BOLK'S COMPANIONS

FOR THE STUDY OF MEDICINE

IMMUNOLOGY

Self and Non-self from a Phenomenological Point of View

Guus van der Bie MD

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About the author

Guus van der Bie MD (1945) worked as a lecturer at the Department of Medical Anatomy and Embryology at Utrecht State University, Holland from1967 to1976. Next to his practice as a general practitioner since 1976, he continued to educate physicians and therapists, and medical students at Utrecht State University and the University of Witten/Herdecke, Germany. He is a member of the Medical Section of the School of Spiritual Science at the Goetheanum, Dornach, Switzerland.

About the project

The project *Renewal of Medical Education* aim to produce Companions that demonstrate how the insights of current biomedical science can be broadened by using the Goethean phenomenological method. This method innovates current concepts and expands the understanding of biochemical, physiological, psychological, and morphological factors in living organisms and their development in time and space, and in health, illness, and therapy. The project is commissioned by the Kingfisher Foundation, which aspires the development, application, and publication of the Goethean phenomenological research method in the widest sense, to complement and innovate the accepted scientific view and research method.

BOLK'S COMPANIONS FOR THE STUDY OF MEDICINE complement current medical education, specifically disclosing human qualities in the fundamental biomedical sciences of today.

BOLK'S COMPANIONS FOR THE PRACTICE OF MEDICINE contribute to a scientific phenomenological basis for integrative medicine and integral psychiatry.

Contents

Preface

Why write this new booklet on immunology when there are already so many excellent texts on the subject?
Modern science, with its reductionist approach, has provided us with an impressive abundance of facts. What it is in the organism that connects all these facts has, however, not been incorporated into a clear concept. Because of this, the reductionist approach has led to a fragmented image of the immune system, which makes it difficult to obtain an overview of the immune system as a whole.

This Bolk's Companion for the study of medicine is about questions such as: why is it that the immune system functions as one organ? What coordinates the immunological functions?
Here, an attempt is made to develop a viewpoint to answer these questions. By using a phenomenological approach, the factual knowledge obtained through reductionism is placed in a larger perspective. That larger perspective has the character of a concept. In this case, a concept is interpreted as a cohesive creative principle. Knowledge of immunology is a big help in being able to recognize the concept presented in this Companion more quickly.
The concept that is presented in this Companion is derived from the functioning of organisms, observed in the way that was introduced by Goethe in his phenomenological method (25). This method also includes the acquisition of insight into the holistic concept behind the immune system. Moreover, the organism as a whole can then be seen as an expression of the same concept. It is not about new or revolutionary immunological facts.
We want to emphasize that this Companion does not replace a textbook on Immunology. The information in this Companion is compact en presupposes the knowledge contained in regular textbooks on Immunology.

Acknowledgements

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Guus van der Bie, Driebergen, September 2006.

1. Context and general aspects of immunology

1.1. Introduction: organism, environment and interaction

Living organisms, only, are capable of immune responses. These immune responses occur because organisms are in continual interaction with their environment. Organism and environment have an intensive relationship and live in mutual dependence with each other. The biotope creates the vital conditions in which an organism can live and without the appropriate biotope an organism will die. The reverse is also true: a natural environment from which all organisms have disappeared ends up dead and inorganic.
For each and every organism, the world is naturally divided into two domains: that of itself and that of the outside world, the surrounding nature in which the organism lives. In immunology, the concept of **self** is used to indicate the organism and the concept of **non-self** to indicate the environment surrounding the organism. In understanding immunological processes, the nature of the difference between **self** and **non-self**, and their interaction, is of essential importance (2, 6, 19, 21).

1.2. The organism

Are there typical characteristics for a living organism? Steven Rose wrote about this in an informative little book entitled: 'Lifelines' (22). In that book, he characterizes what he feels is typical for a living organism. The word 'Lifeline,' as Rose sees it, indicates that an organism displays **life processes (life)** and develops in **a structure in time (line).** Life processes and their development over time are two essential characteristics that differentiate the living organism from a lifeless object.

1.2.1. Life processes

The ability of an organism to survive on its own is based on biological processes that are the expression of the 'self-regulating' ability of the organism (see Chapter 1.4.). This self-regulation also becomes apparent from the biochemical, physiological and morphological processes in the organism. A botanical organism is able to absorb material from the realm of inorganic nature (chemistry) and to provide it with species-specific new molecular structures and functions (biochemistry), and organic forms (morphology). Thus, a plant is able, by absorbing sunlight (photo-phosphorylation), to make species-specific carbohydrates from carbon dioxide and water (photosynthesis) and to convert this into a characteristic configuration. The leaf of the stinging nettle is different from that of the beech tree, and the essential composition of vegetables is different from that of fruit.
This ability to give material a new form and function is also displayed in many places in the immune system (see Chapter 3.3.2.2. and Chapter 4.).

1.2.2. Development in time

Characteristic for an organism is, moreover, that it develops **itself** over **time**. A plant follows the route of the seed, via the seedling to the full-grown plant, which makes seeds again. This is a cyclical process which is obvious to all of us if we take in the entire timeline. After all, the seed looks nothing like the seedling, the seedling has little resemblance to the full-grown plant and the full-grown plant, in turn, does not resemble the seed. Therefore, the formation of an organism over time yields successively completely different forms of that organism. One example of this morphological development over time from the animal world is the cycle **starting from** the fertilized ovum, the immature phase of an organism, progressing to the mature, fertile phase and **ending up with** the involution phase at the end of life.

1.2.3. The environment

The environmental influences that operate on plants, animals and people are of various origins. First of all, there are the influences from the immediate surroundings, the biotope. Biology has in addition to that also familiarized us with influences that come from beyond the earth. Thus, the reproductive rhythm of many animals is determined by the seasons, which are again dependent upon the relationship of the earth with respect to the sun. Another example is the connection between the position of the moon and the appearance of turtles on land to lay their eggs.

Geological, climatological, and ecological developments of the earth have sufficiently proven that radical changes can cause certain life forms to die out and others to appear, together with the changes in the biotope. However, even without knowledge of these huge, dramatic events, we know that every organism is in a dependency relationship with the biotope in which it lives. Often, the reverse is also true: the biotope is dependent on the organisms that live there, because these organisms are also among the factors that determine the soil composition, atmospheric humidity, temperature regulation, etc. Life is impossible without this mutual, biological dependency.
There are two types of influences that come from the environment and have an effect on the organism: influences that stimulate the organism, and influences that threaten its existence. It is, in particular, the latter influences that, via a well-functioning immune system, can often be overcome by the organism.

1.3. The interaction

The outer-world and the inner-world are in constant and developmental contact with each other. We can differentiate the interaction of the organism with its surrounding into three **phases**:

- everything begins with a **contact** between organism and an outside influence
- followed by **internal processes** in the organism as a reaction to the external influences
- and finally a definitive **effect**.

This differentiation into three phases and processes of interaction is so generally applicable that it can be characterized as a basic phenomenon of life: the **organic archetypical phenomenon** (fig. 1.). This **organic archetypical phenomenon** is a threefold process. Thus, within every organism, there is a differentiation of three specific physiological – and often also morphological – specializations. This differentiation takes place through self-regulation (see Chapter 1.4.) within the organism. In these differentiation processes, a processes is never 'added from outside.' Moreover, on the basis of comparative biology and evolution biology, it is clear that it would be incorrect to talk about the 'construction' of the organic archetypical phenomenon from three functions. That would create the impression that each of these functions could also exist in and of itself. Each organic function is based on the organism as a whole. The threefold process is the differentiation **within** the organism and not the sum of specific, assembled functions.
The three phases of the **organic archetypical phenomenon** are:

- **contact phase:** input from the environment
- **reaction and processing phase:** reaction to and processing of the input, as a result of which the organism undergoes a change
- **effect phase:** the effect in the organism and on the environment.

1.3.1. Contact phase

Every interaction between an organism and environment, also the immunological immune response, begins with a contact between something from the outside world (non-self) and something from the inside world (self) of the organism. This phase of making contact occurs in the **surface structures** of the organism. Thus, for example, contact occurs on the surface of cells, mucus membranes and skin. This also applies to the cellular components of the immune system, such as macrophages, B-cells and T-cells. The surface contact area for the immunological response has characteristic properties that will be discussed later *(*see Chapter 4.). This applies to the evolutionistic, older, aspecific part of the immune system (innate immunity), as well as to the specific part (adaptive immunity) that developed later in the evolutionary process.
In certain situations situation, the organism's own tissue, can become an antigen for its

own immune system. Examples of this are spermatozoa and the proteins in the lens of the eye. In autoimmune diseases, there is a failure in the recognition, or a change in the structure of one's own cells (self), such that illness develops.

1.3.2. Reaction and processing phase

The reaction and processing phase is a matter of internal processes within a specific time period **in the organism.** Some immunological processes, such as with aspecific or innate immunity, occur as immediate reactions to contact and are activated within a few seconds. Others are slow and occur over many days, such as in the case of the specific immunity of the more highly developed organisms, the adaptive immunity. Internal processes have a great variety of possibilities (see Chapter 3) among which are humoral, cellular, endocrine, biochemical and genetic.

1.3.3. Effect phase

The result of a successful immunological reaction can lead to two different effects:

- one effect causes the organism to change its **own inner world**.
  In that case, an organism can become immune to pathogenic influences. We see examples of this among people who have undergone such diseases as chicken pox, whooping cough, polio, measles or infectious mononucleosis. After the illness, they have life-long immunity. Vaccination is a method of artificially bringing about this immunity by administering the pathogens of a disease in a weakened form to the organism, in order to evoke a specific immune reaction. This also can result in life-long immunity for a specific disease. Animals can also acquire life-long immunity after a disease or vaccination. Also plants are able to develop antibodies against moulds and other pathogens which leads to resistance to disease.
- the second effect can be the **effect on the surrounding milieu, the environment**.
  Many animals excrete substances which result in providing protection against harmful influences.

In figure 1 the **organic archetypical phenomenon** is represented schematically. It is of essential importance to understand that each and every organism is able, through **self-regulation** (see Chapter 1.4.) to realize the sequence of contact phase, reaction phase and effect phase. Plants, animals and humans all do that in their own specific manner.

In our Companion Anatomy, we already provided the blueprint for a threefold physiological and morphological concept of the organism. Because, in immunology, this blueprint seems to be applicable once again, the Companion Anatomy can be studied as an introduction to the Companion Immunology.

1.3.4. Interactions via non-harmful influences

There are an enormous number of physiological interactions between organisms and environment. Feeding and excretion are examples of this. In the **digestive system** we see a healthy relationship with environmental influences: foreign material is ingested, digested and some digested parts are excreted and may be used for the growth and maintenance of other organism.

1.3.5. Interactions via harmful influences

There are also influences from the environment that are harmful for the organism. The effects of viruses or bacteria and moulds, the effects of antigens and toxins can be pathogenic or even life-threatening. If the organism does not have an appropriate answer, it can die.

> *The immune system plays a central role in the recognition and assessment of harmful and non-harmful influences. Alongside of being able to differentiate and recognize, the elimination of harmful influences is the task of the immune system.*

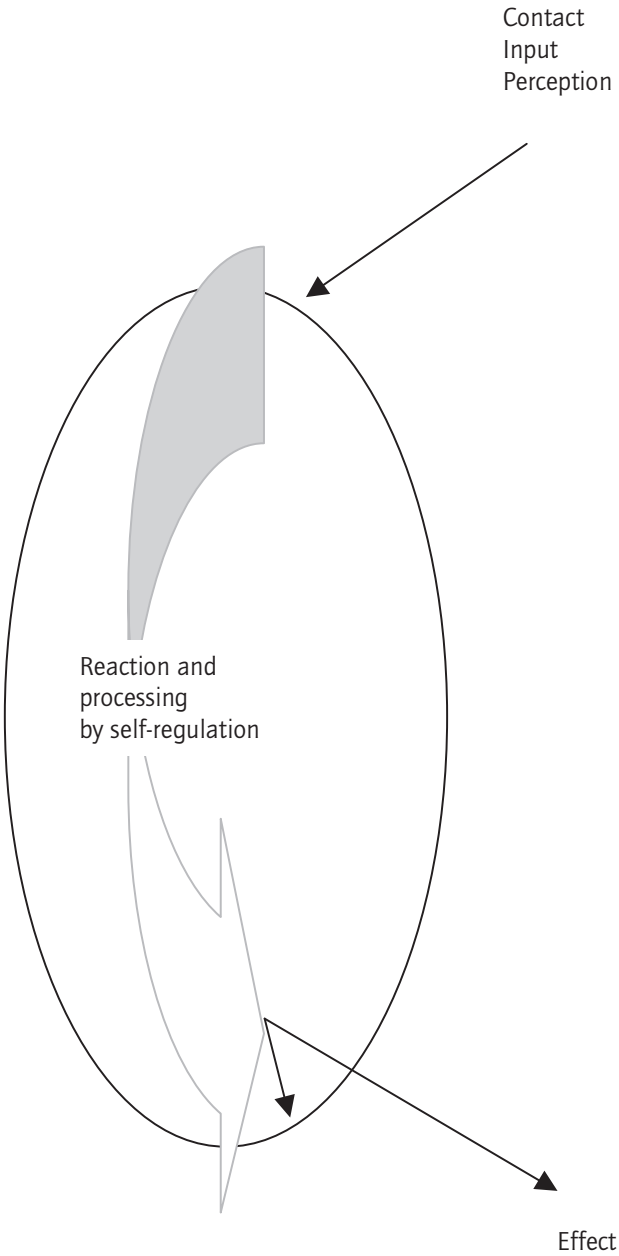

Fig. 1. Organic archetypical phenomenon

1.4. A threefold function pattern

The self-regulating ability of the organism organizes and coordinates the progress of the organism's immune reactions. It is astonishing that immune reactions are almost always perfectly coordinated and phased. Molecular biology has a fascinating description of processes and factors that occur during immunological self-regulation. What drives that self-regulation and how the integration is maintained can, thus far, not be described in terms of molecular biology. Based on this point of view, immunological self-regulation remains an intangible phenomenon. In any case, something like 'the coordination centre for the immune reaction' has never been found within immunology. Who or what drives the immune system? Who or what coordinates, fine-tunes and ensures that an immune reaction of the **'self'** is not insufficient, or does not overshoot its mark, or that it is not too short or too long? In the cases of autoimmune diseases and allergies, it is precisely in these areas that things go wrong, because the coordination and integration of the various aspects of the immune processes fail.

