by the immune system. Antifetal, antiplacental, and antipaternal antibodies are detectable in sera of women with successful pregnancies, clearly showing that

maternal recognition of fetal antigens does not necessarily compromise pregnancy (Szekeres, 2002), because that recognition leads to tolerance. Most pregnant women form antibodies to paternal HLA (Human Leukocyte Antigen) (non-self) which is inextricably linked to maternal tissue (self), thus indirectly attacking healthy non-self tissue in the body. These do not affect fetal outcome. One way or another the immune system starts by making antibodies, but learns that they should not be used or they are counteracted in a way we do not understand yet Perhaps fetal antibodies against the maternal antibodies are produced by the fetus' developing immune system.

We have, however, no idea about the costs for the fetus, the fact that the outcome *is* a child does not mean that the child has not been harmed or 'changed' in the process, or even has become stronger as a result of the fight. As the MDSC facilitates non-self-tolerance of fetal tissues, the associated risk of an increase of infections postpartum in the mother is perhaps a price paid for this tolerance. During pregnancy MDSC may help to prevent maternal rejection of the semiallogenic fetus (Ismail, 2017).

We see this process working when the body of the mother balances the food intake distribution. When food is scarce the protection of the fetus prevails, only in case of high maternal risk (death risk) the mother is favoured (King, 2003).

3.3 From protecting to exchange

Apart from protecting the body – *by helping the body to good foreign resources, protecting the body against harmful intruders and facilitate procreation* – the immune system can also be perceived as protection against the *malfunctioning* of the body itself. The *suicide cell* is such an example of protection against malfunctioning. The idea of suicide exists not only for the body as a whole, but also within the body. Suicide by a person is the ultimate danger, but 'suicide' within the body is to the contrary: protection of the body. It happens when 'altruistic' cells kill themselves in order to save the organism. This means that for the sake of protection of the body as a whole in some cases the body could attack healthy tissue.

Intruders readily enter the human body because of its rich resources. But in biology *reciprocity* is an important factor. There is reciprocity of the bee with the flower, when the bee dwelling on the flower looking for honey also spreads

the seed of that flower. There is to be expected reciprocity too between the human being and his surrounding world. Evolution means that because of the circumstances, an organism adapts to the surroundingsin order to be able to survive (better). This is a crucial element.

Reciprocity in evolution would mean that the environment itself also needs to survive. This means that organisms could stimulate the development of another organism or a virus to enhance the organism's own environment or attack threatening organism's in their environment. Looking at evolution as a *struggle for life* is only one aspect because this struggle does not exist in a vacuum. The interaction of the human body full of rich resources with the environment undergoes a process that is in principle beneficial for both. The environment sends 'intruders' that 'use' the body and the body 'uses' intruders for survival.

The human being is however not always beneficial to its environment, so despite its rich resources it can be attacked by organisms or viruses in the environment for the environment's own benefit. This is not a conscious act or goal-directed behaviour, but a true interaction of elements on their level of compatibility.

One way this attack of the environment could work is dismantling the immune system of the human body, the core of its protection. Such an endangering virus is HIV leading to AIDS (Acquired Immune Deficiency Syndrome). The virus enters cells and spreads the information that no action of the immune system is required. Thus the body does not fight against intruders, because it is misled by the HIV that there is no intruder. The HIV-virus, dismantles the human body. But humankind developed an answer by developing the pharmacological prevention of *AIDS*. The immune system has trouble with dealing with viruses. Unlike (most) bacteria, parasites and fungi, viruses tend to destroy the human body instead of using its resources. The virus could be an element from outside designed to destroy. We will investigate this further in chapter 6 when we look at the autoimmune diseases.

There is another example of misleading the immune system by presenting the wrong information on the cell surface. HIV does this with the cells of the body, presenting the information that nothing is wrong in the cell. Something that is comparable happens with *sialic sugars* in the case of cancer. These sugars are primordial information presenters on the surface of cells about events in the cell. For instance they signal the *blood type* (O, A, B, AB). But they also signal to the immune system that the cell is good. The immune system 'tastes'

the sialic acid sugar and is 'reassured' about the cell. Sialic acid is associated with developing infections in people with HIV (Varchetta et al., 2013).
If a virus is a life-threathening agent we could ask ourselves whether the way the immune system is misled by the sialic sugar cover around the cancer cell (Drake et al., 2008) could be caused by/ associated to a virus, see chapter 6.

Phrased in an encompassing way it means that the world can only exist with all its elements being profoundly attuned to each other, also in- and outside the human body.

The immune system would then need to evaluate the possible advantages of certain 'intruders'. With respect to this the function is not only more than *fighting* and more than *protecting*, it is helping the body to get its necessary resources and prevent it from being killed. From that idea the immune system would be the *exchange system* with the surrounding world. In this way we developed the concept of the immune system from *fighting* to *protecting* to *exchanging*.

3.4 Programs for life and programs for death

The human body is a complex organism. From conception onwards the organism in fact displays two programs: *how can we keep this organism alive* and *how can we let this organism die*. These two processes work together *and* separately at the same time in a chronobiotic relation. They have to find their balance to guarantee the innate maximum time of life. It could be conceived as *programs for life* and *programs for death*.

The immune system would not only function as fighting against intruders, but perhaps even more so by fighting against unintended program changes that emerge, such as the 'program for life' deteriorating into a 'program for death' as a result of the way people live their life. We have to explore further to get a bigger picture of the immune system.

In the context of autoimmune reaction, the concept of *self-tolerance* was developed. Self-tolerance is the ability of the immune system to refrain from destroying the organism's own tissues, which is a prerequisite for proper immune system operation in certain circumstances. This idea of self-tolerance derives from the idea of *fight* instead of *protection* or *exchange*. Phrased from the perspective of protection it would be: due to the detection by the thymus of all tissues that are self or non-self, the immune system does not normally target

the tissues that are recognised and tagged for *self*. Phrased this way, if the immune system attacks self tissues there must be a reason, probably several reasons.

The reason that the immune system attacks self-tissues could be that the self-tissues 1) are tagged as sick cells or 2) are in the vicinity of sick cells. There is a third reason and this one is more refined, because the immune system concerns the body as a whole. So, the immune system could 3) attack certain healthy tissues if this would mean that a new balance could emerge within the body with a totally different part of the body that is dangerously ill, which could lead to death. The *autoimmune reaction* could work by restoring the balance or as a delay for death. This is what the altruistic suicide cells do in a smaller scope: kill themselves for the benefit of others.

3.5 Immune system strategies

From the perspective of *protection* and *exchange*, the immune system develops different actions as strategies for different problems and different circumstances. The organism itself is not only subject to (life threatening) invaders, but can also be destructive to itself. The scope of the immune system in its reactions to cells of and in the body is quite diverse.

Some of its possible actions, *immune system strategies*:

Non-self cells

Kill or destroy a pathogen/vbpf harmful for the body.
Destroy material from outside that is harmful for the body.
Not kill vbpf because it is beneficial to the body.
Not destroy parental tissue of the fetus.
Not destroy foreign tissue because it is beneficial to the body.

Self cells

Not destroy regular healthy cells.
Save cells that give a dying signal.
Kill cells giving off a dying signal.
Destroy a sick cell.
Make a healthy cell sick to stimulate production of antibodies.
Kill a healthy cell to prevent the spread of an illness.
Kill a healthy cell surrounding a harmful event.

Destroy an infected cell.
Cells changing the program from life to death.
Altruistic suicide cell killing itself to help other cells.
Make cells sick to balance the body elsewhere.

In Outline 2 these actions are organised at the level of cells in *'self'* versus *'non-self'* and at the level of action in *'not-destroy/save/self-tolerate* versus *kill/ destroy/quarantine/make sick*.

	Self	**Non-self**
Not destroy/ Save/ Self-tolerate	• regular healthy cells • cells giving off a dying signal	• vbpf that is beneficial to the body • paternal tissue of the fetus • foreign tissue because it is beneficial to the body
Kill/Destroy/ Quarantine/ Make sick	• sick cells • make a healthy cell sick to stimulate production of antibodies • healthy cells to prevent the spreading of an illness/event • healthy cells surrounding a harmful event • cells giving off a dying signal • infected cells • cells changing programs from life to programs for death • altruistic suicide cells • make cells sick to balance the body elsewhere	• vbpf/pathogen harmful for the body • material from outside that is harmful for the body

Outline 2: *Immune system strategies*

3.6 A new pathway

The three pathways of the immune system are all supposed to be aimed at killing, destroying or putting into quarantine of vbpf/pathogens. So, these three could not fulfil all the needs of the immune system as shown above. Going deeper into the immune system we discover quite a broadening of activity. The three pathways are aimed at fighting and destruction: detect pathogen/ destroy

pathogen/ send through for specific destruction/ opsonization for destruction/ destroy by means of specific antibodies/putting into quarantine. But when the immune system is conceived as *protecting* and as *exchanging* with the environment we would need to go further.

Next to the three pathways (1 alternative, 2 lectin and 3 classical), we would suspect a fourth pathway, that needs to be active from the beginning till the end, keeping the optimal life balance by fighting, protecting and exchanging with the surroundings, even sacrificing one part of the body for the benefit of the whole.

4 A new pathway of complement activation

As said before to fulfil the need for protection by the immune system a new pathway is necessary. This one would concern the whole body and the body as a whole. There are some totally new functions that would have to be addressed, for instance save cells that send a dying signal. There is one substance that does exactly that: to protect against cell-death and that is *melatonin*.

In chapter 1, paragraph 1.3.2, we spoke about melatonin in the context of side-effects of medication and described the importance of melatonin in the conclusion: *From three elements together (sleep, reproduction, protection) it can be seen that melatonin has a very refined, important and encompassing role in the body as a whole. It regulates among others sleep, it regulates reproduction, keeps reproduction in good health and is fundamentally protecting the body at an essential level for survival: protecting against cell-death*.

4.1 The scope of Melatonin

Melatonin is very important. It is produced in every organism, even the unicellular organisms. One of its most important roles is to protect against cell death, this is why as we said in paragraph 1.3.2 it would be expected in unicellular organisms, because with only one cell, the protection against cell-death would be of utmost importance.

Several, but not all, functions of melatonin were already addressed in that paragraph: sleep, reproduction and protection against cell death; the ultimate conclusion (3) within that context was:

Melatonin is a fundamental hormone, protecting the organism to fight decline and make survival possible.

We would therefore expect that melatonin would play a role in the immune system, because life and death seems the realm of this hormone and is also the realm of the immune system. What is the connection between Melatonin and the immune system?

We repeat some of the findings concerning melatonin and add further findings to show its connection to the immune system and its role in severe diseases and autoimmune conditions:

- Melatonin is an endogenous regulator of diseases (Roohbakhsh et al., 2018).
- Melatonin is *a*, or better is *the*, pineal hormone that regulates among others circadian rhythms. Its synthesis and secretion comes mainly from the pineal gland during the night, with a peak between 2.00 and 4.00 am (Brzezinski, 1997).
- Melatonin is either stimulated or inhibited by the pineal gland. Its release into the circulation is stimulated by the onset of darkness, followed by a progressive decrease in blood levels with the onset of dawn (Opie et al., 2016).
- Melatonin is also produced in cells of the immune system and in the brain (Ramos et al., 2016).
- Melatonin is the most powerful antioxidant because of its lilophilic feature. Within this feature, it reaches all areas of the body and can easily pass the blood-brain-barrier (Deniz et al., 2016).
- Melatonin plays a role at a very important, deep level. Melatonin has a regulating effect on the brain immune system (Ohgidani et al., 2016).
- Melatonin can modulate the survival of newborn neurons in the adult hippocampus (Ramirez-Rodriguez, 2016).
- Melatonin is an endogenous regulator of diseases (Roohbakhsh et al., 2018).
- The way melatonin works in the disturbance of sleep, chronodisruption, is to repair the clock genes (Acuña-Castroviejo et al., 2017).
- Chronodisruption is associated with alterations of the immune system (Acuña-Castroviejo et al., 2017).
- Melatonin can have a beneficial effect on sleep quality (Fernando & Rombauts, 2014).
- Dysregulations of sleep through jetlag and night shifts provoke an imbalance in the sense of a shortage of melatonin production (Brown et al., 2009; Sack, 2009; Srinivasan et al., 2008; Herxheimer, 2014).
- Melatonin administration can maintain the quality in sleep and help to counteract age-induced cognitive decline. However, the timing of administration of melatonin proves to be more important than the dose (Sack, 2009).
- Melatonin has unique anti-oxidant characteristics and a remarkably benign safety profile in both animal and human studies (Fernando & Rombauts, 2014).

- In the immune system it has a stimulating effect and a potent anti-inflammatory function (Terzi et al., 2016).
- Melatonin plays an important role in procreation. As the immune system can fight against the parental DNA which is non-self material, the role of melatonin in procreation is very important.
- Melatonin exerts a role on the maintenance of a proper follicular function, and is thus important for ovulation and progesterone production (Maganhin et al., 2013).
- Melatonin has been used to foster reproduction. One of the reasons for using melatonin to foster reproduction is that it has a strong antioxidant capacity, and oxidant stress plays a role in infertility (Shiroma et al., 2016).
- Melatonin is considered for treatment of infertility in men (Rad et al., 2013).
- A low melatonin level could be involved in infertility (Rad et al., 2015).
- Melatonin also could play a role to protect the ovarian graft activity in transplantation (Shiroma et al., 2016).
- Being limited to patients with a low fertilization rate in the first cycle (<60%), the fertilization rate dramatically increased after melatonin treatment (35.1 versus 68.2%). The rate of good quality embryos also increased after melatonin treatment (48.0 versus 65.6%) (Nishihara et al., 2014).
- Melatonin is also likely to improve oocyte and embryo quality in women undergoing IVF (In Vitro Fertilization) or IcSI (*Intracytoplasmic Sperm Insemination*) (Batioglu et al., 2012; Kim et al., 2013).
- Melatonin can play a favourable role in PCOS (*Polycystic ovarian syndrome*) and can lead to complete follicular maturation and ovulation (Jain et al., 2013)
- Melatonin can also limit the severity of a variety of cardiovascular and cerebrovascular diseases, diabetes, and cancer (Opie et al., 2016).
- Melatonin increased apoptosis in both tumour cell lines more than twice, while in EA.hy926 cells the apoptosis was increased only by 30%. Antioxidant properties of melatonin were significantly increased in EA. hy926 cells, while in tumour cell lines this effect was much weaker (Chovancova et al., 2017).
- Melatonin plays a role in neuroprotection, stress-depression, excitotoxity and fibromyalgia, has an anti-inflammatory role and secures cell regeneration. Melatonin has an oncostatic property, and inhibits tumour development (Reiter et al., 2008).

