The immune system

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[*This article is a latest* version *of chapter 2 from:* Delfos, M.F. & Gijsel, J. van (2018) Autoimmune reactions and the immune system. Amsterdam: SWP Publishers.
It is reorganization of the existing research to achieve a better understanding of the immune system, partly through a schema of the immune system as a whole, and through methodical and methodological connection of the two specializations: inflammation and immunity.*]*

Introduction

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, especially now that we know that the immune system also resides in the brain (Louveau et al., 2015) and that we discovered a fourth dura, a protecting arachnoid mater covering the whole brain with the cells of the immune system (Mollgard et al., 2023). When we bring together all kinds of yet unconnected medical research related to the immune system - and that is a wealth of research material -, it becomes apparent that the immune system is involved in everything. For example, it plays a role in reproduction, in the programming of pregnancy. It plays an important role in brain development, in the early years of the brain and behavior, and throughout the life course also in later life (Bilbo et al., 2009). Through melatonin (Delfos, 2018), the immune system plays a regulatory, protective and healing role in all important processes in the body, including an inhibitory function in inflammation and a preventive and healing role in invasive diseases such as cardiovascular and cerebrovascular diseases (among others, Roohbakhsh et al., 2018; Ohgidani et al., 2016; Terzi et al., 2016, see further Delfos, 2018).

In the body, *organs* are described by their *components*. Body *systems are characterized by* their *function*. The immune system is also characterized by its function. To understand the immune system, and certainly the body, it makes a difference how this function is defined. We have described that the function of the immune system is to *fight against invaders* (VBPF/ viruses-bacteria-parasites-fungi: pathogens).

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 protect their bodies from invasion by a variety of other organisms. The origin of the subject lies in medical practice and historical observations that people who had survived the ravages of an epidemic disease remained unaffected when faced with the same disease again - they had become* immune *to that particular infection.*

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So, the immune system is about *defense* and is named after the spectacular result of people becoming *immune* to an infection after previously dealing with the disease. This was first discovered by Edward Jenner, when injecting smallpox into a child, the child in question was not infected by the smallpox disease circulating at the time (Edward Jenner in 1790 in Sompeyrac, 2016).

The immune system wages a fierce battle between the very large organism that is the human being and microorganisms (VBPF) that invade the human body. These microorganisms multiply at an incredible rate compared to their host, the human body.

The origin of the framework of the immune system is clear: to *fight against microorganisms that invade the body, making the body immune to another attack*. The - ingenious - preventive medical intervention for a life-threatening disease that resulted from this idea was *vaccination* (injecting the disease itself) or *inoculation* (injecting the antibodies against a disease). Vaccination means a - minor - exposure to the disease, without the risk of getting the disease completely, but with the result that the immune system is activated to produce tags and antibodies against the disease. Inoculation means injecting specific antibodies so that they are ready to fight that particular disease when infected. The terms vaccination and inoculation are - unfortunately - often referred to interchangeably, without distinction as to their nature and function.

As new microorganisms emerged within evolution, the interaction and cooperation of the innate immune system and adaptive immunity in the human body became of primordial importance to protect the organism from invaders.

The innate immune system builds further on the fight against the long-standing pre-existing microorganisms, and continues to evolve because it must organise the fight with the adaptive system against the through evolution newly developed microorganisms. The adaptive immunity also continues to evolve in the human body because it is constantly confronted with new microorganisms. For example, migration to new areas brings new dangers for a human being not prepared for the pathogens in that migration area. The two systems of the immune system (innate and adaptive) must interact and cooperate with each other to cope with the dangers.

The immune system consists of three lines of defense. That the immune system involves the entire body becomes clear when we realize that the first and essential protection by the immune system - the *first line of defense* - consists of the "envelope of the body," which are the skin and mucosal tissues (Helbert, 2017, pp. 138-149). The first *action* of the immune system and the *second line of defense* is to be prepared for external invading organisms (VBPF) that invade the body tissues of the protective epithelium - the skin and mucosal surfaces as well as the respiratory system and gastrointestinal tracts (e.g., the pH of the stomach) - by receiving them through immediate confrontation with the *innate immunity* which is also called the *innate immune system* (Helbert, 2017, pp. 1-6). It has mechanisms that are fast and fixed in their mechanism of action and are very effective in destroying invaders and thus can stop most infections at an early stage. The innate immune system is aimed

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at destroying the VBPF directly (to be killed by the Natural Killer cells, NK cells) or, when killing or destroying is not possible, to transmit information for further action to the *third line of defense*, the *adaptive immunity*, which cooperates with the innate immune system. For this cooperation, the immune cells of the *adaptive* immunity hook into the components of the complement system of the *innate* immune system (Parham, 2015, p. 329).