The immune system has an infinite number of active factors such as tissues, cells and proteins. Immunologically active organs and cells, humoral factors such as complement, antibodies and cytokines, and neuro-immunological substances are examples of these factors. They are, nevertheless, all part of one single immune **system** that functions in an integrated manner.

> *The immunological reaction can be understood as an extraordinary differentiation of the organic archetypical phenomenon that is, at all times, threefold.*

2. The anatomical and functional structures of the immune system

In this chapter, contact, reaction and effect will be discussed as they differentiate in immunological processes. A threefold process in immunology is recognizable in all domains of the immune system. In this chapter cognition, reaction and effect will be discussed with respect to the humoral, cellular, innate and adaptive components. In Chapter 3 a further differentiation in the development of the immune system will be discussed.

2.1. Functional threefold division in immunology

In evolution, the organic archetypical phenomenon differentiates itself among plant, animal and human in various ways and in a multitude of life functions (21). For that purpose, various specific tissues and organs have been formed. For the immune system, that means that the contact phase, reaction or processing phase and the effect change specifically depending upon the level of development of the organism. In the immunology of man and animal, the metamorphosis of the contact phase is named **cognition** for the recognition and binding of the antigen to the host cell. The metamorphosis of the reaction and processing phases is named either **reaction or adaptation.** The ultimate immunological answer that leads to the removal of the antigen by means of apoptosis (programmed cell death by self destruction) or digestion and the acquisition of resistance and immunity, is the metamorphosis of the **effect phase**.
A great deal of research has been done in human immunology after studying immunology in animals. In this Companion, our aim is to place the accent on human immunology.

Cognition, reaction and effect are the immunological metamorphoses of the threefold processes of the organic archetypical phenomenon.

The immunologist, Irun Cohen, describes these three processes in an anthropomorphic manner in his book *Tending Adam's Garden* (4). It is a splendid book in which Cohen clarifies the three phases of the immune process by explaining them in human terms. He chooses to use the words: seeing, changing, doing.

- **'Seeing'** stands for the cognitive phase in which the self recognizes the antigen.
- **'Changing'** stands for the internal processes that occur within the organism, by which the organism changes such that it becomes immune competent, and can decompose the antigen.
- **'Doing'** refers to everything which leads to the decomposition of the antigen, and the acquisition of immunity.

All multicellular organisms are differentiated in extra cellular bodily fluids with dissolved substances the **humoral factors** on the one hand, and **cells** with their intracellular substances on the other. The immune system is no exception to this. It is known that there are innumerable dissolved polypeptides and proteins circulating in the blood, lymph or interstitial tissue and that they play a role in the immune response. This part of the immune system is, in this Companion, described as the **humoral immunity**.
These soluble factors of the immune system have innumerable effects on immune active cells. These cells are responsible for the immune reaction by means of more specific cell activity; these cells are therefore, in this Companion, described as belonging to the **cellular immunity.**

Comments
The author is aware of the fact that the concepts **humoral immunity** and **cellular immunity** are used differently in this Companion than in the current literature on immunology. The reader needs to be aware of how these concepts are used in this Companion. In the current literature, one considers humoral immunity to be that which is specific immunity mediated

by antibodies. These antibodies are introduced into the circulation by specialized B-cells (plasma cells) (see Chapter 3.3.3.1.).
T-cell bound activity is thus considered as a part of the cellular-specific immunity (see Chapter 3.3.3.2.). Humoral and cellular, therefore, denote aspects of the adaptive specific immunity.

In this Companion, however, humoral will be interpreted in a broader sense, as described by Roitt et al.: humoral "belongs to the extra-cellular fluids, among which are serum and lymph" (21). Thus, substances belonging to the aspecific, innate immune system, such as complement and cytokines, are also considered to be part of the humoral defense.
Cellular, in this Companion, will also be interpreted in a broader sense than the immunity that is bound to T-cells. Thus, macrophages, antigen presenting cells (see Chapter 3.3.3.2.) dendritic cells and other cells belonging to the aspecific, innate system can be included in the cellular defense.

2.1.1. Cognition and recognition

Cognition and **recognition** can be seen as the 'perception and observation' of forms at the level of molecular biology (6, 17). Cognition is here related to the recognition of self and of non-self. For an immune reaction, it is primarily the recognition of non-self that is important.

> *Cognition is the immunological metamorphosis of the contact phase.*

Humoral factors, such as antibodies and complement factors, have the ability to 'recognize' and bind with antigens (non-self).
Cognition at the cellular level occurs through receptors on the cell surface. It is chiefly the aspecific innate system, to which, for example, the macrophages, dendritic and Langerhans cells belong, that have the discriminating ability to distinguish between self and non-self. The specific immune system, however, can, recognize molecular structures in a much more

sophisticated manner, but it cannot always distinguish self from non-self and is, therefore, dependent upon the aspecific system.

2.1.2. Reaction or adaptation

Reactions can only occur during functioning **internal processes** such as biochemical reactions, macro- and micro-circulation and cell respiration. Thus, the organism can react and adapt itself to the new condition and activate the necessary immune active cells or substances. Also, the processes of change that can lead to immunological phenomena – to be discussed below – such as antibody production, clonal selection or changes at the genetic level, as in somatic mutation and genetic rearrangement (see Chapter 3.3.2.2.), are dependent upon microcirculation and the internal transport of substances.

> *The reaction or adaptation phase displays an immunological metamorphosis and specialization of the reaction at the level of the internal processes.*

There are various types of immunological reaction and assimilation processes at the humoral as well as the cellular level. It is important here to differentiate between the **congenital aspecific (innate)** processes and the **acquired specific (adaptive)** processes.
Congenital (innate) internal processes are immune responses that are passed on from generation to generation. They are pre-programmed on the basis of heredity and belong to the so-called germ line immunity. These congenital internal processes go quickly and ensure an immediate reaction that is, therefore, called an **immediate type** reaction. We find these types of internal processes in the complement system, macrophages and natural killer cells (NK).
Acquired specific (adaptive) reactions are not hereditarily pre-programmed. These are unique and specific reactions to the molecular-biological form of an antigen. They are coupled with a new ordering of genetic material in the lymphocytes and the production of highly specialized cell lines.

	Innate (congenital)	Acquired (adaptive)
Humoral	**Humoral/ innate** Example: Complement	**Humoral/acquired** Example: Antibody
Cellular	**Cellular/innate** Example: Macrophage	**Cellular/acquired** Example: T-cell

2.1.3. Effect and processing

The effect of the immune response can be seen as the final effect of all processes 'that (in the case of the organism and the antigen) change the world.' That also relates to the world of the interior milieu of the organism: immune proteins and immune active cells consume the antigen.

> *The immunological effect phase is the metamorphosis of effect of the organic archetypical phenomenon.*

2.2. Anatomical structures of the immune reaction

The primary lymphatic organs, thymus and bone marrow, and the secondary lymphatic organs such as the lymph glands, the lymphatic vessels, the spleen, and the organs of the mucosal structures are the main organs of the immune system. All immune competent cells are derived from and differentiate themselves within these tissues and are dispersed throughout the entire body and brought into contact with each other via the circulation. Thus they form together – with the blood and the lymph – the anatomical substrate which makes it possible for the organism to achieve an adequate immune response.
During evolution and in fetal and early childhood development, various immune specific

tissues and organs differentiate. In humans, the liver and bone marrow have a leading role as suppliers of stem cells. The maturation and differentiation of these stem cells into leucocytes, lymphocytes, dendritic cells, etc. takes place in the other tissues, such as that of the thymus, the spleen, the gastrointestinal lymphoid tissue, lymph glands, and for the B-cells, in the bone marrow. Lower organisms do not yet have highly developed immune systems and they miss, therefore, the specific tissues and organs for cognition, reaction and effect. Here, we will discuss the various tissues on the basis of their significance for cognition, reaction and effect of the immune system.

2.2.1. Structures of cognition: the surfaces of tissues and cells of the contact phase

A multi-celled organism makes contact with the surrounding environment via those tissues which mediate the contact between self and non-self. That is the skin and the mucus membranes of the intestines, the airways and the urogenital system. These tissues have an enormous surface and are, therefore, the pre-eminent contact organ for antigens. With the exception of the skin, what all of these organs have in common is that they are, in embryo, originally developmental products of the primitive gut.

2.2.1.1. The skin

As body surface, the skin is, to be sure, the 'outside point of contact' with the environment, although it is, as far as surface area is concerned, nevertheless, the second contact organ of the organism. The organs covered with mucosa have a surface area that is many times greater than that of the skin. Normally, the skin is intact and forms a biomechanical defense for harmful influences. Damage to the skin leads to a quick activation of the immune response system. Scraps of damaged skins cells are powerful stimulators of the cytokines of the immune system, so that the organism reacts quickly and violently to a lesion of the skin.
The skin has, for example, dendritic cells. Dendritic cells are capable of bonding with

antigens. They can process the antigens intracellular and then present the scraps of that antigen to the surface of the cell. That is why these cells are called 'antigen presenting cells' (APC). Then, this processed antigen is transported to a nearby lymph gland or to the spleen where the following step in the immune reaction occurs: the communication with other immune active cells or cytokines (6, 7).

2.2.1.2. The mucosal organs

More than 95% of the contacts that humans have with antigens from the outside world occur via the mucus membranes of the intestines, the respiratory organs and the urogenital system. The total surface of the mucus membranes is enormous. The immune system that lies in the mucosal contact surface is denoted with the term **MALT** (Mucosal Associated Lymphoreticular Tissue). In the mucosa of these organ systems, there are numerous types of cells that are activated upon contact with an antigen. M-cells are specialized mucosa cells that bind antigens and transport them to the macrophages, B- and T-cells that are present in the mucosa. There are also a great many dendritic cells which bond with, process and transport the antigens via lymph vessels to nearby lymph tissue. The role of the mucosal organs for the immune system is also apparent from the large amount of lymphatic tissue that develops from the primitive gut, the embryonic precursor of the gastrointestinal and respiratory system.
Among fish, which have no pulmonary respiration, and thus no pulmonary mucosa, the intestinal wall itself is the most important part of the immune system. The **GALT** (Gastrointestinal Associated Lymphoreticular Tissue) can be found there.
GALT is in humans, as well very important. The **tonsils, adenoids, the Peyer's plaques** and the **appendix** are developmental products of the primitive gut that can be considered to be part of the GALT. The thymus develops from the mucosa of the third pharyngeal pouch of the primitive foregut. The **Thymus** plays a central role in adaptive immunity. It is in the thymus that the T-cell selection takes place, an essential process for the physiology of the **T-cell**.
Among birds, the **Bursa Fabricii** is the place of origin for the B-lymphocytes. The Bursa Fabricii is comparable to the pharyngeal pouches in the primitive foregut: the Bursa is

a pouch of the primitive hindgut that forms a place of origin and maturation for the B-lymphocytes which play a principle role in adaptive immunology. The Bursa Fabricii does not appear in mammals where the B-lymphocyte production of the Bursa Fabricii has been taken over by the bone marrow. A **B**-cell is a lymphocyte that originates in the **B**ursa Fabricii in birds and in the **B**one marrow in higher mammals and humans.

The paranasal sinuses, the bronchial tree, the lungs and the urogenital system also develop from the primitive gut. That is why the intestine plays a central role for the immune system in evolution and physiology. That part of the immune system that is part of the mucosa of the airways is called **BALT** (Bronchial Associated Lymphoid Tissue).

2.2.2. Structures of the reaction phase, processing and adaptation

2.2.2.1. Metabolic reactions

The reaction and processing phase begins the moment after the contact phase (15). During the reaction phase, particles of the antigen are transported via micro- and macro-circulation. Here, this is circulation at the cellular level – the microcirculation of particles in the cell itself – or circulation between intracellular and interstitial fluids as blood and lymph. These processes are part of more general processes in the organism, as is described below.