- Melatonin appears to be one of the most promising agents for its antioxidant and neuromodulatory action to protect against brain injury related to preterm birth. Robust preclinical evidence and some clinical studies have suggested a neuroprotective benefit conferred by neonatal exposure to melatonin (Colella et al., 2016).
- Melatonin also proves to help in case of a stroke and of an inflammatory response in MS, Multiple Sclerosis (Alvarez-Sanchez, et al., 2017).
- Melatonin therapy reduces the risk of osteoporosis and normalizes bone formation in multiple sclerosis (Ghareghani et al., 2018).
- Experimental and clinical aspects of melatonin and clock genes in diabetes. (Peschke et al., 2015).
- The role of melatonin in multiple sclerosis, Huntington's disease and cerebral ischemia (Escribano et al., 2014).

And these are not all the aspects where melatonin plays a role. The research tradition on melatonin is still at a very early stage, but there is already an overwhelming body of evidence. Atukeren and Uzun (2016) call melatonin the '*orchestrating hormone*' of the body.

Herxheimer (2014) says that the many adverse effects of administrating melatonin in case of sleep problems have not been well researched yet With such diverse and important roles of melatonin within the body, we would expect that with administrating melatonin from outside the body disturbances in the body balance of melatonin could take place in many fields, without us understanding what and why.

Of decisive importance for its role in the immune system is that melatonin is produced in the cells of the immune system, which is a generalist role of melatonin in the immune system, and it is also produced in the cells of the brain (Ramos et al., 2016). Melatonin has also a regulating effect on the brain immune system (Ohgidani et al., 2016), for instance the survival of newborn neurons (Ramirez-Rodriguez, 2016).

In its fight against intruders, the immune system is focussed on inflammation, and here melatonin also plays a role.

It is because of the generalist role on a deep level that we suspect melatonin to play a decisive role in the immune system and is the reason that 'we went looking for it', as Jony Kipnis puts it.

4.2 The melatonin pathway

All this calls for a melatonin pathway of complement activation in the immune system, even as the most prominent and first pathway.

This progressing insight changes the order of the pathways into: 1 the *melatonin pathway* is first to act, from the beginning and remains always active till the end; 2 the *alternative pathway* is second to act and should be called the *second pathway*; 3 the *lectin pathway* is third to act and could be called the *third pathway*; and 4 the *classical pathway* is fourth to act and as a consequence could be called the *fourth pathway*.

Considering this it is time to draw a new schema of the immune system with four pathways and including the multiple strategies described in chapter 3, paragraph 3.5, *Immune system strategies*.

5 The schematic representation of a broader perspective on the immune system

A broader schema of the immune system would have to include the function of protection and exchange, it should contain *four* pathways, and above all the immune system would have to prove to be *the* 'expertise centre' about cells as well as what can happen to them and what should happen with them.

In llustration 10 we see the new expanded schema of the immune system, built bottom-up. Before the immune system can take action it has to discriminate between all kinds of cells, all kind of tissues. It would be the first task to organise where to act and where not. This task is there from the beginning, so first in evolution and with a wide scope of decisions and actions. The start comes therefore from the innate immune system.

The first step of the innate system is to discriminate between cells and to recognise familiar cells. This task is performed by the thymus. This discrimination would first have to be between self and non-self cells, recognising the self-cells and recognising non-self cells. At a second level the discrimination within self-cells between healthy self-cells and self-cells in difficult circumstances, as we pointed out in Outline 2, the *immune system strategies.* At the same level the discrimination within non-self-cells should take place between non-self beneficial cells, paternal cells and non-self pathogens.

The different discriminations lead to three groups triggering different actions:

1: healthy self-cells, beneficial non-self-cells and paternal non-self cells from the fetus: *tag for safe, let through*.

2: self-cells in difficult circumstances, such paraneoplastic actions or cells surrounding an epileptic insult area: *take action to save, to tolerate or to destroy*.

3: non-self pathogens: *take action to kill, destroy or put in quarantine*.

4: non-self pathogens in combination with healthy self-cells. AD to balance a pathogen (see next chapter 6).

In case of 1, the first group with benign cells – self and non-self – the decision is not to take action other than tag for safe, tolerate and let be or let through. This would be supported by the first pathway (melatonin).

In case of 2, second group with self-cells in difficult circumstances – near a dangerous event, near an illness, endangering other cells if they stay alive – the decision is to take action depending of what is needed, such as save, destroy or cure the tissue. Here the four different pathways play a role.

In case of 3, third group the non-self pathogens the innate system tries to destroy it with the NK-cells of the innate system through *the second pathway (2 alternative) and if this is not possible send through to the adaptive system for further action through the third (3 lectin) and fourth (4 classical) pathways.*

In case 4, fourth group the combination of non-self pathogens and healthy self-cells associated to the pathogen. Here the four different pathways play a role (see next chapter 6).

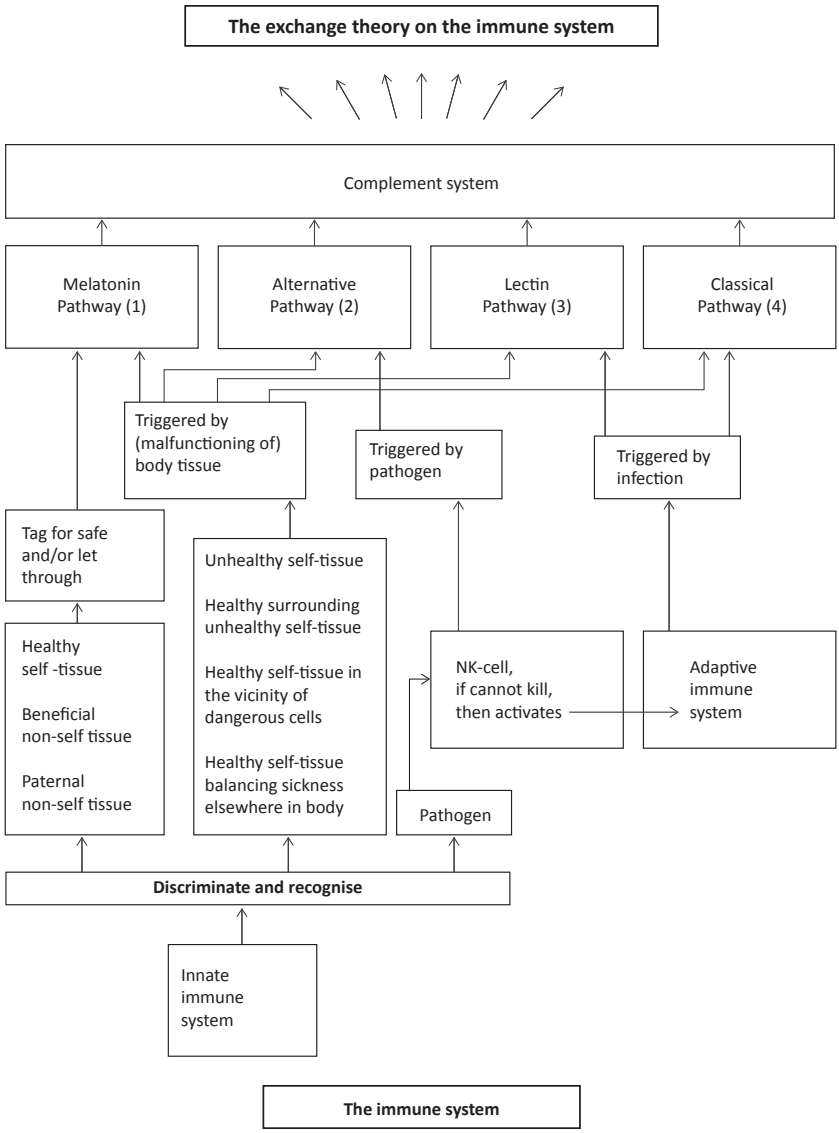
The melatonin pathway (1) and alternative pathway (2) are triggered by the recognition self and non-self. The lectin pathway (3) and the classical pathway (4) are triggered by the ongoing infection.

The melatonin pathway (1) can also activate/hook-up-with the other pathways if necessary. In this way the melatonin pathway (1) is working at the deepest level of life and death.

This is represented in Schema 5.

The theory of exchange could also shed another light on autoimmune reactions, and open the way of thinking about a *protection* instead of a *mistake*, something that has already been proposed because of research showing autoimmune *protection*.

Some actions of the melatonin pathway (1) are called *autoimmune diseases*, and we would prefer to call them *autoimmune reactions*. They are part of the immune system dealing with *healthy* and *unhealthy* own cells.



Schema 5: *A broader perspective on the immune system with the fourth pathway of complement activation and the exchange theory* (Delfos).

6 The autoimmune reactions

We come now to the autoimmune *diseases*, which we said before could be named autoimmune *reactions*.

Two definitions of the *autoimmune disease*:

[Autoimmune disease] …a disease in which the pathology is caused by an adaptive immune response to normal components of healthy tissue (Parham, 2015).

Autoimmune disease results when a breakdown in the mechanisms meant to preserve tolerance of self is severe enough to cause a pathological condition (Sompayrac, 2016).

Along with the terminology (immunity / innate immunity / adaptive immunity) the fight against healthy bodily tissues is called *autoimmunity*. This nomenclature, at first hand, does not seem logical as the concept *immunity,* is used as the – positive – outcome of the immune fight and means protection against a – possible – disease and protecting against a new attack of the disease. In the case of autoimmunity – as conceived until now – the outcome would mean an autoimmune *disease* by attacking healthy tissue and becoming a disease, which would be the other way around to the way we use normally use the term immunity.

As a result of some actions of the immune system when acting from the autoimmunity, we see parts of the body 'malfunctioning'. This is why it seems logical to consider these actions as diseases and call them *autoimmune diseases*. The autoimmune disease is mostly considered a mistake or an error of the body's immune system. It is a phenomenon whereby healthy organs and body tissues are being attacked. In the line of thought of the immune system having the function of fighting against intruders, this explanation would seem logical.

In accordance with this perspective on the immune system autoimmunity is placed as an irrationality of the body, sometimes explained by the accidental production of antibodies that by chance fit to healthy bodily tissues and thus attack them. The idea hereby is that there is an overwhelming production of antibodies in search of the right one needed to attack a certain pathogen and that unintentionally antibodies are produced that hook up to healthy tissue and thereby attack that healthy tissue.

Being narrowly focussed on vbpf which has to be killed, it was a strange idea that the immune system could provoke destruction of normal, healthy tissue. Destruction and killing were associated to the pathogen, not to the healthy tissue.

6.1 Autoimmunity as a derangement

We repeat the remark of Talal mentioned before: *As a phenomenon in immunobiology, autoimmunity affords an opportunity to study the normal regulation of the immune response through examination of one of its major derangements* (Talal, 1980, p. 220). He thus considers autoimmunity as a means to study the immune system when it is 'out of order'. Talal however also states that this perspective poses some problems, because it is amazing that there could be so many mistakes: *The discrimination of self from non-self is an essential and primary function of the immune system, and it is surprising how often and how easily this discriminatory recognition system is disturbed*. Talal felt, and we agree, that with such an ingenious and finely-tuned system as the immune system, the idea of so many errors (autoimmune diseases) would not be logical. Talal goes on with his hesitancy: *The word autoimmunity is used to indicate immunologic self-injury and is not intended to imply an etiology*. And he continues by stipulating that it is not a simple immune reaction: *Genetic, immunologic, and viral factors all play an important role in the pathogenesis of autoimmunity.* Talal gives an example: *Much evidence suggests that genes associated with the major histocompability locus in humans (HLA) may also be important in immune regulation and in the pathogenesis of autoimmunity. For example, some human autoimmune diseases such as chronic active hepatitis and chronic thyroiditis are more frequent in patients with HLA-B8* (Talal, 1980, p. 220).

In their introduction on autoimmunity Pittock and Vincent (2016) mention that many of the disorders now recognized as autoimmune are treatable and reversible, following the line Talal formulated forty years earlier. For instance it became clear that neural antibodies resulted from the body's immune response to cancer. Research shows that a reconsideration of autoimmunity is needed.

Another aspect of the immune system is that it shows important sex differences, also in autoimmunity (Zandman-Goddard, 2006; Nunn, 2009). About

three quarters of patients with AD's are women and the proportion depends on the disease, from 18:1 in thyroiditis/ hypothyroidism to 1:1 in psoriasis to 1:2 in ankylosing spondylitis (Amur et al., 2012). Women are more 'immunocompetent than men (Atukeren and Uzun, 2016).The immune systems of men and women differ in significant ways, especially after puberty. In particular, females are generally more prone to autoimmunity, but 'they experience lower rates of infections and chronic inflammatory disease (Gubbels, 2015). There exist large differences between men and women in prevalence of autoimmune diseases. Women have up to ten time as many autoimmune diseases than men. As research shows that sex differences can have important clinical consequences, it would be interesting to look further at the sex differences in this area.

The *aging process* is also associated with changes in the composition and function of the immune system and these changes may occur at an accelerated speed in men as compared to women. Moreover, after the menopause, the incidence of chronic inflammatory disease in women approaches or exceeds that observed in males. At the same time, the incidence of autoimmunity in post-menopausal women is decreased or equivalent to the rates observed in similarly-aged men. Additional studies addressing the influence of sex on the pathogenesis of chronic and autoimmune diseases in the aged are warranted (Gubbels, 2015).

6.2 From disease to protection

There has to be a deeper reason for the body 'attacking' itself then only by 'mistake'. Probably a mistake is possible, or an inherited mistake is possible, but it is logical that it would not be the only reason for the body attacking itself. There are two reasons why this would not be logical. First, the immune system is so intricate, so ingenious and so vast, working like a perfect orchestra, that simple 'mistakes' seem not so probable. Second, the autoimmune reaction is not a rare event but quite a common one.

Autoimmune reactions should perhaps be viewed as a genuine part of the immune system instead of a mistake of the this system. If *protection* would be the function of the immune system, then autoimmunity would also have to be a protection of the body.

For already a very long time, in fact as an incentive to write this book, we do not view the autoimmune actions of the immune system as just a mistake,

but possibly as purposeful and intended action of the system. In this premise autoimmunity could perhaps and sometimes mean *protection of the body as a whole while attacking a part of the body, or even a desperate attempt to try to save the body being attacked by a life-threatening disease.*

Because real protection is prevention and the ultimate prevention is prevention from death, which certainly concerns the body as a whole, autoimmune reactions could be associated to life-threatening diseases.