The *complement system* is the system by which the action of the immune system fights the invaders through its cells equipped for this purpose. This system is used by both the innate and adaptive immune system. The invaders consist of viruses, parasites, bacteria, and fungi (VBPF), which are pathogens, disease-causing agents.

The innate immune system can detect common and uncommon invaders; it collects and integrates information about an invader that is not directly destroyed by the innate immune system. This information activates adaptive immunity. The *innate* immune system also detects danger signals sent by dying cells.

The reason why organisms enter the human body from outside is to access the rich resources provided by the human body.

Connecting the 'innate' and the 'adaptive'

The immune system consists of two basic subsystems: the *innate immune system* or *innate immunity* and the *adaptive immunity*. The nomenclature (naming) of the first part of these two concepts, "innate" and "adaptive," is consistent with the nature and evolution of the systems: "innate" was the first to appear in evolution and "adaptive" was the second. The second part of the concept is not unambiguous: 'system' or 'immunity in innate and 'immunity' in adaptive. To connect these into an overall system, it is important to adjust the nomenclature at the functional level and make it compatible. Since the word 'immunity' refers to the outcome of a process, this term is less obvious, and it is logical to speak of *innate immune system* and *adaptive immune system*. This is also conducive to categorising them together into a total system.

From an evolutionary perspective, the innate immune system (non-specific) is the oldest and the adaptive immune system (specific) evolved after and from the innate immune system. The evolutionary younger is also evident from the fact that the adaptive immune system appears only in vertebrates arising later in evolution, and the innate immune system already exists in invertebrates and later also in vertebrates. The innate system appears 600 million years ago in evolution; the adaptive immune system about 200 million years later (400 million years ago) (Parham, 2015). The innate immune system evolved further after the adaptive immune system had appeared and developed, but also continued to evolve; this developing together and influencing each other could be called *co-evolution* states Parham (Parham, 2015, p. 329).

The interaction between the innate immune system and the adaptive immune

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system is a natural process because the adaptive immune system builds on the work of the innate immune system (Nairn & Helbert, 2003, p. 3). The interaction and co-operation of the two systems is already evident in one of the first actions of the adaptive immune system: to "hook up" with the innate immune system in case of infection.

Based on different actions of the immune system, medical science generated two specializations within the immune system - one the ‘innate’, the other the ‘adaptive’. Both specializations independently developed their own methods and concepts, for almost two centuries without mutual scientific interaction, because people were not aware that the two systems in the body interacted with each other and formed one whole. This continued for almost two centuries. These two specializations generated a lot of knowledge and understanding in their specific area. For 'innate' the subject was *inflammation* - the *innate immune system* used to be - and still is - for that reason often called *inflammation.* The 'adaptive' it was the richness of *antibody diversity* (Helbert, 2017, pp. 1-6).

The separate treatment of innate immune system and adaptive immunity continued despite increasing evidence of connections between the two systems. Important for the connections was the observation that an inflammatory response is a necessary prelude to produce or deployment of appropriate antibodies. Although implemented in practice, this fact was not yet present in the thinking of most immunologists.

An example of this phenomenon of cooperation between the two parts of the immune system is that they both use the *complement system*, which can be activated by the two immune systems through three different pathways of activation.

The idea that the *innate immune system* and the *adaptive immune system* both have the same general function (action against invaders-vbpf) and the same activation system (*the complement system*) and evidence that the two interacted in the body did not reach scientific consciousness until the 1990s. This was the time to begin connecting the two specializations.

The specializations produced a lot of knowledge, but it is quite a puzzle to bring these two knowledge bases together, as they developed their own concepts, methodologies, and different nomenclature rules. After about 25 years since 1990’s, making this scientific connection at the beginning of the twenty-first century has hardly been done. One of the consequences is, that we do not yet have an overview of the entire immune system, nor a schema of how immune system as a whole works. However, this is necessary to understand events related to the immune system. This applies, for example, to the covid-19 pandemic starting in 2019, which broke loose a year after the publication of the book that made the connection within the immune system (Delfos 2018) and the discussion therefore was more about inflammation and vaccination than about the whole perspective of the immune system.