Respiration and circulation, at macro and micro levels, together bear all the internal processes of self-regulation and energy management. Respiration, cell respiration and the function of the mitochondria are essential at every place in the organism where vital functions occur. Circulation, energy management and respiration are necessary for the internal conversion processes. These are general biological functions that occur during each and every internal process in the processing of external influences, although they do not determine the ultimate effect on the organism. The ultimate effect is determined by the organs that are involved in the effect phase. The following example should clarify this. If a human being takes in carbohydrates in his food, then that is detected via macro

and microcirculation in the internal environment. As a reaction to this, the production of enzymes for carbohydrate digestion is primed via the salivary glands. The enzymes produced there flow, through circulation, to the intestinal contents again for the digesting of the carbohydrates.
If, however, protein is ingested into the intestine, then circulation leads to the mobilization of proteolytic enzymes which are produced via the pancreas and, subsequently, enter the intestines. Thus, circulation is a necessary condition for the assimilation process and the reaction facilities of the organism, but it does not determine the specificity of the ultimate effect.

The same applies for the immune system. In this case, antigens can be compared to foodstuffs with a harmful effect. The organism detects the harmfulness; after antigen processing and internal circulation, the antigens – or particles thereof – are submitted to immune competent tissues and the immune response can be activated and the antigen removed.

2.2.2.2. Specific and aspecific cellular reactions

A large number of cells of the aspecific (innate) system play – after the cognition phase – an essential role in the reaction phase. Macrophages, dendritic cells and Langerhans cells are examples of cells that, after recognition, bonding and assimilation, have the ability to become antigen presenting (see Chapter 3.3.3.2.). Antigen processing can precede antigen presentation. During antigen processing, the antigen is processed by the cell of the innate system such that it can be presented – as it is or in fragments – to the cells of the specific (adaptive) system (13).
The development of the cells providing cellular immunity occurs, for both aspecific and specific immunity, in three stages:

- production of stem cells
  Stem cells are produced in the bone marrow and the liver.
  Stem cells are not yet capable of an immunological response to antigen stimulation
- maturation into immune competent cell

Maturation occurs in the bone marrow for B-cells, macrophages, monocytes and granulocytes. T-cells, however, do not mature in the bone marrow. A number of stem cells migrate to the thymus and that is where they undergo their maturation into T-cell

- activity as immune competent cell
  After maturation, all cells migrate via the circulation to the peripheral lymphoid organs and tissues in the body. There, they meet up with antigens, cytokines and other cells of the immune system, with which they can interact. In these peripheral lymphoid organs, the immune reaction is orchestrated by mutual influence, stimulation or inhibition by feedback.

The maturation process plays an essential role in cognition because it is solely the mature cells in the cellular immune system that are able to achieve cognition (1, 2, 19, 21).

2.2.2.3. Reaction through change at the genetic level

The processes that originate as a specific reaction to antigen will ultimately reach the DNA in the cell nucleus of the B-cells and T-cells. At random or depending on the form of the antigen, new genes can be composed through the recombination of existing components of the DNA (15). The new genes can generate an enormously diverse repertoire of antibodies (immunoglobulins) in B-cells, and specific T-cell receptors (TRC) in T-cells (see Chapter 3.3.2.2.). Antibodies and TRCs can then be used in the recognition and elimination of the antigen through the effect cascade of the immune system.

2.2.3. Structures of the final effect: cytokines, cells, antibodies and antigen receptors

A number of organs and cells were mentioned above which, after internal processing, determine the ultimate effect of the immune reaction. These effects determine the new condition of the organism after coming into contact with the antigen. This new condition

also implies a new relationship to the surrounding environment because the organism is now competent to handle other – previously non-existent – activities and reactions. A child who is vaccinated against polio is now, after the vaccination, an organism that has become immune to infection with the polio virus. For such a child, polio can no longer be a threat.

2.2.3.1. Humoral effects: cytokines

There is a nearly incomprehensible number of different substances that can be excreted by immune competent cells. The general term for these substances is **cytokine**. The word itself makes it clear that these substances put 'cells' into 'motion.' This motion can be a relocation of the entire cell, as well as a change in the internal processes. The ultimate effect of cytokines is once again related to the environment in which they are effective. Thus, in a different context, the same cytokine can have different – and even opposite – effects, dependent upon the time and place of the immune reaction.

2.2.3.2. Labeling: antibodies and antigen receptors

Circulating immune proteins and antigen receptors can bond to the surface of an antigen (opsonization) of non-self cells. Consequently, the antigen becomes recognizable for other immune factors and can then be absorbed (see Chapter 3.3.1.2.).

2.2.3.3. Effect cascade

Immunological reactions often have an effect in the form of a cascade: a consecutive series of metabolic and cellular processes that ultimately remove the pathogen. Substances such as cytokines, interleukins, tumor necrosis factor, complement factors and many others follow each other in successive activities and modify or specify the immune response.

The humoral factors produced by cells play a primary role here. Organs, cytokines, cells and immune proteins form chains of effect that eliminate the harmful influence in a coordinated manner.

2.2.3.4. Cellular effects of the B-cell and the T-cell

After contact with an antigen, B-cells can differentiate themselves into plasma cells and deposit large amounts of antibodies into the circulation (7).
T-cells develop T-cell receptors on their cell surface that are capable of bonding with antigens and developing into, for example, cytotoxic Tc-cells which can induce apoptosis (see Chapter 3.3.3.2.).

All effects occur within the context of the immune system as a whole and form, together, an effective, coherent immune response.

2.3. Phenomenological aspects

2.3.1. Organism and the organic archetypal phenomenon

In order to find the organizational principle of an organism from a phenomenological perspective, a comparative research method is necessary. The comparison of the organic archetypal phenomenon, the threefold physiology and morphology of the organism, as is described in the Companion Anatomy and the three phases of the immune response make it possible to recognize the functioning of the threefold blueprint (fig. 2.). From that perspective, immunological responses reveal themselves as a differentiation of the organic archetypal phenomenon (see Chapter 1.3.3.). The threefold blueprint can be seen as **the organizer** of the organism as a whole.

Justification
A phenomenological relationship cannot be scientifically authorized through a reductionistic approach. At the level of the organism as a whole, the reductionist method does not provide any instruments to make the entire organism also cognizable or visible. Thus, the organism as a whole withdraws itself from measurability and, therefore, from recognizability for the reductionist approach. A logical line of reasoning concerning life phenomena ought to define what an organic connection is. The reductionist approach has proven not to be able to do (22).
On this point in our publication – and based on the phenomenological point of view – we consciously overstep this boundary set by reductionism, in an attempt to achieve scientific holism.

The threefold organization structure forms the blueprint for the organism and the immune system.

In the following paragraphs, the organic archetypical phenomenon will be compared with the various processes of the immune system. By doing this, insight can be acquired into the specific character of the differentiation of the immune system.

2.3.1.1. Perception and cognition

Perception and cognition are activities that are dependent upon the developmental level of the nervous system. The development of specific perception occurs by means of specialized senses. The level of cognition which a human or an animal is capable of is dependent upon the developmental level of, in particular, the sense organs and the brain. In chapter 3, the relationship between the level of development of an organism and the level of cognition will be further elaborated upon.
In the human organism, the organs and functions of perception and cognition are, to a great degree, concentrated in the head (3). The cognition function of the immune system can, therefore, be considered to be a metamorphosis of the cognitive system of man which is, however, in this case, not related to the nervous system but is at the level of digestion and metabolism (see Chapter 2.2.1.2 and 3.3.1.).

2.3.1.2. Reaction and adaptation

The specialization level of metabolic, respiratory and circulatory processes is determining for the assimilation and reaction capacity of an organism.
In the human organism, the most important organs of reaction and adaptation are concentrated in the internal organs and the respiration and circulation organs localized in the thorax. The reaction and adaptation function of the immune system can, therefore, be seen as a metamorphosis of these organs at the level of the immune system.

2.3.1.3. Effect

The specialization of the motor system ultimately determines the possibilities and the effectiveness of behavior. In connection with the development of perceptive reactive abilities, the limbs – or the organs that are determining for the motor system – will determine the ultimate effect. Extremities, claws, horns, venomous glands or metabolites that are excreted into the environment are the effectors at the level of the organism as a whole. Opsonization, fagocytosis, cell membrane perforation and apoptosis induction are metamorphoses of effects at the level of the immune system.

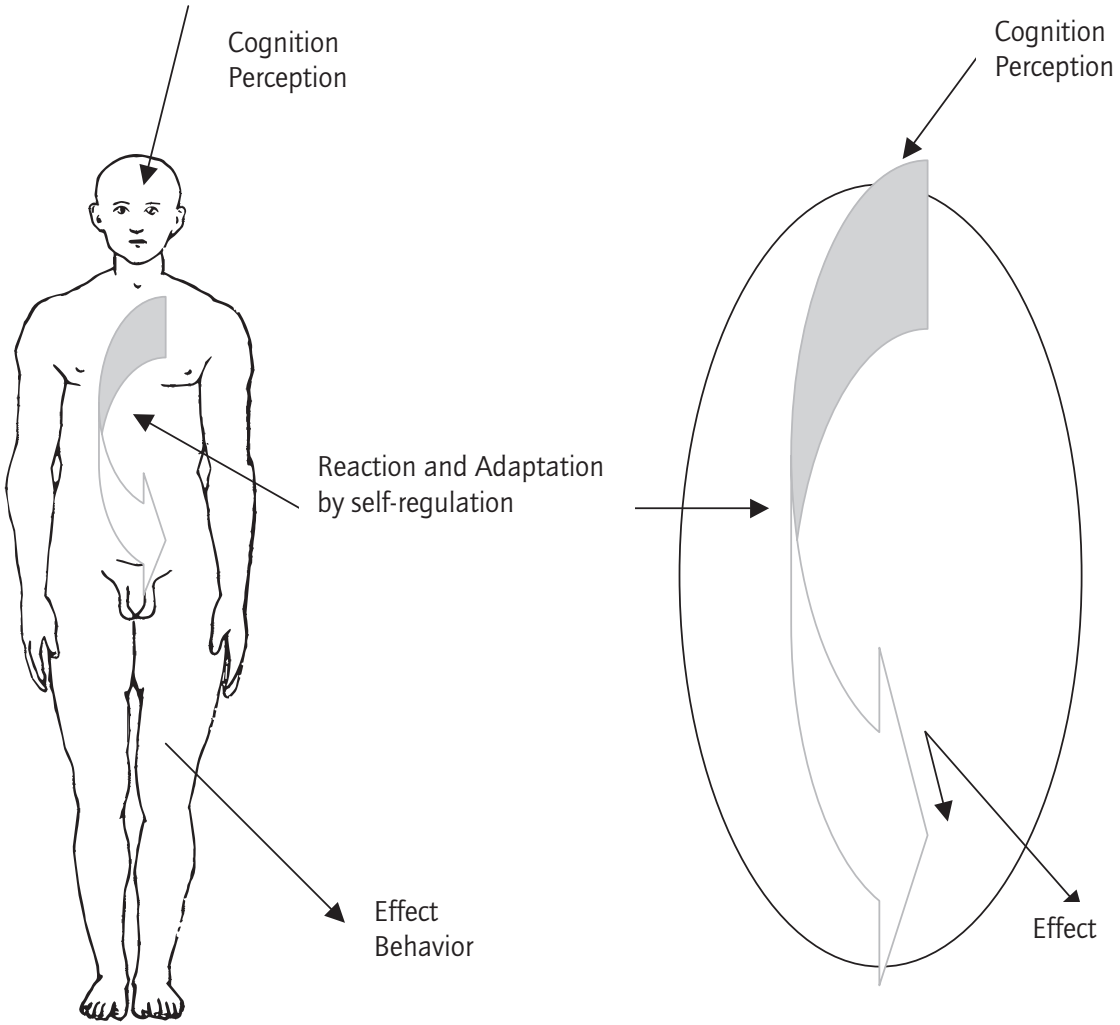

Fig. 2. Comparison of the immunological process with the organization of the threefold human being

3. Developmental levels of the immune system

In this chapter, immunological functions will be described that are characteristic for the **various developmental levels** of the immune system. That developmental level has bearing upon both the evolutionary aspects and the development of the individual human being.

3.1. Introduction: human and animal

The embryological and postnatal development of the immune system of the individual human (ontogeny) displays phenomena that resemble the successive developmental stages in evolution (phylogeny). Thus, there are essential differences in the developmental levels of invertebrates, cold-blooded and warm-blooded animals. The lower animals have a relatively simple immune system that displays a great resemblance to the **aspecific** or **innate** immune system of man. Higher animals (mammals and birds) have an immune system that strongly resembles that of the fully developed immune system of man. Alongside of the aspecific immune system, higher animals and man have also developed a **specific** or **adaptive** immune system.
The developmental stages in both the animal kingdom (phylogeny) and the individual (ontogeny) proceed in a systemic manner. The humoral immunity by soluble factors is, in an evolutionary sense, the oldest and is also the first to be developed in the embryological development of the human being. Cellular and specific immunity is only developed at a later stage and always functions within the context of the innate aspecific system.