When we use a broader perspective, such as *protection* in a specific aspect and even of the body as a whole, we would try to discover whether the attack in one part – the autoimmune reaction – could function as a counterbalance for malfunctioning of the body elsewhere. This opens up to the idea that an autoimmune reaction would not only be a disease but possibly even a 'cure'.

For instance as Talal has already mentioned it is not so clear-cut that autoimmunity is always harmful or an error: *Autoimmunity can be either* transient *and* reversible *or* persistent *and* life-threatening (Talal, 1980, p. 220). Being transient and reversible indicates a possible association of autoimmunity with a balance elsewhere in the body and then not being necessary anymore or being cured or likewise.

In the idea of 'autoimmune' the fact that an autoimmune reaction could be triggered by a *foreign antigen* was not addressed: *…the destruction of normal tissue by the host's immune system in its response to a viral immunogen is considered an 'autoimmune' phenomenon even though the immune response is triggered by a foreign antigen* (Talal, 1980, p. 220). Perhaps we would have to rethink the autoimmunity reaction to a virus, because the immune system has no ultimate strategy for a virus. The simple strategy of firing of antibodies to a virus would not be in order.

Moss (2012) showed *chronic immune system responses* to reactive oxygen species (ROS) in veterans of the Gulf War. The drug used in the Gulf War caused ROS, and the effect of ROS was to modify native molecules, and this then triggered the autoimmune condition we refer to as Gulf War illnesses. Similar mechanisms may apply to other autoimmune illnesses.

Another element that is not easily placed in the concept of the immune system as only a fighting system is the infectious diseases tending to chronicity. For instance the immune responses to several drugs and the process of aging are all associated to a limited form of autoimmunity. The manifestations of autoimmunity disappear upon successful eradication of the infection or discontinuation of the offending drug.

There are 2 main categories of environmental factors involved in autoimmunity: drugs and infectious agents. Many drugs are capable of inducing autoantibodies in large segments of the normal population. These autoantibodies often react against nuclear or erythrocyte antigens. Drug-induced autoimmunity is often asymptomatic and tends to be reversible. Symptoms generally disappear rapidly upon discontinuation of the offending agent, although serologic abnormalities may persist (Talal, 1980, p. 224).

This autoimmune reaction does not seem a mistake, but is elicited by a foreign agent. This would rather indicate a process of protection in balancing the body in case of a problem.

That the idea of an autoimmune disease is too narrow also becomes clear by the fact that there are *many examples of autoimmunity without autoimmune disease* (Talal, 1980, p. 224).

When we presented the melatonin pathway, we showed that the immune system could act against its own tissue. We stipulated before that to have a broader view and stimulate a deeper insight on the immune system it would be better to call those actions of the immune system *autoimmune reactions*.

The body presents an ingenious example of attacking healthy tissue in order to save the whole with an autoimmune reaction in the case of an insult or other CNS injury. From the core of an insult a cell degenerative spread can occur. In order to prevent this, an autoimmune reaction is deployed that kills healthy cells surrounding the insult area, thus stopping the insult area from-spreading, without causing an autoimmune disease (Moalem et al., 1999; Yoles et al., 2001). Moalem and colleagues were the first to speak about protective autoimmunity and Nevo and colleagues call this *protective autoimmunity* (Nevo et al., 2003). As Nevo and colleagues say: *Tolerance to self is thus not a lack of response to self, but the ability to tolerate an active defense response to self without developing an autoimmune disease.* They stipulate that when the injury spreads this means that the intensity of the immune response is weaker than required. In 2004 a mathematical model was conceived by Nevo and colleagues (Nevo et al., 2004) where they postulated that there were three conditions in the fight of autoimmunity against malfunctioning of the body (*autoimmune situations)*:

1: *Autoimmunity operates and wins.*
2: *Autoimmunity cannot compete with the ongoing loss.*
3: *Autoimmunity causes the loss of tissue.*

We think there could be a fourth and fifth *autoimmunesituation*:

4: *Autoimmunity constantly balances the ongoing malfunctioning of the body.*
5. *Autoimmunity has to deliver such a fierce and ongoing fight that the disease elements become the foreground.*

In 2004, Schwartz and Kipnis, eleven years before the discovery of the brain being connected to the immune system spoke about the protective capacity of the immune system (Schwartz & Kipnis, 2004; 2005). At an early stage Schwartz and colleagues already spoke about a function of 'protective autoimmunity' to the CNS immunosurveillance by immune cells circulating in the brain. Schwartz has continuously stressed that autoimmunity has a protective role in CNS injuries and pathological conditions and could play a preventive role (Schwartz & Ziv, 2008; Schwartz & Schechter, 2010; Schwartz & Ziv, 2014; Schwartz & Raposo, 2014).

6.3 Paraneoplastic syndromes

Sometimes neoplasms grow that can be benign or can become cancerous tumours. In the case of cancer an autoimmune reaction very often accompanies the cancer, called the *paraneoplastic autoimmune diseases* or *paraneoplastic syndromes, PNS*. They are considered a side effect of the damaging cancer tumour formation in the body. Somewhere there is an association between the cancer and paraneoplastic syndrome. Instead of thinking that the cancer coexists with autoimmune diseases, it would be interesting to find out if these autoimmune reactions could be an attempt of the body to balance the cancer. It would be logical that it has a role in the case of cancer, because it often occurs when cancer is showing itself.

The PNS is a consequence of remote effects of tumours on different organ systems, sometimes even years before the tumour is apparent (Zaborowski et al., 2014; Höftberger, 2015). Not only is the pathogenesis different, but the PNS is also more severe and often presents a broader range of clinical symptoms (Maverakis et al., 2012). A large number of cancer patients show CNS involvement (Höftberger et al., 2015). The first report of a paraneoplastic syndrome has been attributed to a French physician, M. Auché, who described peripheral nervous system involvement in cancer patients in 1890 (Auché, M., 1890).

PNS is often in found in combination with specific cancers. Paraneoplastic cerebellar degeneration, for instance, is a syndrome that occurs predominantly in patients with cancer of the ovary, uterus, or adnexa; cancer of the breast; small-cell carcinoma of the lung; or Hodgkin lymphoma (Zaborowski et al., 2014; Graus et al., 2014).

We could consider these events (tumours and PNS) as an interaction where the PNS plays a role in the balance of the body as a whole. We need more research on the associations and more insight into the role of autoimmunity to develop this idea. This association between cancer and paraneoplastic syndromes could be what we mentioned before: *4: Autoimmunity constantly balances the ongoing malfunctioning of the body*. But also : 5. *Autoimmunity has to deliver such a fierce and ongoing fight that the disease elements become the foreground.* When a tumour in the end shows itself it could be what was mentioned before: 2 *Autoimmunity cannot compete with the ongoing loss*.

An example to illustrate this:

> ✠ *A man in his forties shows extreme concentration problems and forgetfulness. Psychological treatment does not have any succes. Looking further, two and a half years before the man had prostate problems and showed higher PSA-values. The 'psychological' problems got worse but the PSA disappeared. Then the diagnosis of auto-immune dementia was proposed. As there was not yet evidence of a lymphatic system in the brain, this diagnosis was not valid, and it was called atypical Alzheimer. The prostrate problems were absent, but the 'atypical Alzheimer progressed very seriously, and the man suffered tremendously from 'autoimmune-dementia.'* ✠

6.4 The virus and autoimmune reaction

The one antigen that definitely causes problems for the immune system is the virus. As we said, speaking about the *exchange theory*, the virus does not seem aimed at the rich resources of the human body but at destroying it. The more refined way to destruction is by misleading the immune system. In paragraph 3.3 we referred to sialic acid sugars operating in a way that the immune system can be misled and consider – incorrectly – a cell good while it is actually a cancer cell. Sialic acid could be one of the agents in misleading the immune

system. Thus we would expect an association between sialic acid and viruses, which effectively is the case (Mahajan & Pillai, 2016).

If the virus aims at destryoing the body, the question that immediately asks for attention is whether viruses are associated to *autoimmune diseases*. And effectively they are. Research does not show a direct causal relation between the virus and the autoimmune reactions, but the correlation is not a rare case. We already mentioned that the immune system is more or less helpless against viruses and cannot fire antibodies, so there is no direct connection. And more interestingly, the important devastating viruses are often associated to Systemic Autoimmune Diseases (SAD). Rephrased: when viruses have a *systemic* influence the autoimune system often seemsto also react with *systemic* autoimmune diseases. As said before, it is not always clear that there is a causal relationship, but often it is clear that it is being triggered by the virus. It is also unclear whether the treatment for the virus – for instance *Highly Active Antiretroviral Therapy* HAART in case of HIV – plays a role. But there is also evidence that an autoimmune reaction preceded the virus infection (Iordache et al., 2014).

How could it be triggered? We need a statistical element to explain this, the intervening variable, see Figure 1.

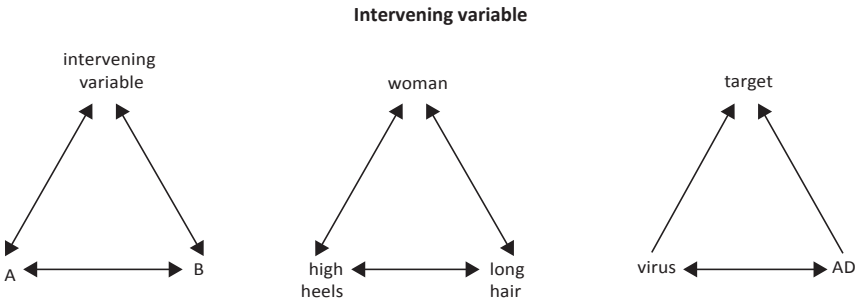


Figure 1: *Left: the intervening variable; middle a far-fetched interpretation of a relation between A and B with its intervening variable; right the target is the intervening variable for the relation between virus and* AD.

From Figure 1 it becomes clear that when there is a relation, one has to look further for the deeper causal connection. A third factor, the intervening variable, may possibly be the explanatory factor. The virus has its target In the systemic virus, the target is multifocal and can change when one area has not been succesful, or when treatment and even better autoimmune reactions stopped the damage from the virus. The autoimmune reaction works on the target of

the virus. That is why it is such a devastating fight when the virus changes its target and the autoimmune reaction also has to do that.

In outline 3 we show some of the evidence of the presence of AD in the case of a virus. We have arranged the evidence per virus: HIV, EBV, CMV, HV.

Virus	Autoimmune reactions
Human Immunodeficiency Virus HIV	• Vasculitis; Immune cytopenias; Rheumatic diseases; Lupus; Sarcodoisis; Thyroid disease; Hepatic disease; Antiphospholipid syndrome. Iordache et al., 2014. • Autoimmune arthritis. Yang et al., 2015. • ITP-Immune Thrombocytopaenic Purpura (systemic autoimmune). Rinaldi et al., 2014.
Epstein-Barr virus EBV	• Systemic Lupus Erythematosus (SLE); Rheumatoid Arthritis (RA); and Sjögren's Syndrome (SS). Holck Draborg et al., 2013; Harley et al., 2018. • Systemic Lupus Erythematosus. Rasmussen et al., 2015. • ITP-Immune Thrombocytopaenic Purpura (systemic autoimmune). Rinaldi et al., 2014. • Autoimmune thyroid diseases, including Graves' and Hashimoto's thyroiditis. Janekova et al., 2015. • Perhaps Multiple Sclerosis (MS). Pakspoor et al., 2013; Harley et al., 2018.
Cymegalo virus CMV	• Systemic Lupus Erythematosus (SLE). Rasmussen et al., 2015. • Systemic Autoimmune Diseases (SAD); Systemic Sclerosis (SSc); Systemic Lupus Erythematosus (SLE). Janahi et al., 2018. • ITP-Immune Thrombocytopaenic Purpura (systemic autoimmune). Rinaldi et al., 2014.
Herpes virus HV	• Autoimmune encephalopathy/anti-NMDAR encephalitis. Venkatesan & Benavides, 2015. • Possibly Rasmussen's Encephalitis (RE) and Febrile Infection-related Epilepsy Syndrome (FIRES) could be diagnosed as AD's. Venkatesan & Benavides, 2015. • Dementia. Chen et al., 2018.

Outline 3: *Viruses and autoimmune reactions*

Aside from the autoimmune reaction to a virus, there has been for a very long time a debate about the autoimmune reaction to vaccination. The article by Wakefield (1998) in *Nature*, where he showed a causal relation between autism and vaccination has been under debate for quite some time and his article was

retracted from *Nature*. The debate however goes on, and not only with the findings of Wakefield. The problem here is an ethical, a methodological and a theoretical one.

1. *Ethical*: The research on vaccination is often under pressure from the pharmalogical industry, and research and researchers should be absolutely without conflict of interest.
2. *The research:* To examine the hypothesis of Wakefield a cohort research was completed about prevalence. This is from the idea that there would be a clear-cut causal relation between A and B, in this case between the vaccination and autism. When we look at Figure 1 we could do better methodologically with *incidence* instead of *prevalence* research. The incidence research would give the result that it sometimes happened, but not always, and not at a high frequency. If we look at *variance analysis* instead of *statistical significance*, we could single out intervening variables.
3. *The theoretical problem:* The question of autism. What had been proven is that sometiems after vaccination an AD occurred: colitis ulcerosa. This AD could be a autoimmune recation to the vaccination in some children. But colitis ulcerosa can be quite a burdening disease and children can be very ill because of that AD. When people are very ill they withdrawn into themselves and operate more in ther surviving than socialising mode. What happens then is 'autistic behaviour', not autism. In the new theory on *autism* this part of behaviour is called ABIM, *Autistic Behaviour Induced by a Medical condition* (Delfos, 2017). Autism is based on a genetic pattern, and we cannot expect a vaccination change a genetic pattern, but it *can* trigger AD's such as colitis ulcerosa and make a child feel ill.

The debate about an autoimmune reaction/disease after vaccination goes on. But it would be sensible to take it seriously and look for the factors that could lead to a highly responsive immune system, even when it is not at a high frequency, it demands further research. Medical science never refused to focus on a low frequency problem.

If sialic acid is an agent associated to viruses, then here too we would expect an association with autoimmune diseases, and again this association is correct (Stencel-Baerenwald et al., 2014).

Of course there are more associations between events in the body. One of them is the puzzle of the Epstein-Barr virus (EBV) that triggers autoimmune reactions and is associated to gene expression (Harley et al., 2018), which we will discuss in the next chapter when we examine the case of Anorexia Nervosa.

7 Anorexia as a case in general and specific autoimmunity[1]

In this chapter we want to present a theoretical case, *anorexia nervosa* (AN), to elaborate on the idea from chapter 6.2, *autoimmunesituations* and examine: *4 Autoimmunity constantly balancing the ongoing malfunctioning of the body*. This idea is what ultimately triggered us researching the immune system and autoimmunity resulting in this book on the immune system.

