Autoimmune Reactions and the Immune System

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In collaboration with Juliette van Gijsel

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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 regulating 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.*

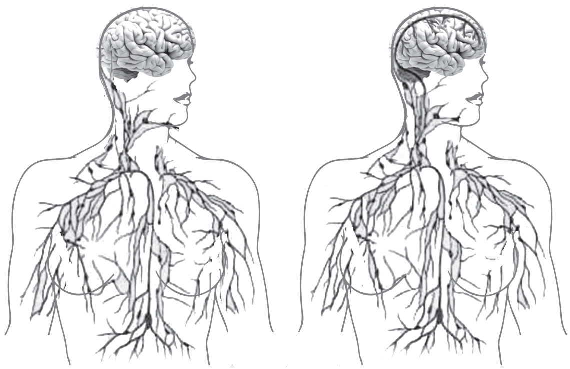

Illustration 1: *The recently discovered vessel in the brain, which proves to be a part of the immune system. Left: how the lymphatic system was visualised in textbooks until this discovery in 2015, and on the right how it should have been* (UVA-University of Virginia School of Medicine, 2015).

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.