Characteristics of the developmental level of the body prove to be related to the developmental level of the immune system in animals. A higher development of the body of the organism means that the immune system can react specifically and at a high level to an antigen.

A precise discussion of the immune system among various animal species goes beyond the objective of this Companion. This chapter concentrates predominantly on the human aspects of the immune system. Modern immunology textbooks generally include a chapter on the evolution of the immune system in the animal kingdom (19, 21).

3.2. Three aspects of development

The developmental stages will be described for three different *aspects* of the immune system. These include the aspects of the *hereditary predisposition* of the response, the *specificity* of the reaction and the *reaction speed:*

in connection to **heredity**, the immune system develops:
- from reacting as a germ line **innate** immune system to reacting as a combined germ line and individual **adaptive** immune system

in connection to **specificity**, the immune system develops:
- from reacting as an **aspecific** immune system to reacting as a combined aspecific and **specific** immune system

in connection to **reaction speed**, the immune system develops:
- from reacting as an **immediate** (immediate type reaction) immune system to reacting as a combined immediate and **delayed** (delayed type reaction) immune system.

Among humans, all these developments have reached a tentative end point and work together to maintain a healthy state.

These developments can be summarized as follows:
Germ line innate (aspecific) immunity, an ancient form of host defense, must have appeared early in the evolution of multicellular organisms, because many genes involved in innate host defense occur not only in vertebrates and invertebrate animals but also in plants. Higher order vertebrates also have an adaptive (specific) immune system whose principles of operation are quite different from those of innate immunity.

The random generation of a highly diverse repertoire of antigen receptors allows the adaptive immune system to recognize virtually any antigen (17).

3.3. Various levels of development of the three-fold immunological process

For all three processes of the immune system, as described in chapter 1 and 2, the **cognition**, the **internal processes of the reaction** and the **effect**, three developmental levels of the aspects of heredity, specificity and reaction speed will be discussed using examples from the humoral response and cellular response (see comments on humoral and cellular immunity in Chapter 2.1.). It will emerge that, in the course of the evolutionary development, interactions of various developmental levels have been created (fig. 3.).
All things considered, there are not two *separate* immune systems in man, one congenital (innate) and one acquired (adaptive) immune system. The mutual interrelationship and mutual dependence of 'both systems' is often so intensive that the human being actually has one immune system, within which the various aspects can be clearly differentiated: innate aspecific and adaptive specific.
The examples have been chosen such that they can contribute to the insight into the human immune system. The examples can be studied in further detail in immunology textbooks.

3.3.1. Levels of cognition

3.3.1.1. Cognition of the humoral immunity explained in the light of the complement system

1st level of cognition: the recognition that inhibiting factors are failing
Example: Alternative route
The complement system consists of a large number of immune active proteins – present at

birth (innate) – circulating freely in the serum. These proteins are in a continual state of activity towards everything that is self or non-self. A cell – self or non-self – can therefore, at this level, only escape destruction when there are factors on the cell membrane that inhibit the complement reaction. This occurs through surface molecules that inhibit the binding of the complement factor C3b. These inhibiting factors *do* appear in the body's own cells (self) but *do not* appear in foreign (non-self) cells. Thus, the complement system 'differentiates' (cognition) between self and non-self. In the limited sense, there is no question of cognition but, rather, a presence or absence of inhibition.
This first complement route is called the 'alternative route.' The form of cognition in this alternative route is **innate, aspecific and immediate.**

2nd level of cognition: the recognition of molecule patterns that is characteristic for pathogenicity
Example: Lectin route
In the construction of their cell membranes, bacteria have invariant carbohydrate structures, such as mannose. These carbohydrate structures are *not* type-specific for bacteria. These carbohydrate structures – mannose, in our example – are, because of their patterns, however, indeed characteristic for pathogenicity. That is why they were given the name Pathogen Associated Molecule Pattern (PAMP). In evolution, only a limited number of different PAMPs have developed for all pathogen bacteria. In evolution various types of receptors for PAMP-recognition have, at the same, time developed. These receptors have been given the fitting name, Pattern Recognition Receptor (PRR), because they can bind with the molecular patterns of the pathogen associated molecule (PAMP). Also, only a limited number of PRRs have been created in the course of evolution.

One important PRR is a protein produced by the liver called Mannose Binding Lectin (MBL) which, during the acute phase of the infection, can bind with the mannose in the PAMP of the bacteria. If the pathogen bacteria carries a *PAMP-PRR(MBL)* combination, then it is recognized within the complement system; the complement cascade is activated and the bacteria is eliminated (see Chapter 4.1.).
This second complement route is called the 'lectin route' and is also: **innate, aspecific and immediate** (17).

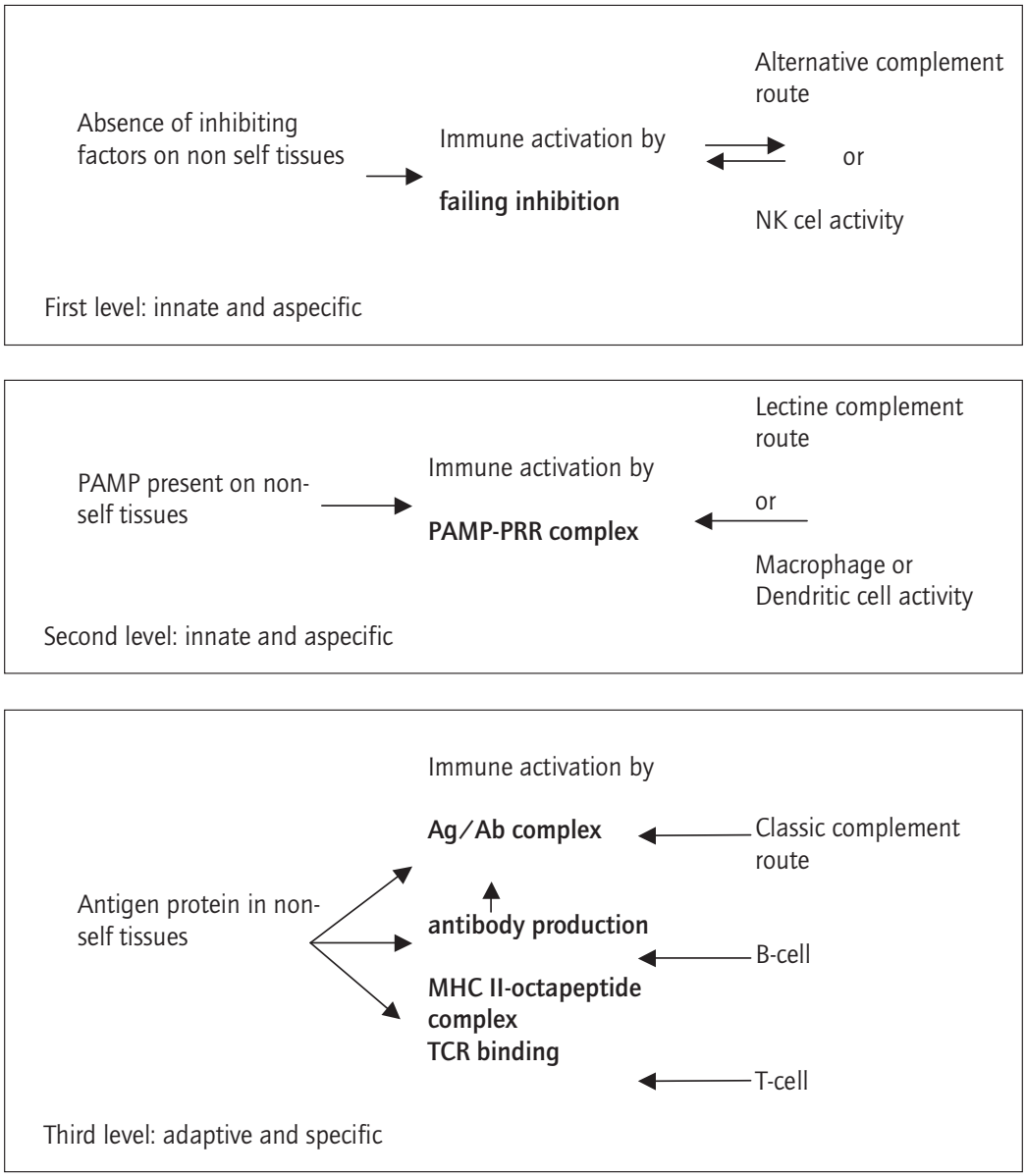

Fig. 3. Developmental levels of the immune reactions

Comment:
Upon reflection, there is actually no longer a question of pure aspecificity. Because the PAMPs are recognized by PRRs, a primary form of specificity occurs which applies to several groups of bacteria, such as Gram negative bacteria or all Pseudemonas bacteria, but which is not individually specific.

3rd level of cognition: the recognition of the antigen-antibody complex
Example: Classic route
In the case of the third route within the complement system, the complement cascade is activated by the presence of antigen-antibody complexes. That means that, for the activation of this complement route, the production of specific antibodies is essential. Antibodies have a high degree of specificity and are produced solely by the B-cells of the adaptive immune system. Thus, this route is directly dependent upon the specific immune system.
This mechanism is called the 'classic route.' The immune system, in this case, reacts such that it is: **adaptive, specific and delayed.** The 'delay' originates through the time span that is necessary to allow the B-cells to differentiate into plasma cells for antibody production.

3.3.1.2. Cognition of the cellular immunity explained in the light of different cells

The development that was described in the previous section of this chapter with respect to cognition in the humoral system, can also be found in the cognition of cellular immunity.

1st level of cognition: the recognition that inhibiting factors are failing
Example: cognition of the Natural Killer cell
Natural Killer (NK) cells belong to the innate, aspecific, immune system. An organism typifies its own tissues with the aid of molecules coded by MHC genes. MHC genes belong to the Major Histocompatibility Complex. MHC molecules are specific for each individual and are therefore essential for the body's own (self) identification. They play a major role in transplant reactions and the allograft rejection. The donor has a different type of MHC

than the recipient. Therefore, the donor organ is an antigen (non-self) for the recipient. In humans, the MHC is denoted by another name: the HLA system (13, 14).
There are two types of MHC genes. The first type is expressed in the normal body cells. These so-called somatic cells carry MHC I molecules on their cell membranes. The second type, MHC II, is expressed in Antigen Presenting Cells, the APC's (see Chapter 3.3.3.2.).

In evolution, the NK cells first appear among vertebrates of a low level of development, such as the jawless fish. No NK cells have been found among the lower orders of invertebrates. It is striking that – just as with the NK cells – the MHC genes that code for 'self,' *do* appear among vertebrates and *do not* appear among invertebrates. NK cells and MHC genes, therefore, also have an evolutionary and direct relationship with each other at the level of the 'self-typification' and 'non-self-recognition' of the organism (9).

NK cells are, of themselves, in a continuous state of activity and would attack all cells – both self and non-self – were it not that MHC I molecules are expressed on the body's own cells. These MHC I molecules inhibit the activity of the NK cells. NK cells have Killing Inhibitory Receptors (KIR) on the surface of their cells. The MHC I molecule can bind to this. Through the KIR-MHC binding, apoptosis induction by the NK cells is prevented. In this way, the body's own cells protect it from NK cells. As long as the MHC molecules are expressed on the somatic cells, the NK cells are inactive towards 'self.'
NK cells also possess 'pseudo specific' cognition, because receptors for IgG antibodies can be found on the cell membrane. If an antigen cell is opsonized with IgG, then an NK cell can be activated and the cell can be brought to apoptosis.
At this level, the cognition is **innate, aspecific and immediate.**
In a more limited sense, this is actually not a question of cognition but, rather, of the presence or absence of inhibition, comparable to what has been said about the cognition via the alternative route of the complement reaction.

2nd level of cognition: the recognition of molecular patterns that are characteristic for pathogenicity.
Example: cognition of the macrophage, dendritic cell and B-cell
Comparable to what has been described for the lectin route of the complement system,

antigen recognition occurs in the macrophage or dendritic cell on the basis of molecular patterns, the PAMPs, that occur in pathogenic organisms. The previously described Pathogenic Recognition Receptors (PRR) can be found on many effectors of the innate immune system. Cells which express PRRs on their cell membranes have the ability to bind PAMPs. After binding, the antigen can be decomposed intracellular (partially or completely) and the particles of the antigen can again be presented on the cell membrane. These cells offer the antigen for further processing by immune effectors, such as the complement system or T-cells. That is why these cells are called antigen-presenting cells (APC).
At this level, the immune system reacts such that it is **innate, aspecific and immediate.**

Comment
Upon further reflection, there is here, in a restricted sense, also no question of pure aspecificity. Through the recognition of PAMPs by PRRs, a first form of specificity occurs which, however, applies to groups of bacteria and which is not type specific.