In textbooks, we see the problems arising from still quite young connections made between parts of the immune system; for example, in the struggle with definitions in which different systems bear the same name and the same systems bear

different names. For example, two concepts with the same system named 'immunity' are totally different concepts regarding the process of the immune system. The concepts from the specialization 'innate' are defined as the *mechanisms* or *processes*, such as *innate immunity*, and the concepts from the specialization 'adaptive' are defined in terms of *their outcome of a process*, such as *adaptive immunity*, while both use the word immunity. In Overview 1, we show four examples taken from four major textbooks to illustrate the problem of terminology. The first book (Nairn & Helbert, 2002) was published (still too) soon after the two specializations began working together; the second (Parham, 2015) is a textbook on the immune system published 25 years after the two specializations began working together; the third (Sompayrac, 2016), also about 25 years after they began working together, is a modern book to help students understand the immune system; and the fourth textbook is a new edition of Nairn and Helbert by Helbert (2017).

All four books still struggle with the concepts around 'innate' and 'adaptive' and do not arrive at a unified, consistent system.

To come up with a whole, definitions of the two terms were searched for and examined with respect to the mentions of 'innate' and 'adaptive' in the *index* and in any *glossary*, where the definitions are addressed, see Overview 1.

Textbook	**Innate / Congenital**		**Adaptive / Adaptive**	
Nairn & Helbert, 2002. In index, no glossary.	Only one keyword in index with multiple words: innate immunity/immune response (natural/non-adaptive).	No glossary, no definition.	One keyword in index: adaptive immunity/ acquired immunity.	No glossary, no definition.
Parham, 2015. In glossary + index.	In index: innate immunity.	In glossary: *innate immunity*: host defense mechanisms that operate from the beginning of an	In index: adaptive immunity.	In glossary: *adaptive immunity*: the state of resistance to infection produced by the adaptive immune response.

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Textbook	Innate / Congenital		Adaptive / Adaptive	
		infection and do not adapt to a particular pathogen or generate immunological memory.		*Acquired immunity*: alternative term for adaptive immunity; pathogen-specific immunity acquired because of infection or vaccination.
Sompayrac, 2016. In index, no definitions in 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 version. In glossary.	Index not available in digital version.	Glossary: innate (non-adaptive) immune system response. The older part of the immune system that responds quickly to infection but with the same response every time.	Index not available in digital version.	Glossary: adaptive (acquired) response of the immune system. A part of the immune system in which genetic recombination is used to recognize specific molecules. Responds slowly but produces lasting memory.

Overview 1: The naming/nomenclature of innate and adaptive in three (and updated fourth) textbooks on immunology.

The entries 'innate' and 'adaptive' in the book's index shortly after the beginning of the two specializations working together are multiple: more names for one concept and no definitions in glossaries or in the book itself. Overview 1 shows that the innate system and the adaptive system, notwithstanding that they are mentioned in the textbooks, do not always appear in the glossary where a definition is needed and

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expected. This is probably due to confusion when two specializations with their own development and concepts are brought together. The most recent book in Overview 1 is the third edition of Nairn and Helbert authored by Helbert (2017) with a glossary of *adaptive immune system response* and *innate immune system response*, which are reaction, but no description of the systems as such.

The different definitions and concepts are not yet connected, and as a result, different components do not yet have their clearly defined place and role in the immune system as a whole. Therefore, we do not find a model or schema of the total immune system with the innate and adaptive systems in the textbooks. There are schemas or models of parts of the immune system, for example models of the pathways with their activation of the complement and the subsequent cascade of cells of the complement system.

Therefore, no schema of the immune system as a whole existed until 2018 (Delfos, 2018). In schemas and models all elements are placed in their interrelationship and thus the overarching processes became clear. To understand and explain the system, but also to develop further theories, it is necessary, and even of utmost importance to place elements in a schema or model.

To connect and place the elements, it was necessary to thoroughly examine the available information and resolve the - only superficially - conflicting material by figuring out what existed in evidence-based research. The names had to be reorganized in the right meaning 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 thing was to connect the extensive material of the two specializations 'innate' and 'adaptive'.