Anorexia as such (Calorie Restriction, CR) is considered one of the general symptoms associated to illness just as fever or fatigue. These are considered adaptive responses to promote survival. For instance in cancer anorexia frequently characterizes the clinical journey of patients with cancer and affects patients' morbidity, mortality, and quality of life (Laviano, 2008).
Anorexia is not only immune but also autoimmune (McCusker & Kelley, 2013). There is evidence that anorexia nervosa is an autoimmune or a dysimmune disease and is associated to immune activity (Gorwood et al., 2016; Fetissov et al., 2002; 2017; Fetissov & Déchelotte, 2008).
Thus anorexia presents as a *general symptom* of (auto)immune reactions as well as *specifically* as an autoimmune disease. This is why we examine the case of Anorexia Nervosa (AN) and focus on the relation between ghrelin and eating disorders.

7.1 The etiology of eating disorders

Anorexia nervosa is an eating disorder which has been under debate with reference to *nature versus nurture* for as long as it has existed. There is probably an intense interaction with the environment and it is considered a multifactorial condition (Gorwood et al., 2016), and there are indications that it is a condition that is predisposed. The etiology of eating disorders (anorexia nervosa, bulimia nervosa and obesity), to an important extent is still a medical mystery. Although anorexia nervosa (AN) is classified as a psychiatric disease, the clinical observa-

1 This chapter was written in collaboration with Fiemke Griffioen-Both

tions that it involves multiple organ dysfunction, in addition to the core behavioral and psychiatric symptoms, underline the need for an integrative pathophysiological approach (Gorwood et al., 2016). Explanations founded only on a psychological or a psychiatric basis show themselves to be no longer uniquely valid. The multifactorial etiology of AN includes psychological, familial, environmental, societal, genetic, and other biological factors (Sokol et al., 2009; Attia, 2010; Scherag, et al., 2010; Gorwood et al., 2016). Several medical markers have been discovered with respect to AN, such as genes (for instance the AgRP-gene, Vink et al., 2001) and hormonal environment (Day et al., 2009) and dysimmunity (Gorwood et al., 2016) and ghrelin-associated immune problems (Fetissov et al., 2017). The search is still going on for the exact genetic association.

Day, Ternouth and Collier (2009) state that eating disorders should be considered as one group of disorders, including obesity, sharing genetic similarities such as the brain-derived neurotrophic factor (BDNF) gene, in which the valine allele of the Val66Met amino acid polymorphism predisposes to obesity, whereas the methionine allele predisposes to eating disorders.

As for a long time AN was not considered a medical condition, but a psychiatric condition involving medical consequences, research was mainly about the medical consequences of eating disorders, such as heart or kidney failure. The physical onset factors in eating disorders are becoming the focus of attention. This is important because eating disorders can have serious consequences and tend to become chronic (Steinhausen, 2009).

Especially mortality in the case of AN is very high (Birmingham et al., 2005; Signorini et al., 2007), higher than in any other psychiatric disorder (Sullivan, 1995; Vitiello & Lederhendler, 2000).It is striking however that this mortality is not so much caused by the physical consequences of AN, but most often by suicide (Papadopoulos et al., 2009.

One of the biological factors discovered to play a role in eating disorders is the hormone ghrelin.

7.2 The 'appetite' hormone ghrelin

The hormone ghrelin was discovered in 1999 (Kojima et al., 1999). Ghrelin is a hormone released in the gastrointestinal tract (Ariyasu et al., 2001). It is a 28-amino acid peptide and stimulates among other things the release of the growth hormone and insulin (Dezaki et al., 2004). Two major forms of ghrelin

are found in blood and tissue: n-octanoyl modified (active form) and desacyl ghrelin (inactive form) (Kojima et al., 2005). The desacyl inactive form can cross the blood-brain-barrier. Ghrelin is mostly produced in the stomach, and in smaller quantities in the pancreas, bowel, kidney, pituitary and hypothalamus (Kojima et al., 2005). Ghrelin is mainly synthesized in the stomach and the gut (Bresciani et al., 2008), but also in the salivary glands (Rauh et al., 2005; Ghelardoni et al., 2006). Ghrelin has also been discovered in human milk, saliva and urine (Aydin et al., 2006; Ilcol & Hizli, 2007; Groschl et al., 2005; Aydin et al., 2005).

Ghrelin level is negatively correlated to BMI (Shiiya et al., 2002; Troisi et al., 2005; Cordona, 2017), that is the higher the BMI, the lower the level of ghrelin and vice versa. The BMI is an index of body weight. It is calculated with the formula weight divided by length multiplied by itself: kg/m^2. The BMI can be a measure for health of weight: normal/ underweight /overweight.

Ghrelin is considered to stimulate food intake in humans (Wren et al., 2001). It peaks before a meal, then decreases shortly after the beginning of a meal and increases again to a peak (Cummings et al., 2001).

Ghrelin is associated with meals, although the level of plasma ghrelin does not correspond to the size of the meal (Callahan et al., 2004). Its function is more general in supporting the metabolism in its appetite and food intake. Ghrelin is more than an appetite hormone which we can deduce from the fact that the highest level of ghrelin is seen during the early morning (2.00 h, see Figure 2) when normally there has been no food intake and no food intake coming up soon (Shiiya et al., 2002; Cummings et al., 2001).

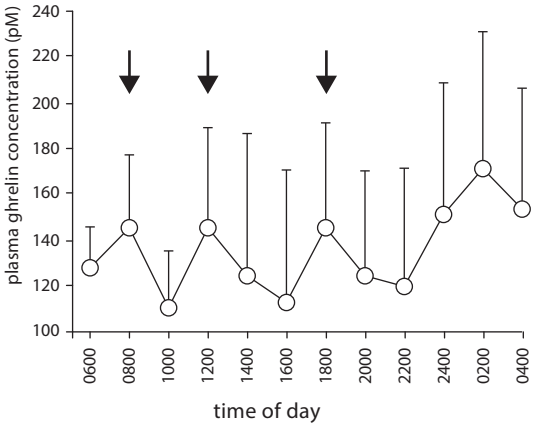


Figure 2: *A 24h plasma ghrelin profile from normal subjects. Arrows denote meal times* (Shiiya et al., 2002).

The ghrelin peak observed in the early morning is likely to be caused by sleep-associated processes, because participants who are not allowed to sleep show a blunted ghrelin peak in the early night compared to participants who were allowed to sleep (Dzaja et al., 2004). Weikel and colleagues (2003) also found a relation between sleep and ghrelin: administration of ghrelin during sleep resulted in an increase in slow-wave sleep and a decrease in REM-sleep. They conclude that ghrelin is a sleep-promoting factor. Another association is the hormone melatonin, which plays an important role in regulating sleep and and also shows a peak production at 2 am till 4 am (Brzezinski, 1997).

Ghrelin is one of many factors involved in the control of appetite. Others are leptin, insulin, cholecystokinin, pancreatic polypeptide, peptide YY, glucagon-like peptide 1 and oxyntomodulin (Murphy and Bloom, 2004). These hormones stimulate or inhibit different areas within the hypothalamus (Cowley et al., 1999). The hypothalamus plays an important role in the metabolism of glucose (Swaab, 2003) and antibodies directed against chemical messengers in the hypothalamus involved in regulating eating and metabolism have indeed been found in the blood of anorexia patients (Swaab, 2004).

7.3 Ghrelin levels in eating disorders

To understand the relation between appetite and eating disorders research was performed concentrating on ghrelin levels involved in appetite and satiety. More specifically, research into the level of ghrelin over time after solid or liquid meals or intravenous glucose administration. Articles in which the baseline level of ghrelin was measured but not the response of ghrelin to food-intake were not used. Also, studies examining (hormonal) response to ghrelin administration were not useful for the current research. In addition, many articles about (measuring the level of) ghrelin in general without linking it to eating disorders could not be used for this ghrelin pattern study in eating disorders.

7.3.1 Ghrelin pattern after test meal or intravenous glucose

The plasma ghrelin levels differ substantially between the different studies. For this, there may be several reasons. First, the different studies have diverse measurement moments during the day, and the ghrelin level depends upon the time of day and the composition of food eaten before measurement. Second, the participants in the control groups are not all comparable, for instance Stock and colleagues (Stock et al., 2005) selected a group of adolescents, the others

selected adult participants. Third, in the case of AN it was not always clear whether patients who took part in the study were receiving tube feeding as a regular treatment or were receiving regular meals, nor did all studies mention the different types of AN: restrictive versus purging.

7.3.2 Obesity

Ghrelin levels are different for obese compared to non-obese, normal weight subjects. Ghrelin concentrates are 27% lower in obese women compared to normal-weight subjects (Tschop et al., 2001; English et al., 2002). Meals do not influence ghrelin levels significantly in obese women compared to healthy participants (English et al., 2002). However, weight loss in obese women increases ghrelin levels (Hansen et al., 2002).

Figures 3 a-c show the plasma ghrelin levels of control and obese participants from three different studies (Figure 3a: English et al., 2002, Figure 3b: Le Roux et al., 2005, Figure 3c: Stock et al., 2005). The solid and dashed lines in the fourth graph (Figure 3d) show the average ghrelin levels for the two groups: obesity versus control.

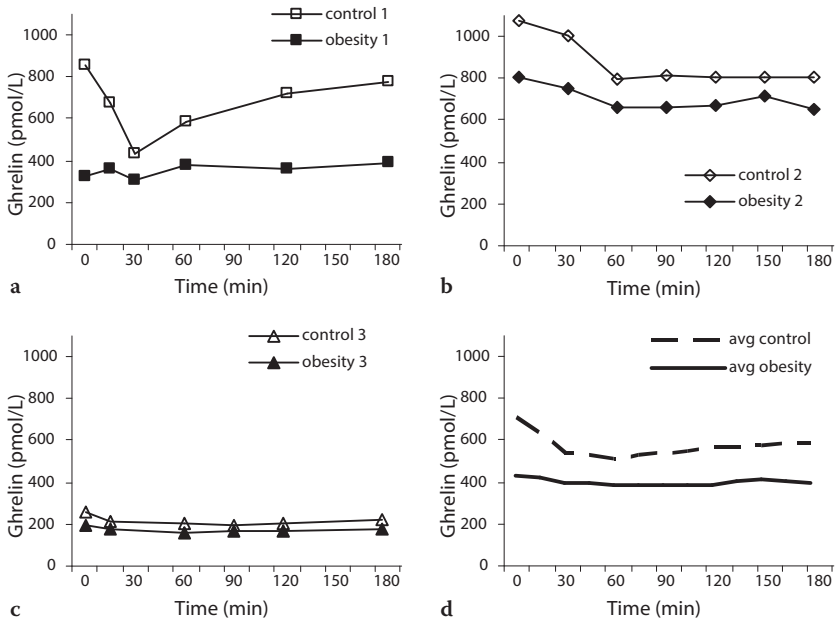


Figure 3 a-d: *Ghrelin levels in obese and control, non-obese participants. Sources: 3a: control and obesity, study 1* (English et al., 2002), *3b: control and obesity, study 2* (Le Roux et al., 2005), *3c control and obesity, study 3* (Stock et al., 2005). *In Figure 3d the average for the three studies is shown.*

The studies we investigated all show the same pattern: in obese participants the ghrelin level is lower compared to the control group. Also, the absolute drop of the ghrelin level shortly after the start of the meal is significantly less in obese participants than in the control group (see Figure 3 a-c) (Stock et al., 2005; Le Roux et al., 2005; English et al., 2002). The same three studies also found that the baseline ghrelin levels are continuously lower in the obese groups than in the control groups, and never reach the baseline level of the control groups. This lower level of ghrelin in general in obese people has been confirmed in later research (Cordona, 2017).

7.3.3 Bulimia Nervosa

In bulimic people both elevated (Fassino et al., 2005; Tanaka et al., 2002) and normal (Troisi et al., 2005; Monteleone et al., 2005) levels of ghrelin have been found compared to healthy people. These four studies have all measured the levels of ghrelin in the morning after the participants had an overnight fast, and as such are not representative for the level of ghrelin over time, and after a meal pertinent to this particular study. The studies that measured ghrelin levels over time, however, agree that the pattern is different for BN and healthy persons (Monteleone et al., 2003; Kojima et al., 2005; see section *Ghrelin pattern after test meal or intravenous glucose*). There is a normal response of other hormones (growth hormone amongst other) to ghrelin when given intravenously (Fassino et al., 2005). Fassino and colleagues conclude that the elevated ghrelin levels may play a role in the specific eating behavior.

Researchers do not agree on the relation between ghrelin and the severity and frequency of binge-purging behavior. Both positive (Tanaka et al., 2003a), negative (Troisi et al., 2005), and no correlations (Monteleone et al., 2005) have been found in different studies between severity of binge-purging behavior and ghrelin.

Both studies with BN groups show a similar ghrelin pattern over time with respect to the drop of ghrelin level after a meal, see Figure 4 a-b. After the test meal, the participants with BN showed a significantly smaller drop in ghrelin than the participants in the control group. The baseline plasma ghrelin level of the BN group (Kojima et al., 2005) is slightly higher than the control group ($p = 0.04$). The second study (Monteleone et al., 2003) found no significant difference in baseline ghrelin levels (see Figure 4 a-b). The solid and dashed lines in the third graph (4c) show the average ghrelin levels for the two groups: BN versus control.