3rd level of cognition: the recognition of specific antigen protein or octapeptide
Example: cognition of the B-cell and T-cell
Specific cognition occurs in the B-cell and the T-cell. Several types of B-cells can react to the same pathogenic protein structure because different BCRs 'see' different parts of the pathogenic protein.
The T-cell has an even more specific cognition than the B-cell. Antigen-presenting cells (APC) can separate **octapeptides** from a pathogenic protein by antigen processing. Then, these octapeptides can be applied to the cell membrane on an APC and be presented to T-cells. This presentation of the octapeptide always occurs after the binding of the octapeptide in an MHC II molecule of the APC. Thus, an **MHC II-octapeptide/TCR** (t-cell-receptor) binding is created, and apoptosis of the octapeptide presenting APC can be started.

3.3.2. Levels of reactive ability

The organism reacts with internal processes (reaction and adaptation) to contact with the environment (cognition). The evolutionistic level of development determines which internal

processes the organism reacts with. In the embryological development of human beings, the ability to react is determined by the embryological and postnatal developmental stages. In man, the reactive ability, therefore, becomes ever more complex during the course of development, before and after birth.

3.3.2.1. Reaction and internal processes of humoral immunity

1st reactive level of internal processes: increased production of immune proteins
Example: acute phase proteins
The first immunological capability arises when an organism can produce substances which are essential for the destruction of antigens. These substances will generally be proteins which circulate through the organism. Among invertebrates, a multitude of these types of immune active substances have become known, such as: agglutinin, cytokine, immobilization factors and lysosomal enzymes. In the case of infection or trauma, an organism is able to immediately increase the production of these immune active substances. They play a central role within the organization of the immune and restoration reactions which are activated by infection or trauma.
During the acute phase reaction in man, there is a fast and quantitatively substantial increase in the production of immune proteins and complement factors. The organism is, through heredity, able to facilitate such an increase in production and the substances produced belong to the innate immune system.
In the acute phase, all kinds of factors are found in the serum that are normally also produced in a healthy state, but then in much smaller amounts. The clinically important acute phase protein, CRP (C - reactive protein), is determined in order to investigate the gravity of an acute process of infection. During the acute phase of an infection, the concentration increases within a few hours by tens – and sometimes hundreds – of percents.
This form of reaction belongs to the **innate, aspecific, immediate type reaction** of the immune system.

2nd reactive level of internal processes: production of soluble receptors for pathogenic molecular structure elements
Example: PRRs
At a higher level of development, an organism is able to produce receptors which can bind to structures of pathogenic micro-organisms. Thus, there are different pattern-recognition receptors (PRRs) which can bind with PAMPs. These are expressed on macrophages, dendritic cells or B-cells which can, consequently, function as antigen-presenting cells. Lower organisms are not capable of doing this.
There are several types of PRRs. Some of them can be found on the cell membrane of macrophages or dendritic cells. Others enter the circulation as a part of the humoral system. The latter are called *secreted PRRs*. One example of that is the Mannose Binding Lectin (MBL), originating in the liver. The secreted PRR (MBL) then binds with PAMP of a pathogenic bacteria. The bacteria is then opsonized and recognizable for other immune competent cells and proteins that see to the destruction and elimination. This form of reaction belongs to the **innate, aspecific and immediately reactive** immune system. It is also here that the reaction is not completely aspecific, as has already been described for the cognition of the lectin route.

3rd reactive level of internal processes: production of cytokines for specific immunity
Example: antibodies and interleukins
Warm-blooded organisms, such as mammals, birds and humans, have the capability to produce freely-circulating antibodies originating from plasma cells (specialized B-cells). These antibodies have the same structure as the B-cell receptor (BCR). However, they do not remain fixed to the cell wall but, rather, are released into the circulation. Consequently, they belong to the humoral system (see Chapter 2.1.).

At the highest level of immunological development, the organism is capable of releasing immune proteins into the circulation which help organize the answer of the **specific** immune system. For example, interleukins are cytokines which help steer the differentiation of the lymphocytes.
If an APC presents antigen to a T-cell, then that APC will also produce the interleukins that determine which differentiation the T-cell will undergo. In the case that there is a APC

with the interleukins IL 4, IL 5, IL 10 and IL 13, then the T-cell will differentiate itself into a T2 helper cell (Th2). These Th2 cells activate, in turn, B-cells to produce large numbers of antibodies. In this way, the Th2-cell plays a major role in antibody-mediated immunity.
If the antigen is presented by an APC in the presence of IL12, then the T-cell will differentiate itself into a T1 helper cell (Th1). The Th1 cell activates, to a high degree, macrophages and cytotoxic T-cells and, consequently, contributes to cellular immunity. One example of this is the role of these T-cells in transplant reactions.

These reactions belong to the **innate, specific and delayed** types of reactions.

3.3.2.2. Reaction and internal processes of cellular immunity

1st reactive level of internal processes: ability to achieve phagocytosis
Example: the macrophage
The most primitive cellular capacity of the immune response is the process of phagocytosis. Through phagocytosis, even single-celled organisms can defend themselves against antigens; the antigen is absorbed in its entirety into the cell (phagocyted) and then eliminated by digestion intracellular.
It is a pure **aspecific** and **immediate** reaction that is **innate** in all organisms, even single-celled organisms.

2nd reactive level of internal processes: the ability to increase the number of immune competent cells with more specific characteristics
Example: proliferative increase of various types of cells
In times of health, the production of new cells via cell division is in a homeostatic equilibrium. Through this homeostasis, the number of the various types of leucocytes and lymphocytes in the peripheral blood remains constant within specific boundaries. This is determined by *leukocyte count and differentiation.* Through infection the production of immune competent cells can increase considerably. The blood count then shows what is called *leucocytosis.* Moreover, a specific group of leukocytes can also proliferate. Some

examples of this are: *lymphocytosis* in case of viral infections, an increased number of *neutrofilic granulocytes* in the white cell count in the case of a bacterial infection, or *eosinofilic granulocytes* in the case of parasitic disorders.
Proliferation is an **innate, aspecific, and immediate reaction** to an antigen stimulus. The reaction displays some differentiation in the types of cells produced, but does not lead to specific immune reactivity.

3rd reactive level of internal processes: selection, clonal proliferation, somatic mutation and genetic rearrangement
Example: antibody and T-cell receptor production
In the production of antibodies by completely differentiated B-cells (plasma cells), or the production of T-cell receptors (TCR) by the T-cell, the organism changes its own genetic information. The organism is, because of this, capable of creating new genes that have **not** been passed on through heredity. This genetic rearrangement and somatic mutation are biologically reactive abilities which are reserved for warm-blooded vertebrates.

Somatic mutation in B-cells and genetic rearrangement in T-cells
Through mutation or rearrangement of the genetic fragments, new genes can be created which are encoding for antibodies or TCRs that have not been previously produced. Somatic mutation and genetic rearrangement are closely related processes. The same localizations of the involved areas in the genome display strong similarities, and similar enzymes play a role in the rebuilding of genetic material.
However, these genetic forms of reaction are not the same for B-cells and T-cells. B-cells achieve immunoglobulin diversity mainly through somatic mutation. T-cells achieve diversity of the TCR through genetic rearrangement.
Somatic mutation takes place during ripening of the B-cell. A gene for an antibody is thereby *changed*, so that its antibody specificity is improved. The antibody to be produced, fits better to the antigen it is related to.
In case of **genetic rearrangement**, parts of the genome are *relocated* to form a new gene with a new antibody specificity. Consequently, a T-cell can react to an antigen it has never been in contact with before and for which no ready-made genes have been inherited in the germ line.

During somatic mutation and genetic rearrangement, the genes undergo structural changes in the light and heavy variable chains for immunoglobulins and TCRs. Somatic mutation or genetic rearrangement occurs both at random and after antigen stimulus. The reaction and change at the genetic level occurs, in the last case, on the basis of the morphological characteristics of the antigen. In that case, it leads to the forming of an optimally binding antibody or TCR.
A discussion of somatic mutation and genetic rearrangement in terms of molecular biology, goes beyond the objective of this Companion Immunology. Textbooks always contain a number of chapters on this subject (4, 19, 21).
Genetic rearrangement and somatic mutation occur only in organisms with an **adaptive, specific** and **delayed** immune system.

Selection
A complicated process of **negative** and **positive selection** occurs in the bone marrow and the thymus. In the case of **negative** selection, a developing B-cell or T-cell is halted in its development and brought to apoptosis. In the case of **positive** selection, further development into immune active B-cells or T-cells occurs. As far as the T-cells are concerned, only 5% ultimately enter the circulation via positive selection as ripened and active T-cells! In this way, the organism supervises which of the randomly formed genes for antibody forming or TCR will not be a danger in the future to one's own (self) tissue.

Autoantigenicity
A great many diseases appear to be based on autoimmune processes. Type I diabetes, colitis ulcerosa, and rheumatoid arthritis are perhaps the best-known examples of this. With an autoimmune disease, the immune system forms antibodies against its own (self) body cells. Selection is, therefore, the regulation mechanism for the organism to prevent autoimmune diseases via elimination of the B-cells or T-cells that are potentially dangerous for the 'self'.
Autoantigenicity is, however, not only negative and a risk to health. With the aid of autoantigenicity, the immune system can also end – 'down-regulate' – an infection or an immune response. Consequently, the immune response can be prevented from overshooting its goal. In this down-regulating of the immune response, feed back processes that must

be considered to be autoimmune processes play a role. The immune system makes, for example, antibodies against the effectors of its own immune system and, in this way, halts the inflammatory reaction.
When there is a negative selection of T-cells, the T-cells that produce TCRs which have no – or, on the contrary, an extremely strong – auto-antigenic potential, are eliminated. Positive selection occurs in T-cells with a weak positive potential for autoantigenicity. They play a positive role in the down-regulating of the immune response. In the case of autoimmune diseases, self-regulation at the point of cognition fails and self and non-self are not longer distinguished.

Clonal proliferation of B-cells
After selection, B-cells can divide and multiply (clone) themselves at a high rate and differentiate into plasma cells. Each specific B-cell line produces a large number of plasma cells which create antibodies against antigens. These antibodies reach the antigen via the humoral route, the circulation.

Clonal proliferation of T-cells
Of the T-cells, clones originate, as with B-cells, such that a large number of competent cytotoxic T-cells against the antigen octapeptides are created. Cytotoxic T-cells are capable of bringing cells that carry *MHC II-octapeptide-complexes* to apoptosis.

3.3.3. Levels of effect

3.3.3.1. Effects of humoral immunity

1st level of humoral effect: the effect of complement and cytokines
Examples: opsonization and perforation of the cell membrane
When a bacteria or virus is capable of penetrating the physical barriers of skin and mucus membranes, the immune system reacts. Cell damage of the skin or the mucosa or penetration of pathogens into the bloodstream or into the cells of the body, lead to a reaction in composition and amount of *complement* and *cytokines.* Initially, there is a local

reaction, but later that becomes a generalized reaction due to the circulation and the effects of cytokines on the nervous system. Fever, general malaise, lack of appetite and a change in consciousness are the symptoms of this (15).

The activated *complement system and cytokines* lead to the following effects:
- *opsonization of the cells,* so that cells which have antigens are marked
- *activating of leucocytes*, which will then produce cytokines
- *lysis* of cells on which the antigen appears. That happens through a protein complex (Membrane Attack Complex) which perforates the cell membrane of the antigen-carrying cell, so that cell and antigen are destroyed
- *fever* and *general reactions.*

There are a large number of cytokines that are classified in specific groups. Growth factors (GF), Interferons (If), Interleukins (Il), Tumor Necrosis Factors (TNF) and Colony-Stimulating Factors (CSF) are examples of groups of cytokines. Through the functioning of cytokines, stem cells are activated to differentiate and proliferate, macrophages are activated and chemotactically guided to the 'contaminated area,' mest cells begin degranulation, B-cells are activated to start clonal proliferation and antibody production, and T-cells to form TCRs.
The effect of complement and cytokines has the character of a cascade. In a divergent chain reaction, the effect of a specific cytokine is guided forward. Because of this divergent cascade, an intensification of the immune response occurs simultaneously which is denoted by the term: *amplification.* To the extent that complement and cytokines have an activating effect on membrane receptors of somatic cells, such as G-proteins, a diverging biochemical cascade will again be created in the cell in question. Antigen processing in an antigen presenting cell (APC) is an example of this. The divergence that occurs during this process is of enormous magnitude and appears to be unlimited. From the moment that the immunological reaction is activated by cytokines, that immunological reaction can have disastrous consequences without adequate *self-regulation.* One example of this is the allergic reaction (10, 11, 18). In the case of an allergic reaction or during anaphylaxis, the effect phase of the immune response far overshoots its goal and, thus, threatens the integrity of the organism.

Self-regulation as a holistic phenomenon

In various immunology textbooks, the effect of cytokines in the organization of the immune response is described, using the term 'orchestration.' This means that the composition of the cytokines orchestrates the ultimate form and the process of the immune response *within the blueprint of the organization*. This metaphor deserves further study. Just as the instruments in an orchestra are the elements that determine how the piece of music will sound, the cytokines determine the form and possibilities of the immune response. Naturally, a concert will only be worth listening to if the various instruments are playing at the right moment and in the right tempo; otherwise there will only be chaos. The precise moment for the precise instrument to play is determined by the composition and not by the instrument playing it. The same applies to cytokines. The *self-regulating ability* of an organism (the threefold composition or blueprint) determines the unity, harmony and suitability in the immune reaction.