Many terms are used, but in textbooks and articles they often talk about the *innate immune system* and the *adaptive immune system*, when they talk about the process, not the outcome, both these terms are at the same organizational level. In a schema, we need the process, not the outcome. And these two systems are the basis, the bottom line of immune system activity. So, we chose to use terminology at the same level of meaning: the *innate immune system* and the *adaptive immune system* with their corresponding definitions:

Innate immune system: The innate part of the immune system that can handle almost all pathogens through pathway 1 (alternative pathway) and then destroys them or forwards information to the adaptive system.

Adaptive immune system: The part of the immune system that comes into action when the innate immune system cannot kill or destroy a particular pathogen. This system hooks up with the innate immune system. It produces a wide variety of antibodies to cope with the diversity of pathogens. It is triggered by a pathogen and uses pathway 2 (lectin pathway) and pathway 3 (classical pathway).

The pathways of complement activation

The first pathway of activation that was discovered was that of antibodies. This pathway, because it was discovered first, was called the *Classical pathway*, but in fact

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occurs only as the third action in line. The second pathway discovered, was the one that occurred first in evolution and shows the first action of the immune system, which is to kill or destroy the invader (vbpf). This was called the *Alternative Pathway*. Finally, a third pathway was discovered, the *Lectin pathway*, it comes into action after the Alternative pathway and before the classical pathway (Helbert, 2017, pp.138-149).

To ensure that we gain not only knowledge but also understanding of how the immune system works and to avoid confusion, we name the pathways by their chronological actions.

First action, pathway 1: destroying cells and passing information to the adaptive system (non-specific NK cells, innate immune system; alternative pathway).

Second action, pathway 2: preparing the cell for destruction (hormone, adaptive immune system; lectin pathway).

Third action, pathway 3: destroying through specific cells (specific antibodies, adaptive immune system).

The part of the immune system that can identify and attack a pathogen (VBPF) is the innate immune system that has the ability to kill or destroy this pathogen. When the innate immune system has detected a cell penetrated by a pathogen, it triggers the first pathway (pathway 1, alternative pathway) to destroy the pathogen through part of the immune cells of the cascade of the complement system, those belonging to the innate immune system. The role of this pathway is to kill, destroy the pathogen. This pathway does not involve antibodies. It is the oldest pathway and is characterized by the NK cells, the Natural Killer cells. With these cells, the innate immune system can protect the body against almost any invader. NK cells form the basis of the innate immune system and therefore these cells of the immune system are the oldest in origin. The NK cell is capable of killing or 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, pp. 162-171).

When the innate immune system was not able to kill and destroy cells over time this was probably caused by evolution as new microorganisms arose that NK cells could not cope with and therefore required a more specific response (Helbert, 2017, pp. 14-17). A new branch evolved from the innate immune system into the *adaptive immune system,* which can form antibodies to those invaders that the innate system failed to eliminate. The adaptive immune system acts through the innate immune system when the innate immune system cannot kill or destroy the cell containing the pathogen and thus has been unable to prevent and stop the infection.

Whereas in the innate immune system the detection of a pathogen is the trigger for action, a persistent infection is a trigger for the adaptive immune system. The role of the adaptive immune system is the *recruitment of inflammatory cells* It responds specifically to specific pathogens through specific antibodies.

The adaptive system is therefore slower; it has first to build on the information

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from the innate immune system, then mark (tag) the pathogen and finally stimulate production of the appropriate antibody. The adaptive immune system is able to stop almost all infections beyond the innate immune system, with the innate immune system itself being able to stop almost all pathogens (Helbert, 2017, pp. 7-13).

When the immune system is not able to develop a successful response, this may stem from inherited deficiencies in the immune system, from the pathogen's ability to escape, avoid or undermine the immune response, or because it is difficult to eliminate because it is not living material like bacteria, parasites, and fungi, but dead material such as a virus.

The pathways associated with the adaptive - selective - immune system are pathway 2 and 3. There are three groups of molecules of the adaptive system that specifically recognize foreign *antigen*, another term for the invaders, a term used for the targeting antibodies or T cells). The first two groups that recognize antigen are the cell surface receptors found on B and T cells, the third group the Major Histocompatibility Complex (MHC) genes.