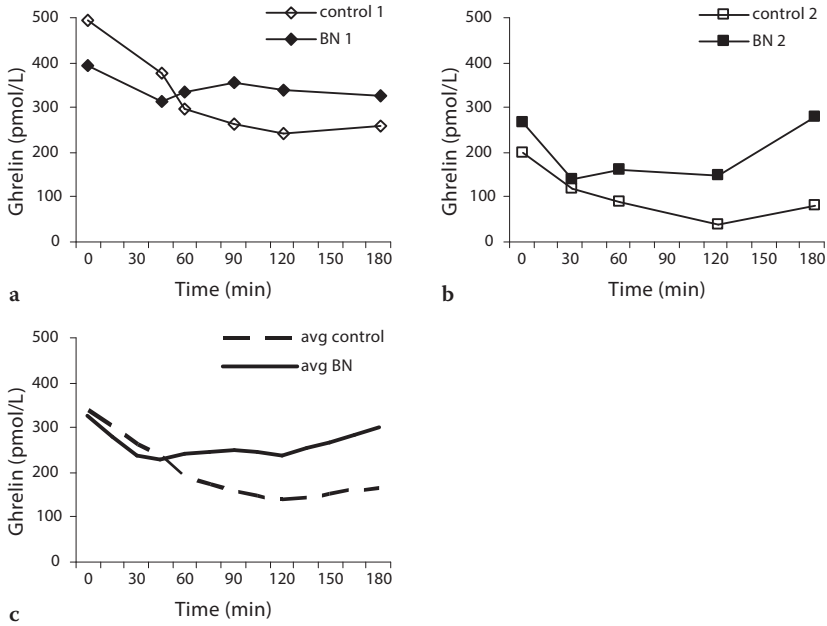


Figure 4 a-c: *Plasma ghrelin levels in pmol/l in control and bulimic participants. Sources: 4a: control and BN, study 1* (Monteleone et al., 2003)*, 4b: control and BN, study 2* (Kojima et al., 2005)*. In Figure 4c the average for the two studies is shown.*

Two studies that are slightly contradictory are not enough for a solid conclusion, but it is interesting that the graphs in both studies show a change, a kind of breaking point that seems to be associated to the changing eating behavior: taking in food and purging the food. Both studies show high ghrelin when the purging is in order, not following the ghrelin pattern of obesity but of AN as we will see.

7.3.4 Anorexia Nervosa

Persons with AN have high levels of ghrelin, hyperghrelinemia (Shiiya et al., 2002; Troisi et al., 2005), and an abnormal endocrine and appetite response to intravenous ghrelin (Broglio et al., 2004; Miljic et al., 2006) compared to healthy subjects. Intravenous ghrelin does not seem to increase appetite in AN patients, despite the elevated baseline level of ghrelin, while it increases appetite in healthy persons with low body weight (Miljic et al., 2006). The response of growth hormone and glucose to ghrelin was blunted compared to healthy persons (Broglio et al., 2004). Both studies conclude that AN patients seem to have

an 'insensitivity' to ghrelin. The effect of therapy of anorectic patients on their ghrelin levels has been researched. The results were conflicting: one study found lower ghrelin levels after a diet and cognitive-behavioral psychotherapy (Janas-Kozik et al., 2007). Others found no change in ghrelin levels after therapy (Nakahara et al., 2006).

A difference has been found between AN restrictive type and AN with binge-purging behavior: the latter show even higher levels of ghrelin, while their BMI's were the same (Tanaka et al., 2003a). According to the researchers, these results suggest that BMI as well as binge-purging behavior are associated to the ghrelin level.

Figures 5 a-c show the plasma ghrelin levels of control and anorectic participants from three different studies (Nakai et al., 2003; Stock et al., 2005; Nedvidkova et al., 2003). All studies showed a higher baseline value of ghrelin compared to the control groups, never returning back to the level of healthy controls. The pattern after a meal is inconsistent: some found a rise instead of a clear drop in ghrelin level in the anorectic group compared to the control group (Nedvidkova et al., 2003), others found a similar drop in ghrelin level in the AN group compared to a control group (Nakai et al., 2003; Stock et al., 2005), see Figure 5 a-c. The solid and dashed lines in the fourth graph (5d) show the average ghrelin levels for the three groups: AN versus control.

All studies observed continuous higher ghrelin levels over time in anorectic groups compared to control groups.

This high level of ghrelin in general in people with AN has been confirmed in later research (Cordona, 2017).

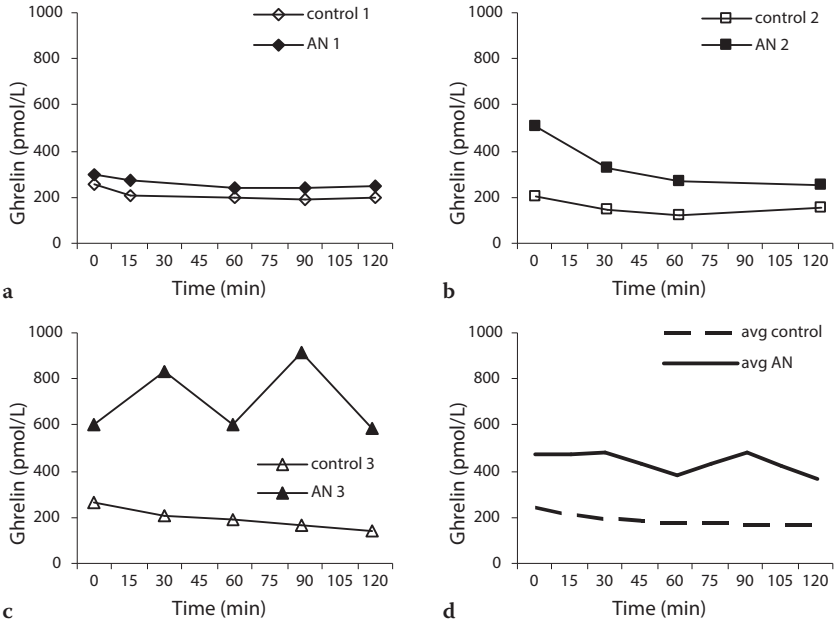


Figure 5 a-d: *Ghrelin levels in control and AN participants. Sources: 5a: control and AN, study 1* (Stock et al., 2005)*, 5b: control and AN, study 2* (Nakai et al., 2003)*, 5c: control and AN, study 3* (Nedvidkova et al., 2003)*. In Figure 5d the average for the three studies is shown.*

7.3.5 Binge Eating Disorder

Binge eating disorder, BED, was not considered to be a regular eating disorder. It would be more correct to call it a deviant eating pattern, consisting of eating large quantities of food on a regular basis, without restrictions. The DSM-IV-R (APA, 2000) did not consider binge eating as an eating disorder, but Binge Eating Disorder has been introduced in the DSM-5 (APA, 2013). For that reason not much research on BED exists, and the fact that we have only one study on the level of ghrelin in people with BED, we do not include this eating behavior in our analysis. We only give a brief impression to compare this eating problem with eating disorders, especially obesity.

Geliebter, Gluck and Hashim (2005) found a significant difference between BED and 'normal' obese participants, the first having a lower ghrelin level. Monteleone et al (2005) found a significantly lower baseline value of ghrelin in participants with BED, with no difference between BED with and without obesity. In the case of Binge Eating Disorder (BED) the level of ghrelin is not signifi-

cantly lower than healthy people when measured after overnight fasting (Troisi et al., 2005).

To our knowledge, there exists only one study with a BED group that measured plasma ghrelin levels before and after a test meal (Geliebter et al., 2005).

The results for the simple obese and BED groups are shown in Figure 6. Considering that the ghrelin patterns of the obese groups from Figure 3 all show a blunted response to ghrelin compared to the control groups, and assuming this is true for the participants in Geliebter's study too, the BED pattern in Figure 6 (persons with BED and obesity) can be considered as even more blunted.

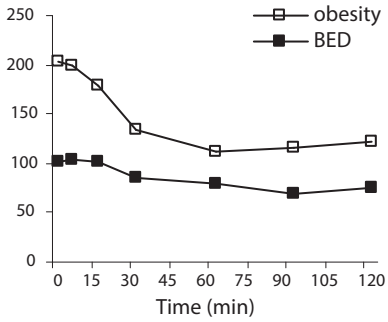


Figure 6: *Average plasma ghrelin levels for obesity and BED (with obesity)*

7.3.6 Summarizing graphics

To summarize the results of our literature study, Figure 7 shows the relative difference in plasma ghrelin levels between the obese, BN and AN groups and their accompanying control groups. The very high level over time in AN patients is very distinct, as is the continuously low level in obese patients. Both do not reach the baseline levels of the control groups. The difference with healthy persons is quite obvious. BN patients show a complex pattern in two phases, in the beginning a low level, resembling the obese patient, and further on at a higher level more similar to an AN patient. The higher level in BN persons is a consequent pattern, but not as extreme as is the case with AN.

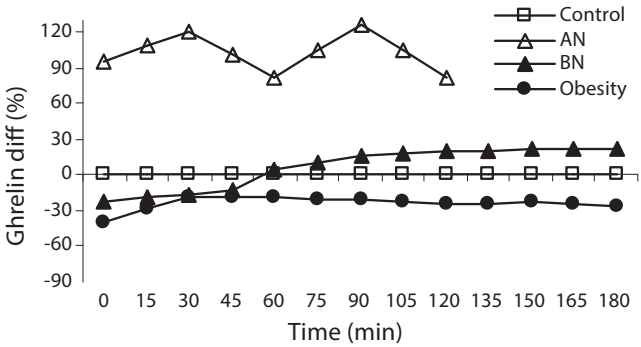


Figure 7: *Relative differences between the average plasma ghrelin level of each eating disorder (AN, BN, obesity) and the corresponding control groups.*

We only can give a tentative interpretation of the mechanism as it shows itself from the studies incorporated in this review. Many factors should be taken into account, but we choose to limit ourselves to ghrelin in combination with insulin. There exists a distinct relation between ghrelin and insulin; the drop of ghrelin stimulates the production of insulin, important in the processing of food (Dezaki et al., 2004). High levels of ghrelin are supposed to go along with low insulin and vice versa. The high level of ghrelin in patients with AN could thus help the metabolism to limit the production of insulin, which would be wise as there is nearly no food to process. The low level of ghrelin in obesity perhaps reflects the tendency of the body to keep producing insulin to process the large quantity of food intake on a daily basis. The two phase ghrelin mechanism in patients with BN could reflect the metabolism starting with the meal coming up to enable the production of insulin for the large food intake. Then the metabolism could shift to the opposite process by augmenting the level of ghrelin and thus refraining from the production of insulin as the food will be not have to be processed because it will be purged. Taken from this perspective ghrelin would not only stimulate food intake but if necessary also inhibit food intake. Instead of speaking about an insensitivity to ghrelin in the case of AN (Miljic et al., 2006; Broglio et al., 2004), we would prefer to consider it *an interaction between ghrelin and insulin* in order to keep a balance between food and insulin. The one study about BED supports the hypothesis that ghrelin tends to regulate the food intake of the body, stimulating insulin production by keeping the ghrelin level low.

7.3.7 Resuming our results

To end paragraph 7.3, an interpretation towards a tentative hypothesis:

> ⊠ *The level of ghrelin tends to be higher in the case of* AN*, keeping the body 'hungry' and refraining from the production of insulin. In obesity the level is lower, tending to keep the body 'satiated' and trying to process the food by stimulating insulin production. In the case of* BN *the body shifts from 'satiated' to 'hungry' along with the behaviour of food intake and purging.* ⊠

The body is kept in 'hunger' and 'fear of eating' at the same time.

7.4 Smelling favorite and unfavorite food and the level of ghrelin

How is it possible that the body is kept hungry, without eating? In AN it seems about high ghrelin and low body weight. How could this be organised in the body?

In a study about the kind of food intake and plasma ghrelin levels, healthy subjects were compared to AN subjects and weight-restored subjects. There were two sessions, one with favorite food (hedonic), one with unfavorite food (non-hedonic). The subjects were exposed at a first session to their favorite food (most subjects chose chocolate) by smelling the food for 5 minutes and then asked to eat it within 10 minutes. In the second session, one week later, they were exposed in the same way to their unfavorite food. The results for plasma ghrelin levels are shown in Figure 8.

The healthy and weight-restored subjects showed more or less the same pattern of plasma ghrelin level, that is a small rise of plasma ghrelin level with the smell of unfavorite food and a much stronger rise with the smell of favorite food. Both groups showed a drop half an hour later and following this a small rise until 135 minutes after the start. The level after 135 minutes was still higher than before starting the session. For people with AN the situation was totally different. At the start of both sessions (favorite/hedonic and unfavorite food/non-hedonic) the level of ghrelin was higher in the subjects of the AN group than in the healthy and weight-restored groups. Instead of plasma ghrelin levels increasing as in both other groups, in the AN group by smelling the food

(favorite and unfavorite) the plasma ghrelin level decreased rapidly and went on decreasing more slowly. All three groups showed that after 135 minutes they had not regained their normal ghrelin level from the beginning. The level of ghrelin was higher in all three groups for the favorite food and much less for the unfavorite food, and the level for ghrelin was higher in the AN group than in the healthy and the weight-restored group in both sessions.

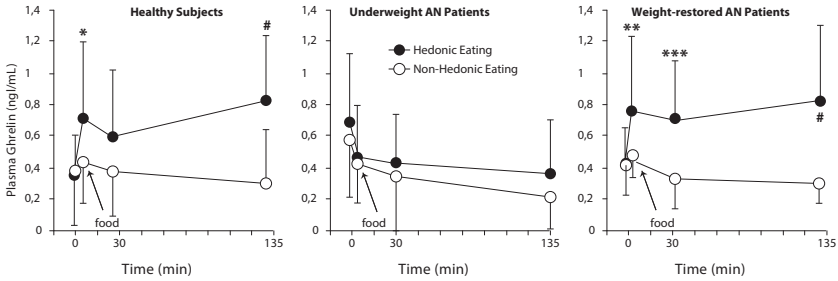


Figure 8: *Plasma levels of ghrelin after hedonic and non-hedonic eating in healthy subjects (n=7; left panel), underweight patients with anorexia nervosa (AN) (n=7; middle panel) and weight-restored patients with AN (n=7; right panel). Data are expressed as mean ± SD. The arrows indicate when the subjects started to eat the test meal. *P<0.05, **P<0.02, ***P=0.005, P#<0.001 as compared to non-hedonic eating (post-hoc Tukey's test)* (Monteleone et al., 2016).

The comparison with the plasma ghrelin levels from the studies we showed before is difficult to make. First is that in the last study it was about 'extreme' food, that is favorite and unfavorite, and we do not know what would happen with 'normal' food. Second is the difference in food intake. In the last study food intake was preceded by smelling the food for 5 minutes. It is remarkable that in both situations (first studies and last study) the ghrelin level in the AN-group was higher at the start than the healthy/weight-restored/control groups, which is consistent with the result of the previous studies.

These results suggest a derangement in the ghrelin modulation of food-related pleasurable and rewarding feelings, which might sustain the reduced motivation toward food intake of acute AN patients (Monteleone et al., 2016). It also suggests that the food intake in AN is less related to the kind of food but to food in general and that the level of ghreline is higher in the AN patients than in any other group. The question is how and why that derangement could take place.

7.5 The protective role of calorie restriction

The beneficial effects of *calorie restriction* have been described at both organismal and cellular levels in multiple organs (Hornsby et al., 2016). The relation between high CR and high ghrelin are also well-documented as shown before. Bayliss and colleagues stress the importance of Calorie Restriction (CR) in protection against a number of pathological conditions including diabetes, cancer, heart disease, and neurodegeneration. CR is also protective, neuroprotective, in Parkinson's disease (in mice) (Bayliss et al., 2016).