The comparison with a piece of music can be taken even further. A cytokine (instrument) never has only one single effect. *Depending upon the context,* the other cytokines, the cellular elements and the combined action (ensemble work), one and the same cytokine can bring about different effects. One specific cytokine can even, under different circumstances, have an opposite effect. Thus, a cytokine network is just as receptive to self-regulating influences of the organism as an orchestra is to the direction of a conductor. An orchestra without a score will never be able to give a well-coordinated and meaningful performance.

2nd level of humoral effect: the functioning of secreted PRRs

Example: secreted PRR

The most important effect of secreted PRRs (pattern recognition receptors) is that pathogens are opsonized by them. Thus, an antigen is made recognizable to the immune system as non-self and comes within reach of immune competent cells or immune active proteins (as with the complement system) of the innate system. Elimination of the antigen is then possible. The effect belongs to the **innate, aspecific and immediately reacting system.**

3rd level of humoral effect: the functioning of antibodies
Example: immunoglobulin
Antibodies which are produced by plasma cells, bind specifically with an antigen (opsonization) after which elimination can be initiated. It is the effect of the **acquired, specific and delayed** system.

3.3.3.2. Effects of cellular immunity

1st level of the cellular effect: fagocytosis
Example: macrophage
Macrophages thank their name on their ability to 'gulp down' antigens. Their name is nothing more than the description of their activity. It is the basic activity of aspecific innate cellular immunity: an antigen is bound, gulped down and then eliminated intracellular by the macrophage. Fagocytosis also occurs as an immune response in lower animals, such as invertebrates, through various types of blood cells and body cells. This does not yet, however, resemble a classic macrophage such as occurs in humans. The effect belongs to the **innate, aspecific and immediately reacting system.**

2nd level of the cellular effect: antigen presentation
Example: antigen presenting cells (APC)
Often, an antigen is 'predigested' before it is eliminated in the subsequent immune response. This predigesting occurs in Antigen Presenting Cells (APC). Dendritic cells, B-cells and Macrophages can function as APCs. APCs differentiate self from non-self and are found in places where there is a good chance of contact with an antigen. In case of infection, the APCs are the first cells to recognize the antigen and can then bind to the antigen and process it (antigen-processing).
The effect belongs to the **innate, aspecific and immediately reacting system.**

3rd level of the cellular effect: apoptosis induction
Example: T-cell
Cytotoxic T-cells (Tc-cells) posses cytokines that incite the target cell to **apoptosis** (suicide). This killing of self in the form of apoptosis also means the end of the antigen that has infected the target cell in question.
TCRs form the place of binding of the cytotoxic T-cell with an antigen-presenting cell.
For apoptosis of the target cell, the T-cell is dependent upon:
- self/non-self discrimination by APCs
- presentation of octapeptides (after the processing of the antigens) in a MHC(HLA) groove on the APC. This phenomenon is called the 'MHC restriction' of the T-cell
- co-stimulation by factors such as Toll receptors, in order to introduce the induction of apoptosis by the T-cell.

This effect is of the **acquired, specific and delayed** system.

Th1 and Th2 and regulatory Tr cells
Cytokines determine the balance, the interaction and the fine-tuning between the various types of **T-helper** cells: the **Th1** and **Th2** cells. The Th1 cells stimulate (help) cellular immunity by, among other ways, macrophage activation. The Th2 cells stimulate the antibody-mediated immunity by their stimulating effect on, among other things, the B-cells. The balance between Th1 and Th2 cells is believed to be of great significance in relation to allergy and auto-immunity (18). Allergy can develop through a Th2 dominance and auto-immunity through Th1 dominance, but both abnormalities must be seen as a deregulation of the Th1-Th2 balance.
Active suppression of immunological reactions by a different subset of T cells, the **regulatory T cells (Tr)**, plays an important role in the down regulation of T cell responses to foreign and self-antigens.

Memory cell
Immunological learning effects occur fairly early in evolution. Lower animals can react more quickly and more effectively after repeated contact than after the first contact.
In the course of evolution, this learning effect developed into the **ability to remember.** Memory cells can live on in the organism, in a state of hibernation, after they have had

contact with an antigen and been actively involved in the immune response. After a repetition of the contact with the same antigen, these cells are immediately 'reawakened' and activated such that the immune response progresses specifically, quickly and effectively. At the same time, there is again proliferation from the memory cell for a new clone which causes a strengthening of the immune response. There are memory B-cells and memory T-cells. That means that both the humoral and the cellular responses possess a memory function.

With of the memory cells, the organism creates an extraordinary hybrid of specific immunity combined with an immediate reactive ability

Critically considered, the term 'memory cell' is incorrect. Memory implies that a cell can remember the antigen *in the absence of that antigen.* No phenomenon is known that would indicate that a memory T-cell or B-cell is capable of doing that. They could better be termed 'recognition cells.' In the case of recognition, repeated contact with the antigen is a necessary condition. Without that repeated contact with the antigen, the 'memory cell' will never be activated.

3.4. Summary

The immune system displays a development in the three aspects of the immune response: the cognition, the internal processes of the reaction, and the effect. This creates, in humans, an immune system that develops from one that reacts aspecifically to one that reacts specifically, from innate immune reactions to adaptive immune reactions, and from a system that reacts immediately to one that reacts delayed. What is newly developed always comes into being, while retaining that which has been thus far developed and it never 'replaces' a previous situation. It is, therefore, always about a further differentiation of the system as a whole. Thus, there are organisms without specific adaptive abilities in their immune systems, but no organism without an aspecific, innate immune system. The innate immune system always remains the basis of the immune response within which the specific system can differentiate itself.

There are numerous transverse connections which guarantee intensive cooperation and mutual dependence of both 'systems.' These concern:
- discrimination between self and non-self
- co-stimulation as a condition for T-cell activity
- the balance between Th1 and Th2 cells.

The internal communication within the immune system is for the inflammatory reaction, the prevention of allergy, auto-immune diseases or other diseases, dependant upon the interaction between humoral and cellular components and between innate and adaptive immune processes.

Self-regulation is the complete 'orchestrating' organizer for all immune reactions. How self-regulation comes about is not known.

3.5. Phenomenological aspects

In evolution, the three-fold organization in the animal kingdom passes through a development from a lower to a higher degree of differentiation. In addition, the differentiation of specific organs and tissues keeps pace with the differentiation of physical stature, consciousness and behavior. One example is the often-mentioned, parallel differentiation of the nervous system and the immune system (see Chapter 5).
Therefore, this development can be described on two levels:
- differentiation of specific organs and tissues
- differentiation of consciousness and behavior.

It is this achievement within the development of the three-fold blueprint in the various systems, in the consciousness and in behavior that is so determining for the specificity of an organism. This observation inspired the German embryologist, Erich Blechschmidt, to make the following striking statement:

"That which has not been physically learned in embryo, can later never be psychologically practiced."

With this, he was pointing to the inseparable connection between the forming and the organization of the body in embryology (morphogenesis) and the later possibilities at the level of consciousness and behavior.

> *Insight into the specificity of the organization of an organism shows us that the physical as well as the conscious and behavioral phenomena all belong to one organization. These phenomena display themselves at various levels of emergence; first morphologically, then physiologically, and then psychologically and behaviorally.*
>
> ***An organism can only be holistically understood at the level of organization.***

A description of animals of various developmental levels can support this viewpoint. We will therefore compare here shortly the body structure, the immune system, the nervous system, consciousness and behavior. An extensive description goes beyond the parameters of this Companion. A global outline can, however, clarify our meaning.

Invertebrates do have fagocytosis and complement reaction but have not developed Major Histocompatibility Complex (MHC).
Vertebrates do develop an MHC, alongside of fagocytosis.
Jawless fish (agnates) do have a primitive type of lymphocytes but have not yet developed differentiation of lymphoid tissues.
Jawed fish (gnathostomata) develop lymphoid tissues such as the spleen, GALT and thymus but this lymphoid tissue still has no germ center for the further maturation of lymphocytes.
Amphibians develop B-cell activity as an expression of lymphoid maturation.
Warm-blooded organisms, such as birds and mammals, have a differentiated and matured

lymphoid system and T-cells. Thus, they have a specific and adaptive reacting immune system with the ability to carry out somatic mutation, clonal selection and a highly specialized cytokine network.

The above-named groups of animals have the same developmental series for the organizational level of the complexity of the body structure, the nervous system and the senses, for the circulation and the respiration, and for the differentiation of consciousness and behavior.

> *Using the phenomenological approach, it becomes clear that the blueprint, as the organizer of the organism, develops as a whole from a lower to a higher degree of differentiation.*

4. Threefoldness at the molecular biological level

4.1. General aspects of the structure of PRR and antibodies

The Pattern Recognition Receptors (PRR), antibodies, or B-cell receptors (BCR) appear to have a structure that matches the threefoldness of the immune response processes. A number of complement factors and the TCR have a form with comparable molecular structures. The basic model of all of these structures is in the form of a Y with, at the divided ends, binding places (receptors) for the recognition – the Fab fragment – and, on the other side, the molecular structure which triggers the immunological effects, the Fc fragment (fig. 4.). Within the form of these molecular structures, there are, therefore, specific elements for recognition and for effect.

Between the Fab fragment (the receptor) and the Fc fragment (the effector), a so called Hinge region can be found, which can vary in length for various classes of antibodies. Because of the mobility in the Hinge region, the antigen binding places (paratopes), on the Fab fragment, can 'move' with respect to each other. The Hinge region can be considered to be a morphological metamorphosis of the reaction and adaptation process of the immune response.

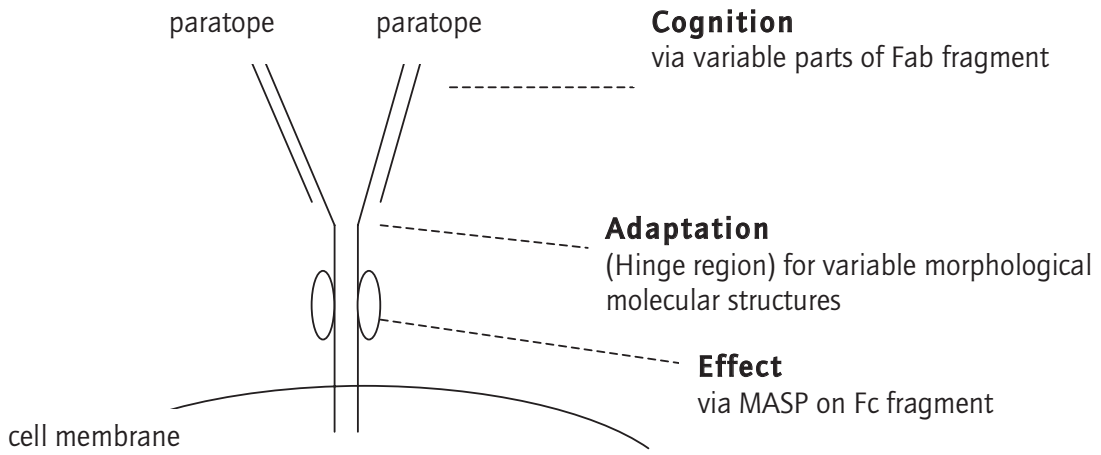

Fig. 4. Basic threefold structure of PRR, antibody or TCR

4.1.2. Recognition by PRR, BCR, antibody or TCR

Using a few more specific examples, we will demonstrate why the three-fold function pattern at the molecular-biological level is a meaningful approach.

4.1.2.1. Receptors of the PRR

In figure 5 the structure of a Pattern Recognition Receptor (PRR) is described schematically. In this case, this is a PRR with Mannose Binding Lectin (MBL) as a receptor.
In the case of the PRR, in contrast to the BCR and TCR, the part focused on recognition is *not* variable. The MBL-PRR plays an essential role in the recognition of bacteria (see Chapter 3.3.1.2.).