As a result of the actions of the three pathways, there is the *complement cascade* of immune cells that attack the pathogens by destroying them or quarantining them to free the body from infection and immunize the body - where possible - against a repeated attack by the pathogens.
See Overview 2 for a summary of the three pathways of the complement system.

Three pathways of the complement system			
Pathways	Pathway 1	Pathway 2	Pathway 3
Name	*Alternate pathway*	*Lectin pathway*	*Classical pathway*
Action	Action 1	Possible action 2	Possible action 3
Immune System	Innate immune system	Adaptive immune system	Adaptive immune system
Target	Destroy endangered cell (VBPF)	Preparation of pathogen (VBPF) threatening a cell for destruction by pathway 3, if pathway 1 is not possible: opsonization.	Handling (destroying or quarantining) endangered cell (VBPF)
Cell	NK cells-natural killer cells	Hormone Lectin	Specific antibodies, T and B cells, MHC genes
Specificity	Non-specific with respect to endangered cell	Specific, the cells informed about by pathway 1	Specific, the cells informed about by pathway 1
Autonomy	Autonomous	Hook up with	Hook up with innate

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	and forward information to adaptive system	innate system for information	system for information

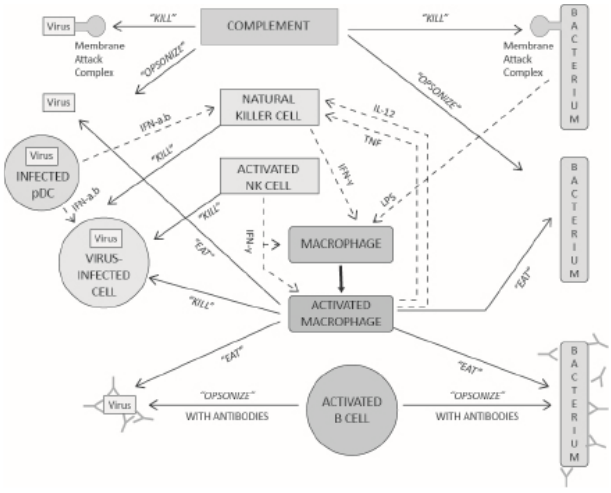
Overview 2: *The three pathways of the complement system (based on Helbert, 2017; Sompeyrac, 2016 and Parham, 2015).*

The schematic representation of the complement system with the pathways

The complement system with its pathways and cascade is the part of the immune system which has already been mapped. Several schemas already exist that visualize this part of the immune system in response to a pathogen.

The existing schemas are based on the premise of the immune system's function as fighting against invaders (vbpf). They are based on the knowledge of the complement system, the pathways, and the cascade. When the definition of the immune system is extended, the schemas will also be extended (Delfos & Van Gijsel, 2018).

The (part of the) immune system shown in schemas 1 and 2 works from top to bottom, whereas a schema is about a sequence, the bottom should be the beginning – the cause, the top, would be the end- the result. The cascade of cells, being the end-result, should be the top in a schema, and the complement, the bottom, and the pathways even lower. However, schema 1 and 2, which are common in books on the immune system, are the other way around: at the bottom, the cascade with the cells eliminating the pathogen.



Schema 1: *The complement and cells of the cascade interact with each other.*

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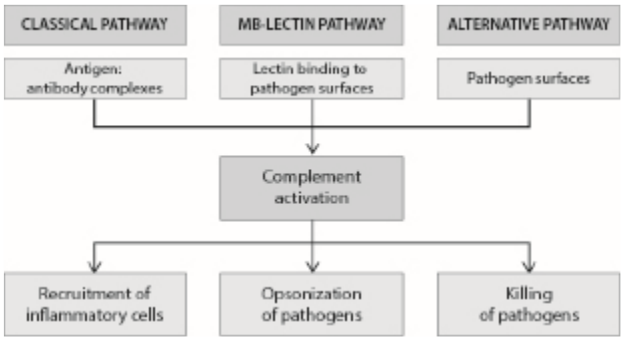
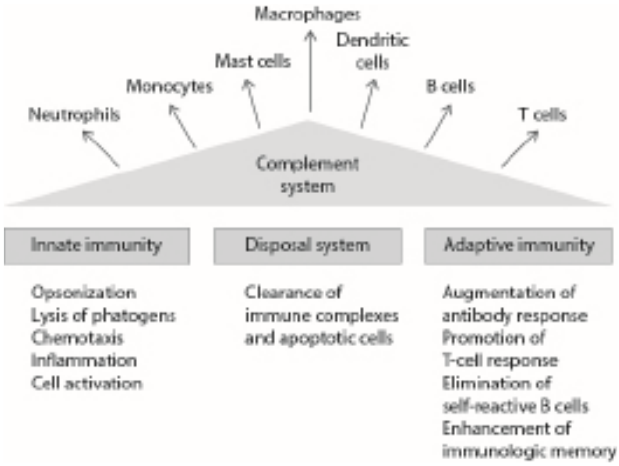