Bayliss and colleagues hypothesize that elevated ghrelin mediates the protective effect in Parkinson's disease. Short-term calorie restriction raises ghrelin-levels and enhances maturation of newborn neurons and remote contextual fear memory (in mice) (Hornsby et al., 2016). High levels of ghrelin also protect in Alzheimer Disease (in mice) (Santos et al., 2017). It has positive effects on brain functioning (Kent et al., 2015).

In chapter 6 we formulated the possible protective function of autoimmunity as a more general characteristic instead of malfunctioning in disease. We want to show how AN could be considered a protective measure of the immune system.

In this chapter we already made a case to show that AN is accompanied by ongoing high levels of ghrelin, which is the opposite in obesity. Fetissov and colleagues (Fetissov et al., 2002) showed that AN could be an autoimmune disease (reaction). The antibodies playing an important role in AN.

The combination of elevated ghrelin and (neuro)protection has already been established for several (neuro)diseases. If we consider AN as a condition with a continuous and high-level ghrelin, we could hypothesize that AN has a protective function in the body.

Jaworek and Konturek (Jaworek & Konturek, 2014) stipulate that ghrelin together with leptin and melatonin could be part of an *innate resistance system* which might remove noxious factors.

At a lower level of CR than in AN it has already been clear that sickness in humans and animals goes along with low CR (McCusker & Kelley, 2013). Observation of people with AN showed that they are seldom ill, even when everyone around them is ill. We cannot substantiate this with research, only with observation. Substantiated by research is the fact that people with AN seldom die as a result of AN (Papadopoulos et al., 2009), they even can be in a

terrible condition with a BMI that defies imagination, and still lead an active life. In one way or the other it can be healthy to restrict calorie intake.

As research shows us that ghrelin has (neuro)protective capacities, this is a support for the idea of protective, lifesaving mechanism of the body with AN. The problem with AN probably is not the condition itself but the addiction to not-eating, and the high CR that it engenders. Food restriction is shown to be healthy, just as the opposite (obesity) is shown to be unhealthy. People with AN even show much evidence of health, they seldom catch a cold, or a virus, and even with extremely low weight they can show a strong, healthy body. They seem to have an extremely alert immune system, fighting everything that could attack the body.

From the perspective of the *theory of exchange* this autoimmune reaction would find its counterpart somewhere in the body. From our extensive personal experience of working with people with AN (Delfos, 2012), it became clear that before the anorexia nervosa showed itself the people had often gone through another disease that seemed to trigger the AN. Very frequently it was the Epstein-Barr virus. We cannot substantiate this with research, but our experience embraces several countries.

When examining the Epstein-Barr virus it does not seem too far-fetched. It is a complicated virus that can show itself as *glandular fever*, also called *Pfeiffer disease*, *infectious mononucleosis*, *Filatov's disease* and the '*kissing-disease*' because it affects many adolescents. Resulting in sore throat, fever, enlarged lymph nodes in the neck and (extreme) tiredness. After the symptoms are gone and the tiredness is over the glandular fever that was triggered by the Epstein-Barr virus is also over.

Some viruses however have a broad spectrum of consequences some dangerous, some seemingly more benign. The Epstein-Barr virus has many possible consequences ranging from Pfeiffer disease, alcohol abuse, depression to cancer. The Epstein-Barr virus (EBV) infection has been implicated in the autoimmune mechanisms and epidemiology of Systemic Lupus Erythematosus (SLE), increasing SLE risk by much as 50-fold in children. SLE patients also have elevated EBV loads in blood and early lytic viral gene expression. But also an association with Multiple Sclerosis (MS), Rheumatoid Arthritis (RA), inflammatory bowel disease and type-1 diabetes.

Despite suggestive relationships between EBV and multiple autoimmune diseases (Harley et al., 2018), the underlying molecular mechanism remains

unknown. The way it ravages the body at multiple levels it seems a systemic virus, such as HIV.

Anorexia Nervosa could also be called a *systemic problem* causing problems in many parts of the body. Perhaps AN should be included in the list of afflictions after the Epstein-Barr virus, or from the perspective of a protective immune system as an antagonist against the severe afflictions resulting from the Epstein-Barr virus. But that would be for future research. Of course EBV is a widespread virus. In China the EBV prevalence was 50% in children before 3 years old and more than 90% after 8 years old (Xiong et al., 2014). The prevalence for the researched part of the world is 90% (Smatti et al., 2018).

In Anorexia Nervosa we want to suggest the role in the body as a whole that is factor: 4: *Autoimmunity constantly balances the ongoing malfunctioning of the body*.

Notwithstanding that AN could ultimately develop in a fierce fight in the body towards:

5. Autoimmunity has to deliver such a fierce and ongoing fight that the disease elements become the foreground.

This was a theoretical experiment about a possible case of autoimmunity. To be able to study autoimmune reactions we need an overview of the autoimmune reactions to date.

8 Autoimmune Diseases/ reactions

In order to develop insight on autoimmune reactions, an overview of autoimmune reactions is necessary. In research these reactions are called diseases, *autoimmune diseases* (AD). As a digital appendix to this book we established a list of all the AD's to date with their antibodies and affected organs or systems, and those suspected to be an AD. It is available as a digital appendix belonging to this book.The digital table (TAD – Table Autoimmune Diseases) will be updated regularly and be available on internet (autoimmune.swpbook.com).

In this book a new perspective on the immune system is introduced as well as a new perspective on autoimmunity. To establish an overview of AD's in these two chapters (8 and 9) we used the *regular* perspective on AD, so autoimmune *disease*. We do not refine it from disease to protection, nor the exchange theory or the balance in the body. To establish the overview we construct a list of those auto immune reactions that are are already considered and named autoimmune diseases.

In 1980 Talal states: *Autoimmunity may arise whenever there exists a state of immunologic imbalance in which B cell activity is excessive and suppressor T cell activity is diminished. This imbalance occurs as a consequence of genetic, viral, hormonal, and environmental mechanisms acting singly or in combination. A central mechanism in this concept involves a disturbance of the delicate balance between suppressor and helper activity of regulatory T cells* (Talal, 1980, p. 230).

For some time, autoimmune diseases (AD's) have become a focus of attention, with a proliferation of research books and articles, certainly since 2000. However, there existed no overview of all the AD's with their evidence. It is important to compile such a list because it can help discover related diseases and processes. An overview of all AD's could increase insight in autoimmunity as a reaction and as a function of the body.

In medical research AD's are generally viewed as diseases associated to a specific organ or to the specific system affected. In daily practice it is generally limited to the medical specialism of the organ involved or of the particular disease. As a result, an overview encompassing the different specialisms and the

dynamics of an autoimmune disease and the functions of the body and the health situation of the body is still missing.

Because thisis the first time, as far as we know, that such a list is being compiled, we consider the list as a starting point for future research. As the knowledge on autoimmunity will progress, so will more diseases become known that involve an autoimmune reaction of the body. There exists already an Autoimmune Disease Database [1], based on AD's, organised as a 'dictionary' of AD's with the possible genes and proteins associated with the AD's. In our book the AD's are organised from the point of view of autoimmunity as such, as a function of the body. The AD's are organised at organ level with its associated eventual evidence, and categorized in main and subcategories. The name of an AD is not the organizing principle, but autoimmunity as such.

The immune system is best known for its role in defending the body against invasion by internal and external detrimental elements such as infectious pathogens (vbpf) or tumour cells. This reaction often causes an infectious process. The immune system includes innate, adaptive and memory responses that are constantly activated, adapted and improved to defend against pathogens more efficiently. In addition, the immune system must be tolerant and distinguish between self and non-self elements, so that substances that are identified as non-self in need for an immune response will be stimulated, while no harm is inflicted upon unintended self-elements. The general picture of reactions of the immune system could be described in four types of reaction of the immune system, see Outline 4 (this is without taking into account the theory in this book):

Reactions of the immune system	
Classical reaction	fighting against vbpf
Underreaction	• less effective fighting of diseases • susceptibility for diseases • sensitivity to infections
Overreaction	• allergies • autoimmune diseases
Immaturity	atopic syndrome

Outline 4: *The different reactions of the immune system* (Delfos)

The *first type* of reaction is the *classical reaction* of the immune system that is fighting against vbpf. The *second type* is an *underreaction* as a weak response of the immune system, which causes the immune system to have trouble adequately reacting to harmful elements, internal and external. Internal elements would be for instance when the body as a result of stress hormones causes the RNA (ribonucleic acid, replaces DNA as a carrier of genetic codes in some viruses) to malfunction in signalling negative elements [4]. Men often have a weaker immune response than women have [5]. The *third type* of reaction is an *overreaction* or *excessive* or from the theory of exchange possibly a *protective* immune response. There are two subtypes: *allergies* and *autoimmune diseases*. This excessively functioning immune system is the result of a stronger immune system, which we see more in women than in men [5]. The *fourth type* of reaction is the *immaturity* of the immune system, which causes a hampered reaction to non-self elements. As a result diseases occur such as *atopic syndrome* which occurs primarily in young children [3,6,7]. One of these sub-diseases of the atopic syndrome is *food allergy*, and no allergens nor IgE reaction can be found in the blood, suggesting that it would not be an allergy [8]. This fits into our idea of a weak immune system instead of an allergy. Which is also supported by the idea that most children grow out of atopic syndrome with age [7].
Autoimmune diseases (AD's) are the third leading cause of morbidity and mortality, after heart disease and cancer, in the industrialized world [9].

For autoimmune disorders to develop, a combination of genetic, immunologic, hormonal and environmental factors is required, comprising what is known as 'the mosaic of autoimmunity' [10,11,12].

To establish an overview of AD's we developed the methodology to discern the AD's by evidence.

9 Evidence for autoimmune reactions

Autoimmunity is an immune response directed against an antigen within the body of the host. The definition does not distinguish whether the response is innate or acquired and, if acquired, whether it is induced by a foreign or autochthonous *antigen*; it is also not restricted to a T-cell or B-cell response. It only requires that the immune response be directed to a self-antigen. The references from this chapter are noted in [ ] and refer to the reference list of the TAD (Table of Autoimmune Diseases) on the website (autoimmune.swpbook.com).

9.1 Methodology for finding evidence of AD

An autoimmune disease is considered a pathological condition caused by an autoimmune response. However – apart from the theory about protection – this definition can be unclear since it is frequently difficult to assign causality when dealing with a human disease, the vast spectrum of possible, interrelated causal factors being involved. It is useful, therefore, to consider the evidence of an autoimmune aetiology of a human disease with three degrees of stringency [13,14]:

- Direct evidence
- Indirect evidence
- Circumstantial evidence

The *direct evidence* of causality implies that an autoimmune response can be shown to produce the disease. This usually involves transfer of autoantibody from a patient to a healthy recipient, either another human or an animal. A few instances of such transfers have been successfully performed. One striking example is the reproduction of the disease, pemphigus, by injection of patient serum into a neonatal mouse [15]. Human-to-human transfer of autoantibody may also result from trans-placental transmission of the disease. Examples of maternal-fetal transmission have been well documented [16,17,18].

The *indirect evidence* involves the autoimmune antibodies (AA). The AA are the serological hallmark of most autoimmune diseases [19].The demonstra-

tion of autoantibodies is the first step in the diagnosis of autoimmune diseases, although the antibodies may not be the actual pathogens of the disorder. They can serve as a biomarker and classification criteria for a number of autoimmune diseases. AA's are not evidently specific for an AD. Natural antibodies (NAs) are common in all immunologically competent people and may even rise non-specifically during the course of disease or injury. Even in the absence of disease they are considered necessary for the development of effective immune responses against infectious agents or cancer cells [20]. Also autoantibodies could be functional in a stimulating and suppressive way [21]. They are immunoglobulins produced at tightly regulated levels in the complete absence of external antigenic stimulation. These antibodies are produced mainly, if not exclusively, by a subset of long-lived, self-replenishing B cells, known as B-1 cells or CD5+ B cells. They show low affinity to many microbial pathogens but are mainly cross reactivity, even binding to some self-antigens [22].

It seems likely that NAs fulfill an important role in homeostasis of the immune system, which appears to be confirmed also by the high rate of conservation among species [23,24]. Moreover, several regulatory mechanisms to avoid autoimmune reactions from B-1 cells have been demonstrated. On the other hand NAs are still heavily considered to facilitate the development of AD [25].

Thus, the mere presence of autoantibodies does not necessarily establish a cause-and-effect relationship, since the autoantibodies may be the result, not the cause, of the disease process. We emphasize, however, that the presence of autoantibody responses has great value in diagnosing and prognosing many human diseases [26].

We may think that the presence of self-reactive lymphocytes in the peripheral repertoire of healthy subjects indicates that the mechanisms leading to immune tolerance are intrinsically imperfect, however it seems more precise to affirm that the window between self defense and autoimmunity is extremely narrow, sometimes even overlapping [22].

A kind of *circumstantial evidence* comes from the finding that autoimmune diseases tend to cluster, probably because they share some genetic susceptibility traits. As examples, a single individual will have more than one autoimmune disease, and members of the family share the same or even other autoimmune diseases. In addition, the association of one disease of unclear etiology with another of authentic autoimmune etiology strengthens the possibility that the former is also an autoimmune disorder [27].

It is suspected that genetic defects play a role in the etiology of autoimmune diseases. Modern high throughput technologies, like mRNA micro- arrays, have enabled researchers to investigate diseases at a genome-wide level. In contrast to classical inherited genetic diseases, such as *sickle cell anemia*, autoimmune diseases are not caused by the defect of a single gene, but by the dysfunction of the complex interaction of a group of genes. System genetics is considered to be helpful in discovering underlying systems in the immune system and autoimmunity [28].

However, defects of one or more of these genes do not cause an autoimmune disease, but only predispose a person for an autoimmune disease [29], and perhaps not any AD, but one within a cluster of AD's. Epidemiological evidence shows that AD's cluster in genetic vulnerability [30].

Also most of the autoimmune diseases show a particular bias to certain HLA haplotypes, usually the Class II category. Since the Class II MHC encode genes that are important in regulating the immune response, some rational connection may exist between the genetic constitution and susceptibility to a particular autoimmune disease [31].

Furthermore, most, but not all, autoimmune diseases are more common in women than men. A sex bias, therefore, provides increased circumstantial evidence of an autoimmune etiology. Female susceptibility to autoimmunity is much discussed, and likely depends particularly on estrogenic hormones. The possibility exists of immuo regulatory genes on the X chromosome [31].