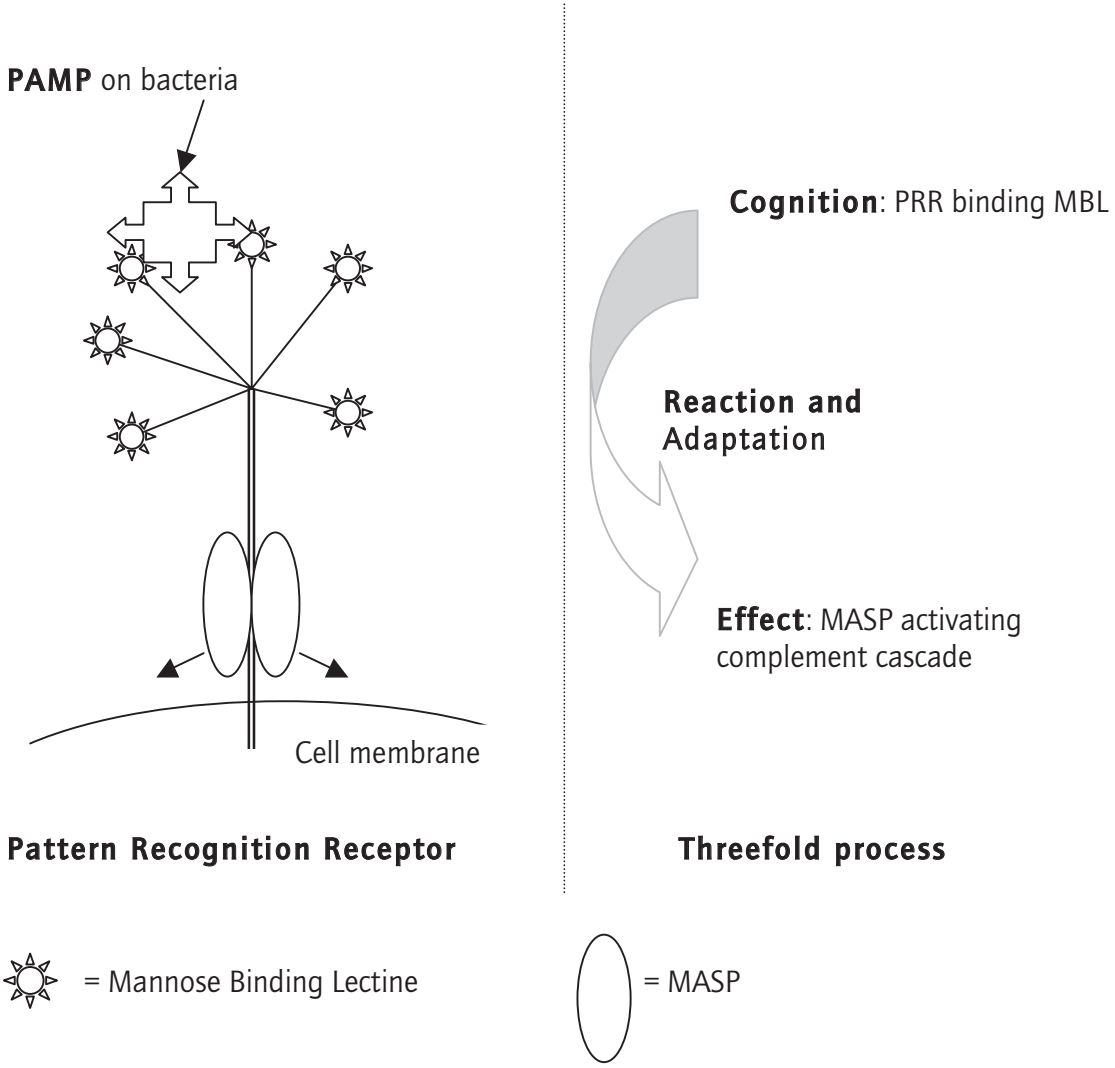

Fig. 5. Schematic structure of threefoldness of Pattern Recognition Receptor

4.1.2.2. Receptor of antibody, B-cell receptor and T-cell receptor

In figure 4 we provide a schematic description of the structure of antibodies, B-cell receptors and T-cell receptors. The antibodies (BCRs) and the TCRs can have specific receptors for antigen recognition on their Fab fragments. This is because of the existence of the so-called variable chains on the Fab external ends of the antibodies, the BCR or the TCR. The variability in these chains leads to a great diversity of molecular receptor structures. Thus, the receptor proteins fit better to the form of the antigen. The variability of the receptor proteins is, therefore, the cause of the origin of the specificity (see Chapter 3.3.2.2.) of antibodies and TCRs. The binding between the antigen and the paratope of BCR and antibody or TCR is maximized, because the antigen and the receptors can bind themselves to several places.

4.1.3. Reactive adaptation

The second phase of the threefold immune response is the adaptation of the organism to the morphology of the antigen. The antibodies and the BCR have, through their Hinge region, a hinged transition from the Fab fragment to the Fc fragment. Because of this, the paratopes can change position. Because of this spatial change, the binding to the form of the antigen can be optimized. This adaptability on the molecular level is reserved for the specific immune system. The basis of specificity is formed by the variability of the receptor proteins and mobility in the Hinge region.

4.1.4. Effect in terms of PRR, immunoglobulin (BCR) or TCR

4.1.4.1. Effector of the PRR

There are molecular structures on the Fc part of the PRRs that have an activating effect on the complement system. One example of this is the previously-mentioned Mannose Binding Lectin Associated Protease: MASP. When activated, this MASP is responsible for triggering the complement cascade. After the binding of the antigen to the paratope, the destruction of the antigen is started via the MASP on the Fc fragment. This reaction belongs to the immediately reacting aspecific immune system.

4.1.4.2. Effectors of the BCR and TCR

The immunological effects of the immunoglobulin, BCR or TCR are also seen in terms of the membrane bound Fc fragment. For the TRC, this involves the transmembrane part that reaches into the cytoplasm. For the freely-circulating antibody that is produced by plasma cells, this involves the free Fc extremity. Although the T-cell has the most subtle recognition apparatus, it is not capable, on its own, of triggering apoptosis of the cell carrying the MHC II-antigen peptide (see Chapter 3.3.3.2.). For a T-cell, a second stimulus is necessary to start the apoptosis of the target cell. The T-cell, therefore, has a more complete separation between recognition and effect than the B-cell.

4.2. Phenomenological aspects

As shown in figure 6 the threefoldness of processes is recognizable at different levels. Differentiation takes always place within the threefold blueprint of the organization.

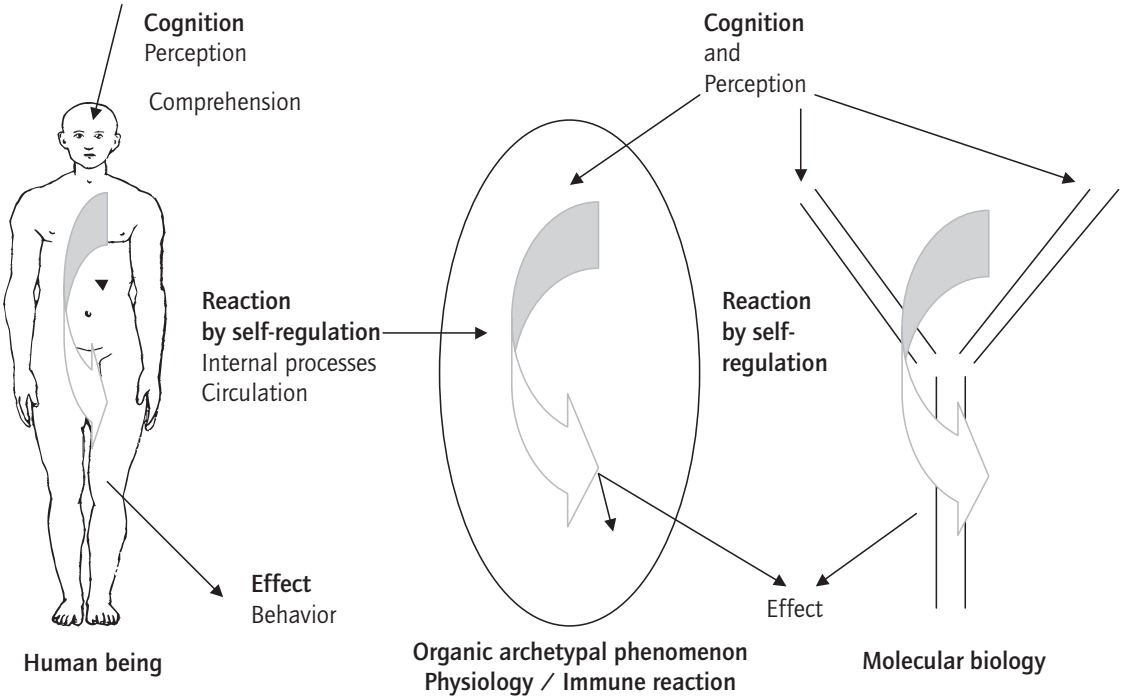

Fig 6. Comparison of the structural organization of the human being, the physiology of the immune response and the structure and function of PRR, BCR/TCR or antibody

5. Is mind as real as matter?

5.1. Psychosomatic perspectives

"Is mind as real as matter?"
The above was the title for a publication by Colloca and Benedetti (5) working at the Department of Neuroscience in Turin, Italy. They explained their research results thus:

"Considerable progress has been made in our understanding of the neurobiological mechanisms of the placebo effect, and most of our knowledge originates from the field of pain and analgesia. Today, the placebo effect represents a promising model that could allow us to shed new light on mind-body interactions. The mental events induced by placebo administration can activate mechanisms that are similar to those activated by drugs, which indicates a similarity between psychosocial and pharmacodynamic effects. These new neurobiological advances are already changing our conception of how clinical trials and medical practice must be viewed and conducted."

In their study, Colloca and Benedetti were able to demonstrate that purely psychological phenomena ("verbally induced expectations") had an effect on the immune system. They administered a long-lasting pain stimulus to test subjects. Subsequently, these subjects received medication and were told that it would make the pain more or less severe. Some of the subjects received a painkiller and others received a placebo according to a double-blind protocol. The expectation that was created concerning the effect of the administered medication had a demonstrable effect on the immune system, comparable to that of the real medication. Thus, their question: "Is mind as real as matter?"

The work of Colloca and Benedetti is an example of the growing amount of research that is being done in the area of psycho-neuro-immunology. In this chapter, we will explore the possible relationship between consciousness and the immune system.

5.1.1. Equivalent and simultaneous differentiation of behavior and immunological processes

In evolution, the development of behavior and consciousness is correlated to the development of the central nervous system and the differentiation of consciousness (see Chapter 3.). Human insight has always determined human behavior. In humans, self-consciousness and the unique cognitive abilities are important sources of behavior. The scientific, artistic, religious and cultural expressions of this are innumerable.

5.1.2. Psycho-neuro-immunology or neuro-endocrine-immunology

Psycho-neuro-immunology, also called neuro-endocrine-immunology, studies the effect of the processes of consciousness on the immune system. That a relationship can exist between consciousness and immunological processes has been made clear from the above (see Chapter 3.5.). Both man and animal display a variety of experiences that can be described as phenomena of consciousness. Human psychological phenomena are a-priori phenomena of consciousness. Fear, stress, hope, pleasure and feelings of well-being are examples of conscious psychological phenomena. In healthy situations, conscious experiences alternate with each other in quick tempo. Feelings and impressions follow each other in succession and, in one's consciousness, there is a coming and going of experiences. The recognition of and reactions to experiences such as fear, tension, hope or disappointment generally begins as a more or less conscious perception (recognition), after which a physical adaptation process occurs (reaction) which results in (effect) heart palpitations, racing pulse, perspiration, dry mouth, motor symptoms of the intestine

and urinary tract, etc., etc. The sequence of these events follows the trajectory that was described above for the immunological reaction: first, there is the recognition (for example, fear), followed by the adaptation of the organism to the fear and, finally, the effect on the bodily functions.
Under pathological conditions, this physiological sequence can also become disturbed. The level of consciousness of the psyche is then lowered. The pathological symptoms then precede the awareness. Many people with such symptoms as hyperventilation, asthma, irritable bowel syndrome, headaches or various kinds of muscular pains, appear – after becoming adequately conscious of an underlying psychological problem – to be able to recognize that that problem is the cause of their complaints. With adequate treatment, they will then be able to solve their physical problems. There has already been extensive research on the effects of acute and chronic stress (24). The effects of impressions, expectations, hope, stress and other consciousness phenomena on the immune system have, by now, been established (8, 12, 16, 20, 23, 24).

5.1.2.1. Acute stress

During acute stress, the HPA axis reacts by stimulating the adrenergic system via the adrenal medulla. It is the mechanism that becomes effective during acute reactions, known as the 'flight, flight, fright' reactions. However, other activities which are coupled to a state of intensified consciousness have the same effect. Taking an exam, giving a performance or presenting a lecture, all stimulate the adrenergic side of the HPA axis. Thus, the organism is put into a heightened and healthy state of alertness, operating capacity and also immune competence (fig. 7.).

5.1.2.2. Chronic stress

Long-term stress leads to a different reaction via the HPA axis. In this case, there is an increase in the adrenal cortex activity resulting in an increase in the cortisol levels. Cortisol has a negative, suppressing effect on the immune competence of the organism.

During chronic stress, there is an increased susceptibility for infections (fig. 7.). A recent meta-analytic study showed that: "acute stressors (lasting minutes) were associated with potentially adaptive up regulation of some parameters of natural immunity and down regulation of some functions of specific immunity. Brief naturalistic stressors (such as exams) tended to suppress cellular immunity while preserving humoral immunity. Chronic stressors were associated with suppression of both, cellular and humoral measures" (24).