Schema 2: *The complement and cells of the cascade with the pathways and their different roles*

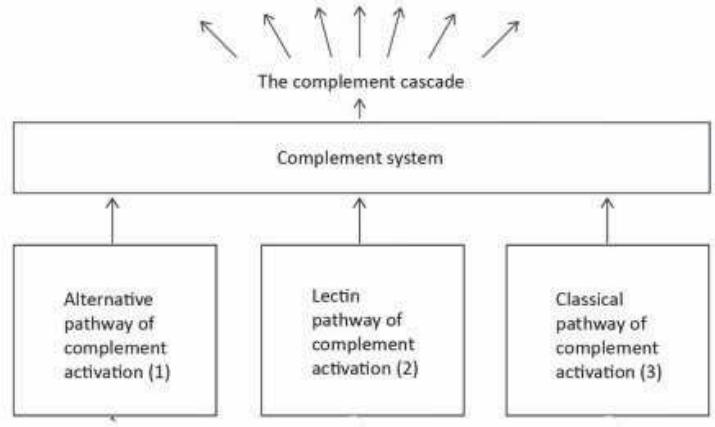
In schema 3, the visualization is expanded to include the basic immune systems and their roles, but without interrelationships, more descriptive than according to how the system works. However, the order is causal: from beginning to end, i.e., reversed with respect to schemas 1 and 2.



Schema 3: *The complement system with the three systems (innate immune system, adaptive immune system and complement system) and the disposal /deletion system - pathway 2, Lectin pathway - and signaling dead and dying cells; leading to the cascade of immune cells. Visualized without the underlying relationships.*

Schema 4 shows the complement system with the three pathways of activation and

the cascade in their mutual relationships from start (bottom: pathways) to result (top: cells of the ca)



Schema 4: *The complement system with pathways and activation in relation to each other (Delfos)*

Most of the knowledge (body of knowledge) about the immune system includes the immune cells and their actions; more at the cell level than at the system level therefore schemas 1 to 3 concern mainly cells and functions, but not yet how the immune system as a whole works.

A total schema of the immune system should 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.

The schematic representation of the immune system

By connecting 'innate' with 'adaptive' progressively and placing the two with the three pathways and the complement system with its cascade, it became possible to construct the schema of the immune system. The total schema must be formed according to the compiled and researched knowledge about the total immune system. In fact, everything is evidence-based, because it cannot be other than to group the known knowledge in a pure and logical way.

Schema 5 shows the immune system mapped with its three subsystems (*innate immune system*/ *adaptive immune* system/ *complement system*) in their mutual chronological-causal relationships. From the beginning (the pathogen penetrating the human body) to the end (possibly killing, destroying, or quarantining the pathogen through the cascade of immune cells), this constitutes the process and operation of the immune system.