Although there is now experimental evidence that deletion of self-reactive lymphocytes occurs in the thymus, this mechanism seems to be effective principally for the most prominent antigens, such as those of the major blood groups and histocompatibility complex [32]. By comparison, in the case of most other self-antigens, deletion of self-reactive T cells in the thymus is either lacking or incomplete. Fortunately, there are mechanisms in the periphery that retard the activation of those self-reactive T cells that escape deletion in the thymus.

One well-studied mechanism is clonal anergy [33]. This term describes the unresponsive state of T cells that have encountered their specific antigen without co-stimulatory signals. Such cells may remain unresponsive for long periods of time. There is a risk that anergy can be terminated by an encounter with appropriate, non-specific, co-stimulatory signals from injured tissue.

Another mechanism of peripheral self-tolerance involves immunological ignorance; that is, the lack of a productive encounter between the T cell and its

corresponding peptide/MHC complex on an antigen-presenting cell. Ignorance can be overcome by changes in antigen availability, such as presentation by an infecting microorganism [34]. These events can cause autoimmunity and possibly give rise to autoimmune disease. Autophagy was also discovered to be a possible agent in the breakdown of tolerance and development of autoimmunity [35].

A novel possibility is that autoimmunity may be triggered by the production of antibodies directed against peptides translated by anti-sense strand DNA, in which the sense strand translates an auto-antigen [36]. These antibodies, in turn, induce anti-idiotypic antibodies that may cross-react with the auto-antigen.

Finally, the autoimmune response is kept in check by active regulation, and eliminating regulatory cells can initiate or extend autoimmune diseases [37]. Among the regulatory cells under study are a subset of T cells bearing the markers CD4 and CD25. Two different subpopulations of CD4+ regulatory T cells (Tregs) can be distinguished. Naturally recurring Tregs exert their suppressive effects by cell-to-cell contact of membrane-bound molecules, such as CTLA-4. Induced Tregs, in contrast, are cell-contact-independent and operate mainly through soluble suppressive cytokines, such as IL-10 and TGF-beta [38]. A specialized population of natural killer (NK) cells that express a T-cell receptor (called NK-T cells) can also regulate autoimmune disease [37,39]. A heritable defect in the suppressive effects of CD4+ CD25+ regulatory T cells appears to be the mechanism underlying the rare lethal autoimmune human disease "immune dysregulation, polyendocrinopathy, enteropathy, X-linked" (IPEX syndrome, OMIM 304790). Mutations in the forkhead box protein P3 (FOXP3) located on the X chromosome have been noted in most of the affected patients [40].

Whether autoimmune disease will follow an autoimmune response depends upon both the quality of the immune response and the availability of the corresponding antigen.

Many other autoimmune diseases are not due to the direct effects of autoantibody. Rather, they are associated with T-cell-mediated immune responses [41]. Sometimes, cytotoxic T cells may be generated that can damage their respective target cell. In other cases, cytokines are produced that are harmful to surrounding tissue cells. Finally, T cells may activate macrophages, which can produce a great deal of tissue injury through their soluble products, including cytokines and reactive oxygen intermediates. A functionally significant polymorphism of a lymphocyte specific phosphatase known as the protein

tyrosine phosphatase non-receptor 22 gene (PTPN22) has been linked to T cell hyper-responsiveness.

High-throughput genetic and genomic studies have also focused attention on innate mechanisms in autoimmunity [42]. The innate immune system uses dets of molecules known as pattern-recognition receptors that have been selected through evolution to recognize molecular patterns found in microorganisms. Families of pattern-recognition receptors include the Toll-like receptors, the nucleotide oligomerication domain (NOD)-like receptors, and the NACHT leucine-rich-repeat proteins (NALPS) [43,44,45].

The factors that trigger an autoimmune disease are still unknown. Studies with monogenetic twins have revealed that genetic influences only account for 25–40% of the disease risk making gene environment interactions and environmental influences the predominant factors. The environmental influences are very diverse rendering research in this area extremely difficult. These influences may be toxic substances like mercury in one case and ultraviolet light or even certain nutrients in another. Moreover, several bacteria, viruses or hormones are among the suspected triggers of autoimmune disorders [29]

As said before, finding autoantibodies are the hallmark for diagnostics of AD's [19]. This does not mean that finding AA's is evidence for an AD. Autoantibodies can play a role in other biological processes [2]. Autoantibodies and B-cell and T-cell reactions can be considered as *indirect* evidence for AD's. The association between the AD and the presence of AA's does not mean by definition that the AA are the indirect evidence for that AD. The association could come from another source. In our table the AA's and other evidence (B-cell and T-cell reaction and viral trigger) are considered indirect evidence for the specific AD, because the disease is our perspective. Still, further research must show if it is effectively an indirect evidence or a simple coincidence, or that general AA's are associated with not only that specific disease, but a cluster of AD's.

9.2 Method for constructing the table of autoimmune diseases, the TAD

In order to determine the state of the art in AD we performed a thorough literature research – which took us some years – and interviewed some specialists in the field.

The literature search was based on four elements:

1: Handbooks on immune diseases.
2: Handbooks and literature on organs and systems.
3: Recent research on every autoimmune disease we discovered.
4: Literature on autoimmunity to determine what can be considered an autoimmune disease and which diseases are still in debate whether they are autoimmune or otherwise.

Handbooks on autoimmune diseases: Bijlsma, Geusens, Kallenberg, Tak, 2004 [49]; Lahita, Chiorazzi, Reeves, 2000 [50]; Morrow, Nelson, Watts, Isenberg, 1999 [51]; Nairn, Helbert, 2002; Helbert, 2017[52]; Rose, Mackay, 1998 [53]; Theofilopoulos, Bona, 2002 [54];) do not offer an overview of all AD. We also used handbooks on general medicine (Kumar & Clark. (2005) [55]; Kumar, Abbas & Fausto. (2005) [56]. Meer, van der & Stehouwer. (2005) [57].

We searched for AD's at the level of organs and systems. For each AD we tried to find the 'state of the art' by exploring the most recent research on each subject. An entry in the list was accepted when at least two references (peer-reviewed journals) mentioned the disease as an AD.

We also wanted to maintain the information at organ and system level. This is helpful for practical diagnostic purposes and further research. An overview at the level of organs and systems enables research to be more specific. For that reason the indication to which organ or system is affected is indicated in the list before the disease. For instance (N) for Nerve System or (Bl) for bladder. The legend can be found in this chapter in paragraph 9.2.

One of the problems we had to deal with was that the nomenclature is not always unequivocal with respect to some diseases. Sometimes a disease is known under different names. To make it easier to find them in the list we entered both names, referring to each other. The Good Pasture Syndrome for instance is sometimes called the *GBM disease*. In that case the second name can be found in the list with a reference to the first name.

Diseases that begin with 'Acquired', 'Anti' or 'Primary' are entered in the list in alphabetical order under these prefixes. That is if the prefix is qualifying for the fact that it is considered an AD. *Acquired Angio Edema* for instance will be found under 'Acquired' and not under Angio or Edema which both are not AD. Only one entry for each disease is used in counting the total number of AD.

After each disease the literature reference is mentioned in a brief notation. See for the full reference the reference list available with the table on internet (TAD) (autoimmune.swpbook.com). For instance:

(B) ***Antiphospholipid Syndrome*** (APS = Hughes Syndrome), [72-75]

In the case of some diseases there exist related diseases. To take that into account we made a distinction between main category and sub category. As a result, some diseases have been arranged in main categories with sub categories. For instance:

- (L) ***Autoimmune Hepatitis***, [87]
  - ***Autoimmune Hepatitis type 1***
    (often in combination with other autoimmune diseases [88]
  - ***Autoimmune Hepatitis type 2***
    (often in combination with other autoimmune diseases [88,89]
  - ***Autoimmune Hepatitis type 3*** [87]
  - ***Drug-induced Autoimmune Hepatitis***
    (after: Tielinsäure, Dihydralazin, Halothan) [90]
  - ***Posttransplantaire Autoimmune Hepatitis***
    (after bone marrow transplantation and use of cytostatica) [87]

With respect to AD, one area poses a problem as to whether it should be inserted in this overview. The reason is that they are not AD's as such, but that they are present with cancer, called *Paraneoplastic syndromes*, PNS. There are many of these autoimmune reactions that specifically accompany cancer. For that reason we inserted the paraneoplastic syndromes in the list, without the exhaustive list of autoimmune reactions that fall into this category. Only some examples are given. The paraneoplastic syndromes as such is inserted in the list under main categories, but the specific reactions are not counted in the sub categories.

The list contains a total of 159 AD in 102 main categories plus 57 sub categories (paraneoplastic diseases, PNS, excepted).

9.3 The TAD Table of Autoimmune Diseases

The AD are classified in alphabetical order in the digital table (autoimmune.swpbook.com) with 7 columns, see Outline 5.

The TAD	**Table Autoimmune Diseases**					
Organ/ system	name	status	subtype	subsubtype	antibodies	other

Outline 5: *The format of the TAD, Table of Autoimmune Diseases*

In the *first column*, preceding each autoimmune disease or disease being suspected to be an AD, the medical area concerned (most of the time the organ concerned) is indicated between parentheses. The legend is as follows:
A = Adrenal, B = Blood(barrels), Bl = Bladder, Bo = Bone, Bow = Bowel, C = Cardiology (heart), Ca = Cartilage, Cs = Complement System, Ct = Connective Tissue, D = Dermis, E = Ear, Ey = Eye, H = Hormone, Ha = Hair, Hy = Hypofyse, J = Joints, K= Kidneys, L = Liver, Lu = Lungs, Ly = Lymph nodes, M = Mammae, Mu = Muscles, N = Nerve System, No = Nose, P = Pancreas, Psy = Psychiatry, R = Reproductive organs, S = Stomach, Sp = Spleen, Sy = Systemic, T = Thyroid
In the *second column* the name of the AD or suspected AD.
After the name, in the *third column,* the status is listed with reference to the literature in the field. This can be: a possible AD, called as such (in some literature), a definite AD, paraneoplastic or a viral trigger. The brief references after each disease contain a number. Some AD's have subtypes and sub subtypes which come in the column after 'status'.
In the *fourth* and *fifth column* the subtypes and subsubtypes.
Then comes in the *sixth column* the antibodies concerned.
The last, *seventh column* is reserved for evidence other than antibodies.
The brief references are numbered in order of appearance with repeated numbers in the case of reference to the same article or book.

The TAD is on internet in a digital form to make updating for research possible and to make it available for further research (autoimmune.swpbook.com).

10 Epilogue

This book took some time to mature in my mind, nearly 10 years, and if I look at the entire process as such it is more like 25 years. Medical science is not my specific field, but I have already developed several models on hormones (Delfos, 2018). During the maturation process of the book the scientific support for my ideas grew. When finally the presence of the immune system in the brain was evidence-based (Louveau, 2015), I felt the time had come to start writing the book. The immune system had come to its end in the very place where the beginning is: the brain.

My interest started with the puzzle I experienced as a scientist with treating anorexia nervosa. The contradiction in the young people between not eating, their loss of appetite and their urge to eat at the same time was an interesting scientific puzzle which was much too easily solved by saying that they copied fashion models. The tremendous energy of those extremely skinny girls and sometimes boys, their good health, seldom falling ill, or only when they had gone much too far. The research showed that people with anorexia seldom died of anorexia, but more likely of suicide when they were much older (Papadopoulos et al., 2009). The loss of appetite AN joined the loss of appetite that goes along with any disease in humans and animals. That is when I thought that the immune system could have an important role in anorexia nervosa. The idea of protective immunity became apparent. Could this extreme loss of appetite indicate a hidden disease somewhere in the body perhaps? And the repeated experience that the people with anorexia nervosa often had glandular fever or another big disease before the outbreak of anorexia, was stimulating to seek further. It was just a theory. I needed to understand deeper what the immune system was to be able to refine my hypotheses about protection through the immune system.

That is how the immune journey began. Seeing the wealth of all the medical evidence-based material gathered through multiple specialisations, it demanded to be organised. To understand the first step is a schema. But a total schema of the immune system did not yet exist. I discovered that as a result of specialisations the connection between the two most basic systems in the immune system was not yet made. The innate system and the adaptive system

were solitary pieces of the one puzzle the immune system presents. That is where trying to lay the pieces together started.

The beauty of the discovery that in case of an insult, the brain closed down the injured area so that the insult could not spread throughout the brain, by digging kind of trenches around it. In the brain that means killing healthy brain cells surrounding the injured area (Moalem et al., 1999; Yoles et al., 2001). How ingenious the immune system proved to be! The image of one gigantic orchestra where everything has it place and every sound balances the other sounds came up in my mind.

It was an endeavour and an adventure to build a theory that would do justice to the immune system and justice to the already enormous quantity of evidence-based material about the immune system.

I felt surrounded by that beautiful mind, Leonardo da Vinci who brilliantly put into words that to him science felt 'vain and full of error' if it had not passed the five senses, had not been moulded by experience. Experience is certainly the keystone of medicine. But we can add to this that the mind can take the gathered material and build the form where everything fits together and where experience as Leonardo da Vinci would say finds its 'true end', see the motto of the book on page 8.

It was intriguing to see how medical science could advance by building stone after stone of solid material, but at the same time get lost in the wealth of all the gathered material in all those specialisations.

Aside from organising medical scientific material by a process of actively switching from deductive to inductive thinking and back again, it was also a road of discovery. The vast importance of the immune system became visible, holding literally and figuratively the human body together, already with the envelope of the skin as its first line of defence. The role of melatonin figuring in a new, fourth pathway of activation of the complement system, seemed evident.

The first sentence of the book is: *If it was not for medical science, I would be a widow*. It is the only personal remark in the book before the epilogue, but it sets the tone. This book on the immune system is a way to convey my scientific gratitude to medical science. Just as for many medical scientists their specialisation was inspired by their own experience.

Hopefully the book will bring insight into the immune system a step further by generating many testable connections and multiple testable hypotheses.

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Appendix I

Digital appendix, TAD-Table of Autoimmune Diseases,
website: autoimmune.swpbook.com

Appendix II Glossary

Adaptive immune system (1 standard): Part of the immune system which comes into action when the innate immune system cannot kill a specific pathogen. Hooking up with the innate immune system. It produces a large diversity of antibodies to address the diversity of pathogens. Triggered by a pathogen. Using the Lectin and Classical pathways.

(2 Delfos): Part of the immune system which comes into action when the innate immune system cannot address the full processing of cells. Working together with the innate system and getting information through the innate system. Triggered by pathogens, infections and malfunctioning of the body. Using the Alternative, Lectin and Classical pathways.

Anorexia: 1 Low CR – Calorie Restriction: CR, low calorie intake, usually accompanies any illness in the body.

2 Anorexia Nervosa: 1 (standard): Very low calorie intake, considered a psychiatric disorder.

2 (Delfos): Very low calorie intake, reaction of the autoimmune system in balance with a malfunctioning part of the body.

Antibody: Form of immunoglobulin expressed by a B-cell to counteract a pathogen or a self-cell.

Antigen: Recognized by an antibody or B-cell receptor and target for an antibody or a T-cell.

Apoptosis: Cell-death from within the cell, also called programmed cell death: 1 programmed cell-death as part of the ongoing rejuvenation of tissues; 2. Repelling of dead tissue, for instance a skin crust, 3. hair loss. 4. autoimmune caused cell-death.

Autoimmune Disease, AD: Disease caused by antibodies against self-tissue.

Autoimmune Reaction (Delfos): Reaction of the autoimmune system towards (healthy and unhealthy) self-tissue.

Autoimmune system (Delfos): Part of the immune system which targets self-tissue.

Blood-Brain Barrier, BBB: Barrier between the circulation in the brain and the systemic circulation in the body, also conceptualized as an interface between the brain and the rest of the body. Considered to protect the brain against pathogens.

Coevolution (Parham): The evolutionary process whereby both the innate immune system and the adaptive immune sytem evolve in interaction together by stimulating and influencing each other's development.

Complement cascade: (1 standard): The immune cells active in processing the destruction of pathogens.

(2 Delfos): The immune cells active in organizing the processing of cells of the body.

Complement system: Part of the immune system which can be activated through four pathways to process cells: healthy, unhealthy, viruses, bacteria, parasites and fungi.

Exchange theory (Delfos): Extension of the evolution theory from the species adapting to the surroundings with the surroundings processing the species. Principle of reciprocity. The human body is presenting rich resources but also poses challenges to the environment. Interaction between the human being and its surroundings can be beneficial as well as harmful in a reciprocal way.

HLA complex, Human Leukocyte Antigen complex: The major histocompability complex in humans. HLA is linked to immune regulation and pathogenesis of autoimmunity.

Immune: The result of the condition of the immune system when through the presence of available antibodies the body is resistant if it is confronted with the same disease again.

Immune cells: Lymphoid stem cell > Lymphocytes >NK-cell, B-cell; T-cell; ThCell; TcCell; Plasma Cell; Memory Cell. Myeloid progenitor > Granul Ocytes > Neutrophil; Eosinophil; Basophil; Mast Cell; Monocyte > Dendritic Cell; Macrophage.

Immune system (1 standard): the system whereby the body defends itself against intruders/pathogens.

(2 Delfos): the system whereby the body organizes the processing of the cells of the body, self-cells and non-self cells.

Immune system strategies (Delfos): The diversity of strategies of the immune system in order to process cells in the body, self-cells and non-self cells.

Immunization: The process whereby the body is protected against a specific disease by provoking production of antibodies through introducing an antigen into the body.

Infection / Inflammation: The condition of a cell when a pathogen has infected the cell.

Innate immune system: (1 standard): The innate part of the immune system that can handle almost all pathogens and destroys them or sends them through to the adaptive system.

(2 Delfos): The basic part of the immune system and the first to appear in evolution. Discriminating self from non-self, healthy from not healthy cells and harming from beneficial for the body. This can be pathogens and other non-self cells; (healthy and unhealthy) cells from malfunctioning parts of the body or associated to malfunctioning parts of the body. Basic general function assessing cells and tagging them for recognition in the body by the immune system. Triggered by pathogens, infection and malfunctioning of the body. Using the four pathways (1 Melatonin pathway; 2 Alternative pathway; 3 Lectin pathway and 4. Classical pathway) to process cells and organize the basic – most healthy – body functioning.

Lectin: Hormone that can and helps preparing cells for destruction, that is opsonization of cells. It does so by informing the adaptive immune system by mannose-binding lectin (MBL) activity on the surface of many common pathogens. The complement system can be activated by the Lectin pathway.

Line of defence, LOD: Organization of defence mechanism of the immune system.

First LOD: This consists of the 'envelope of the body', *skin and mucosal tissue,* to prevent foreign bodies entering the body.

Second LOD: Directly behind the skin and mucosal tissue, the respiratory system and the gastrointestal tract is the *innate immune system.* It has mechanisms that are fast and fixed in their mode of action and very effective in destroying intruders and thus stopping most infections at an early stage. The innate immune system aims at destroying the vbpf directly (kill through the Natural Killer cells, NK cells) or sending through information for further action to the *adaptive immune system*, which cooperates with the innate immune system.

Third LOD: When the innate system cannot fully process cells, information is sent through to the *adaptive immune system.*

Lymphatic system: The 'road' infrastructure of the immune system with vessels and lymph nodes.

Melatonin: (1 standard): Basic hormone of organisms. It is produced in the pineal gland, the brain and in immune cells.

(2 Delfos): Basic hormone in the immune system through the melatonin pathway

Meningeal lymphatic system: part of the lymphatic system/immune system residing in the brain.

Myeloid-derived suppressor cells, MDSC: A heterogeneous population of granulocyticormonocytic cells that suppress innate as well as adaptive immune responses.

Nomenclature: Official namegiving to elements in different scientific branches, in this case medical science.

Paraneoplastic syndromes, PNS: (1 standard): Neoplasms that very often accompany cancer.

(2 Delfos): Neoplasms that appear through actions from the autoimmune system to balance damage from cancer to the body.

Pathogen: A foreign body threatening to harm the body. These are viruses, bacteria, parasites and fungi.

Pathway of activation of the complement system: Process of activation of the complement to process cells of the body and stimulate the complement cascade.

1 Melatonin pathway (Delfos): The basic pathway to activate the complement system. Its function ranges from discrimination between cells via organizing functioning of the body to working at the deepest level of life and death. This pathway can also activate/hook-up-with the other pathways if necessary. The melatonin pathway is always active.

2 Lectin pathway: The second pathway to activate the complement system through the activity of opzonizing cells for destruction.

3 Alternative pathway: The third pathway of complement activation through the activity of destroying infected cells or sending cells through with information for further processing by the adaptive immune system.

4 Classical pathway: The fourth pathway to activate the complement system through the activity of attacking specific pathogens or (Delfos) target self-cells with specific antibodies.

Preventive Medicine: The part of medicine that aims at preventing illnesses.

Program for death (Delfos): Conglomerate of organized and programmed cells from conception onwards which aim at letting the organism die within the programmed time.

Program for life (Delfos): Conglomerate of cells from conception onwards which aims at letting the organism live as long as the programmed time permits it.

Self-tolerance: The normal situation when the immune system does not act in a way to attack self-tissue of the body.

Systemic Autoimmune Disease, SAD: Group of autoimmune diseases caused by the immune system attacking self-tissues in a body systemic way.

Thymus: The basic organ for the immune system where self-tissue is discriminated from non-self tissue. Is said to be the basisc element of the immune system and has been called the biological self.

Virus (1 standard): Pathogen that replicates in living cells and cannot have independent life. The genetic material is either DNA or RNA. Viruses can only multiply with the aid of the cellular device that they penetrate.

(2 Delfos): Pathogen which is an interface between the human body and its surroundings.

List of Outlines, Schemas, Illustrations and Figures

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Authors' information

Martine Delfos

Dr. Martine France Delfos studied clinical research psychology in the late sixties, and French language and literature in the early nineties, both at the University of Utrecht. In 1999 she completed her PhD at the university on a double subject: psychological and literary research on bereavement in French writers. She is trained as a researcher and since 1975 she has also worked in practice as a therapist. In 1997 she founded the PICOWO: Institute of Psychological Consultation, Education and Research in order to form a research group where she develops biopsychological theories and models. The models she develops are in direct relation to both the social and scientific reality. She carries out her research projects in various fields, both in the Netherlands and internationally.

Between 2008 and 2012 she was appointed as a Professor at the Edith Stein University /Twente School of Education in The Netherlands. Since 2010 she has been a Visiting Professor at the International University of Sarajevo in Bosnia-Herzegovina and from 2011 a Visiting Professor at the Universidad Central del Ecuador, Quito, Ecuador.

She has written several textbooks and specialist books, including a quadrilogy of textbooks in the field of developmental psychology and psychopathology.

Information about her work can be found on the website: www.mdelfos.nl

Juliette van Gijsel

Juliette van Gijsel studied medicine and completed her GP training in 2016. During her studies, immunology and especially autoimmune medicine piqued her interest and she followed a number of elective courses in this area. She worked on research projects, resulting in a publication in The Lancet, about neonates with suspected early-onset sepsis. Since the start of her studies she was also involved in the scientific research group of Martine Delfos, who researched various fields, including (auto)immunology.

Fiemke Griffioen-Both

Fiemke Griffioen-Both, PhD, is founder and CEO of Lyla Coach BV and has a background in Artificial Intelligence. After her studies at the VU University, she received her PhD in the area of agent systems for eHealth / depression and workload. After a few years of working as a knowledge engineer, she was back in research at Utrecht University working on the SleepCare-project since 2013. The project was so successful, she started her own company together with her colleague based on their research, Lyla Coach BV.

Authors and the Book

With respect to this book: Martine Delfos is the main author. Juliette van Gijsel was the main author of the TAD, the Table of Autoimmune Diseases. Fiemke Griffioen-Both was co-author in Chapter 7 concerning the level of ghrelin and eating disorders.

The PICOWO series

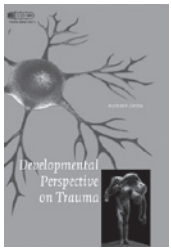
The PICOWO series is based on research results of the Psychological Institute for Counselling, Education and Scientific Research. These are both empirical and theoretical studies. The series includes different disciplines each with its own main colour with sub shades for different books per domain. Psychology books are green, Autism books are red, the Virtual environment books are blue, Eating Disorders books are yellow, Medical books are white and expected are the Literature books in purple. Together they form a rainbow of colours.

Part 1.
Autisme vanuit een ontwikkelings-perspectief
(Autism from a developmental perspective)
(in Dutch)

Part 2.
In 80 dagen de virtuele wereld rond
(In 80 days around the virtual world)
(in Dutch)

Part 3.
Ik ben aan ze gehecht!
Over gehechtheid als een boei in nood
(I am attached to them! About attachment as a buoy in distress)
(in Dutch)

Part 4.
Eetstoornissen van binnenuit belicht.
Nederlandstalige egodocumenten
(Eating disorders viewed from within. Dutch egodocuments)
(in Dutch)



Part 5.
Developmental Perspective on Trauma
(in English)

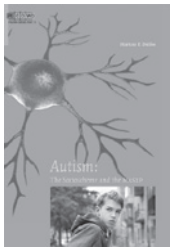
Part 6.
Moet ik nu huilen?
Rouw bij kinderen en jongeren met een autismespectrumstoornis
(Should I cry now? Grief in children and young people with autism spectrum disorder)
(in Dutch)

Part 7.
Trauma vanuit een ontwikkelingsperspectief
Translated from English
by Laura Dekkers of part 5, *Developmental Perspective on Trauma*
(in Dutch)

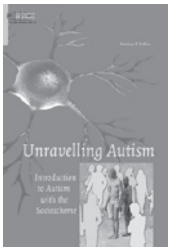
Part 8.
Autismo desdo una perspectiva de desarollo
Translated from Dutch by Marcella Solano, Maria Martina and Norbert Groot of part 1, *Autism from a developmental perspective*
(in Spanish)

Part 9.
Grafische dossieranalyse. Een leven in beeld
(Graphic dossier analysis. View of a life)
(in Dutch)

Part 10.
Autoimmune Reactions and the Immune System
(in English)

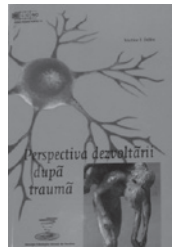


Part 11.
Autism: The Socioscheme and the MAS1P
(in English)

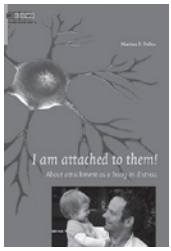


Part 12.
Unravelling Autism
Introduction To Autism with the Socioscheme
(in English)

Part 13.
Autisme ontrafelen
Introductie over autisme met het Socioschema
Translation of part 12, *Unravelling Autism*
(In Dutch)



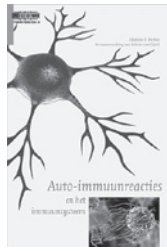
Part 14.
Perspectiva dezvoltării după traumă
Translation of part 5, *Developmental Perspective on trauma*
(In Romanian)



Part 15.
I am attached to them! About attachment as a buoy in distress.
(Vertaling van deel 3, vanuit het Nederlands)
(in English)

Part 16.
Descifrând autismul
Translation of part 12, *Unravelling Autism.*
(in Romanian)

Part 17.
Ataşamentul şi siguranţa de sine
Translation of part 15, *I am attached to them.*
(In Romanian)



Part 18.
Auto-immuunreacties en het immuunsysteem
Translation of part 10, *Autoimmune Reactions and the Immune System*
(in Dutch)

Colophon

Autoimmune Reactions and the Immune System
PICOWO series Part 10
Martine F. Delfos, PhD
In collaboration with Juliette van Gijsel

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Internet: www.swpbook.com

Autoimmune Reactions and the Immune system presents an overview of the immune system. For the first time a schema with all the elements of the immune system was possible due to all the evidence-based material meticulously gathered in centuries of medical science. This schema has been elaborated with a new perspective on the immune system, encompassing not only the fight against viruses, bacteria, parasites and fungi, but as the system organizing the processing of the cells of the body. A perspective shifting from *fighting to protection* and ultimately to exchange between the human body and its surroundings. To enable this broad perspective a fourth pathway of complement activation was developed, the *melatonin-pathway*.

Dr. Martine F. Delfos is a scientist active in a broad scientific area, combining different scientific fields, who also works as a practitioner.

From the foreword of Prof. Dr. Dick Swaab: *Martine Delfos is one of those exceptional people who, at a very early stage in her career, successfully started to build bridges between the fields of psychology, medicine and neuroscience. For a long time she was one of the few psychologists truly interested in neurobiology. She is a scientist by trade but corroborates her scientific insights as a clinical psychologist and a therapist. As she says: "A scientist needs to be confronted with his mistakes through real life". Martine contacts me a couple of times a year with in-depth biomedical questions. Her questions always concern a very different topic, are never easy to answer, and are always original and force me to look at a problem in a new way. The latest fruit of her labours is the present volume 10 of her PICOWO-series on 'Autoimmune Reactions and the Immune System'.*

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