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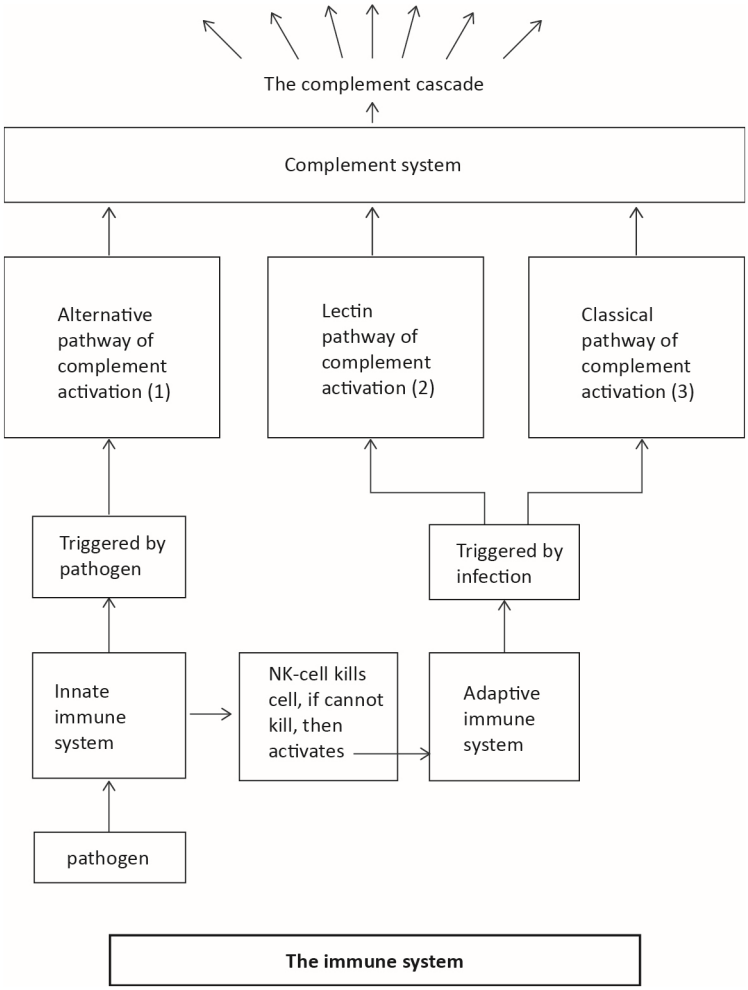

*Schema 5: Schematic representation of the immune system in the case of a pathogen (vbpf) (*Delfos, 2018).

What needed to be mapped into an overall schema of immune system function was the process from the pathogen entering the human body to its eventual destruction.

When a pathogen enters the *first line of defense*, that is the skin or mucosal surfaces, it triggers the immune system through the *innate immune system*. The innate immune system is activated by the pathogen as a *second line of defense* and in a *third line of defense* the adaptive system activates direct action against the invader. The complement system is activated to perform these tasks through three pathways, and, as a result, the complement cascade opens with all the applicable elements

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(immune cells) of the cascade. When the pathogen cannot be destroyed, an infection may occur and the innate immune system determines whether there is a role for the *adaptive immune system*, which then connects to the innate immune system. The innate system then relays information to the adaptive system The adaptive immune system then hooks up with the innate immune system to activate the *complement system* with B and T cells through the *classical pathway* (pathway 3) (Helbert, 2017, pp. 7-13).

Both the innate immune system and the adaptive immune system have their own pathways to activate the complement system leading to the complement cascade of immune cells with its NK cells, the killer cells that kill cells infected with pathogens (pathway 1, alternative pathway; innate immune system), the opsonization of a cell to prepare to kill the pathogen (pathway 2, lectin pathway; adaptive immune system) and the many antibodies (pathway 3, classical pathway; adaptive immune system) with specifically adapted attack cells that the body also produces itself (Helbert, 2017, pp. 138-149).

References

Delfos, M. F. & Gijsel, J. van (2018). *Autoimmune Reactions and the Immune System*. Amsterdam: SWP Publishers.

Helbert, M. (2017). *Immunology for medical students* (third ed.). Philadelphia, PA: Elsevier.

Louveau, A., Smirnov, I., Keyes, T.J., Eccles, J.D., Rouhani, S.J., Paske, D., Derecki, N.C., Castle, D., Mandell, J.W., Lee, K.S., Harris, T.H. & Kipnis, J. (2015). Structural and functional features of central nervous system lymphatic vessels. *Nature,* Vol. 523, 337-341. Doi: 10.1038/nature14432.

Mollgard, K.; Beinlich, F.R.; Kusk, P.; Miyakoshi, L.M.; Delle, C.; Plá, V.; Hauglund, N.L.; Esmail, T.; Rasmussen, M.K.; Gomolka, R.S.; Mori, Y.; Nedergaard, M. 2023). A mesothelium divides the subarachnoid space into functional compartments. *Science, 379,* 84-88.

Nairn, J. & Helbert, M. (2002). *Immunology for Medical Students* (first ed.). Philadelphia: Elsevier Mosby.

Parham, P. (2015). *The immune system* (fourth ed.) New York: Garland Science.

Sompayrac, L. (2016). *How the Immune System Works* (fifth ed., p. 10). Chichester, UK: Wiley Blackwell.

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