5.1.2.3. The hypothalamus – hypophysis – adrenal gland axis

Research on the physiology of the reactions to stress has led to the discovery of the hypothalamus – hypophysis – adrenal gland axis (HPA axis). Psycho-neuro-immunological reactions travel via this neuro-endocrine path (fig. 7.) and thus intervene in the organism. What is striking here is the role of the central nervous system. Once again, the intimate relationship of the general level of development to the various somatic systems is visible. The somatic part of the psycho-neuro-immunological reaction begins with the neurological influencing of the areas surrounding the third ventricle: the hypothalamus. Via the neuro-hypophysis, the adeno-hypophysis is activated. The hormones of the adeno-hypophysis influence the end organs, such as the adrenal glands.

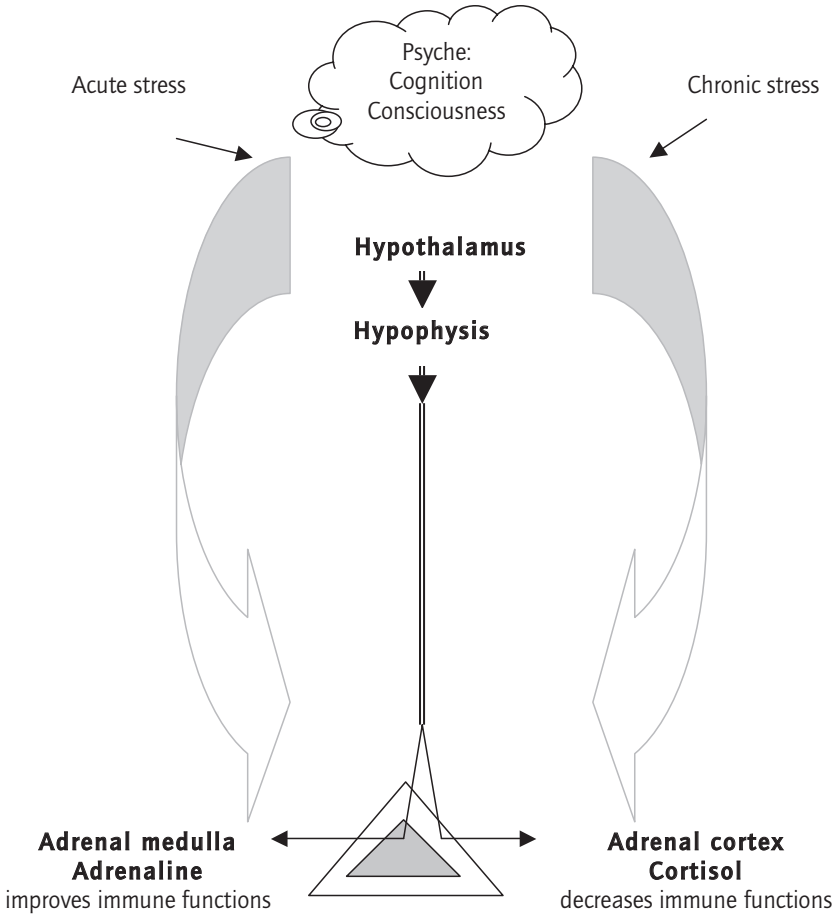

Fig. 7. Psycho-neuro-immunological processes and HPA axis

5.1.3. The consciousness

The question of what consciousness actually is, has occupied researchers from time immemorial. The mind-body problem, in particular in human psycho somatic medicine, is still an on-going central issue for which unequivocal answers have not yet been found.

Waking and sleeping, dreaming, near-death experiences, out-of-body-experiences, hypnosis, and clairvoyant experiences are phenomena that call for an explanation. The current scientific paradigm appears to offer no room for a consciousness which is free of the body. It is, in particular, the psycho-neuro-immunology and the research of near death experience that questions this vision.

5.2. Humans and animals

The occurrence of stress differs in humans and animals. An animal can only cope with stress by fleeing, surrendering or fighting, while a human being is capable of influencing the effects of the stress factor through his own inner psychological activities. That which a human being experiences as stress depends, to a high degree, on how he deals with the problem and on his individual coping abilities. General education, psychological maturity, psychological training, meditation activities and skill in dealing with stressful situations have a demonstrable effect on coping abilities and stress, thus, also on the immune system. An animal is not capable of such self-conscious activity. The negative effects of stress and captivity on animal behavior are examples of this. Self-development and self-education are purely human competencies.

This aspect of self-conscious stress management is a purely human phenomenon.

By now, a path along which psychological experiences may lead to somatic reactions has been mapped out. The existence of psycho-somatic influencing has, thus, become incontrovertible.
"Is mind as real as matter?" remains a burning question. Further research on the nature of one's own consciousness would appear to be a stipulation for finding an answer to this question in the future.

6. Synopsis

6.1. Phenomenological aspect: the three-fold phenomenon as the blueprint on several levels, immunology as differentiation within the threefoldness

In figure 6 a schematic description is given of how the principle of the three-fold division of structure and function can be recognized at the various levels of the (human) organism. It is essential to a phenomenological approach that the similarities on the various levels cannot be found as *measurable* quantities. Morphology is different from physiology and evolution is different from the individual creation history of an organism. In that sense, these aspects are not comparable. What these various aspects of the immune system have in common can, however, certainly be *characterized*. A characteristic does not have the earmark of a measurable quantity, but provides a reliable indication of the similarities in the qualitative sense.

Characteristic similarities are found at the level of the *structure of the organization.* That can have bearing upon the morphology, but also on the physiology or the molecular biology.

The *organizational structure of the organism as a whole* proves, time and again, to be determining for the organizational structure of the subsystems of the organism. That specific structure can be retraced in the morphological and physiological details.

Here, a comparison with music can help us a second time (see Chapter 3.3.3.1.). Musical compositions generally have a theme and variations on that theme. We also find several themes in the animal kingdom, such as the theme of the invertebrates, the theme of the vertebrates, of the mammals and of the human being. Within each theme, there are a large number of variations. The large number of different invertebrates, vertebrates, mammals and people are a witness to this.

The most fundamental theme seems to be that of the threefoldness that stretches back into the paleontological age, in which the trilobites – the first three-fold organisms? – can

be found. Even the name *tril*obite expresses their three-fold organization.
In the comparison to the human and animal organism as a whole, the three-fold blueprint can be found:

- **macroscopic in the morphology of the human and animal body and their differentiation of the specialized tissues**

- **physiological in the process of the immune response**

- **microscopic in the structures and functions in immunology**

- **molecular-biological in the structure and function of antibodies, PRR, BCR and TCR and complement factors**

- **psycho-somatic in the neuro-endocrine-immunology.**

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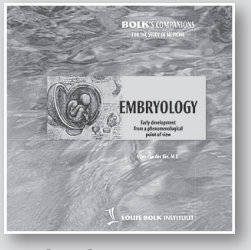
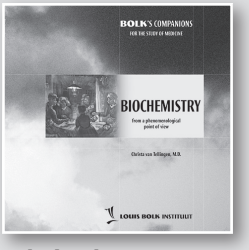


Embryology
Early development from a Phenomenological Point of View

Guus van der Bie MD
Publicationnumber GVO 01

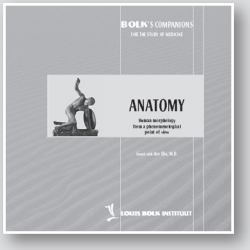
Can we give a scientific basis to our feeling that humans have unique human features? Are the human mind and the human organism 'nothing but' another variation of animal life? Can we find answers for the questions that satisfy both head and hart?
How these quetions are answered depends on the scientific method we use: the current scientific method to learn about biological facts and the phenomenological method to understand more about the meaning of these facts.
Early embryological development can teach us about the unique and characteristic qualities of the human being.
The result is, for example, a possibility to understand the relation between consciousness, psychology, and behavior and the shape of the body.



Biochemistry
Metabolism from a Phenomenological Point of View

Christa van Tellingen MD
Publicationnumber GVO 02

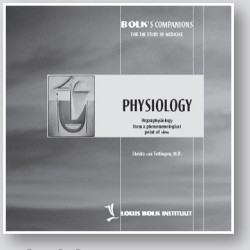
Biochemistry offers insight into the continuous changes within the human organism. But can we maintain awareness of the coherence of the (changing) organism as we study the details? How can the many processes be understood as prototypical aspects of a unique organism?
The scope of the answers to these questions can be enhanced by using a combination of the current scientific method and a phenomenological method developed specifically to research the coherence of processes within living organisms. The current scientific method is used to discover biological facts. The phenomenological approach helps us in finding the meaning of the facts.
What emerges is a new grasp of the interrelations between biological processes, consciousness, psychology, and behavior.



Anatomy
Morphological anatomy from a Phenomenological Point-of View

Guus van der Bie MD
Publicationnumber GVO 03

Can we give a scientific basis to our feeling that the human being has unique human features? Are the human mind and the human body 'nothing but' another variation of animal life? Can we find answers for these questions that satisfy both our head and our heart?
How these questions are answered depends on the scientific method we use. In this publication two methods are used: the current scientific method to learn about anatomical facts and the phenomenological method to understand the meaning of these facts.
Human morphology can then be understood as an expression of the unique and characteristic qualities of the human being.
This results in new possibilities for understanding the relation between consciousness, psychology, behavior, and morphological aspects of the body.



Physiology
Organphysiology from a Phenomenological Point of View

Christa van Tellingen MD
Publicationnumber GVO 04

Can physiology give more insight into the living human organism than the mere facts reveal at first? Is the level of activity the same for all organs? Are the vital qualities at work in organs unique for organisms and limited to biological activity? Can we find a scientific basis to research the coherence between organ systems?
By enhancing the current scientific method with phenomenological points of view we can find meaning in the facts and understand them as an expression of life itself. The phenomenological method makes the relation between organs visible and comprehensible. It approaches scientific facts from the point of view of their coherence and can give totally new insights this way.
What emerges is a grasp of the interrelations between biological processes, consciousness, and nature.

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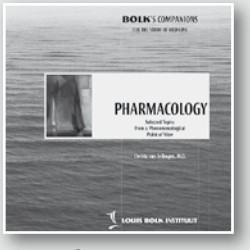


Pharmacology
Selected Topics from a Phenomenological Point of View

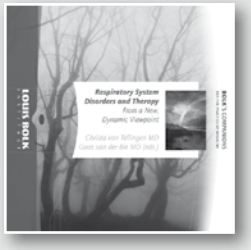
Christa van Tellingen MD
Publicationnumber GVO 06

Pharmacology gives us insight into the way organic processes change when foreign compounds are introduced into the organism. Pharmacology is a changeable subject, depending on the needs and knowledge of the time. Can we find an inner coherence in the manifold ways compounds influence organisms? What should such a framework be based on? How can we understand the effect on human consciousness that most compounds have?
We can enhance the scope of the answers to these questions by using a combination of the current scientific method and a phenomenological method. It illuminates the known facts about the activity of compounds in organisms, and provides the means to find their significance.

The Healing Process
Organ of Repair

Guus van der Bie MD
Tom Scheffers MD
Christa van Tellingen MD
Publicationnumber GVO 07

After finalizing the series BOLK'S Companions for the Study of Medicine for the moment, this module on The Healing Process introduces a new series of BOLK'S Companions that studies the Practice of Medicine. In it, we research the healing process itself. There proved to be an enormous volume of scientific literature on the subject. It is easy to loose oneself in the countless details included in the descriptions of this process.
The phenomenological method of systems biology makes it possible to examine physiological and pathological processes in terms of the processes themselves. This results in a characterization of the various phases of the wound healing process. Out of this, new insights into the origin of health and disease emerged that also offer possible leads for medical practice.



Respiratory System Disorders and Therapy
From a New, Dynamic Viewpoint

Christa van Tellingen MD
Guus van der Bie MD (eds.)
Publicationnumber GVO 08

In this Companion, the experience of three of our own patients with asthma and pneumonia is used as backdrop for our study of airway disorders. Nearly all of us have had some experience with respiratory disease, given that colds, flus, sinusitis, and bronchitis are so common. Most physicians and therapists know people with asthma and pneumonia from own experience and will readily recognize the descriptions we provide.
The experience with these patients leads us through a study of airway disease which eventually opens up to a wider view with new insights and innovative avenues of treatment for respiratory disorders in general.
Our research has alerted us to the part rhythm plays in the healthy respiratory tract and in the treatment of its disease. Rhythm, consequently, is the subject of the final paragraphs of this Companion.

Depressive Disorders
An Integral Psychiatric Approach

Marko van Gerven MD
Christa van Tellingen MD
Publicationnumber GVO 09

The treatment of depressive disorders is increasingly under scrutiny. We classified the risk factors of depressive disorders according to the scientific method applied in systems biology and phenomenology. The ordering in four biological levels that resulted from this, helps clarify the causes of the disorder. Together with the developmental history, it can lead to an individualized treatment of the patient, tailored to his or her specific situation. The treatment aims at restoring the deficient forces of self-healing.
This Companion presents a working model based on this methodological approach, as well as a variety of case histories to illustrate how applying this model can aid diagnosis and treatment in practice. Tables are added ordering well-researched regular and integral treatment methods according to the four biological levels.

For ways to order the Companions see inside of front cover or check our website: **www.louisbolk.org/companions**

IMMUNOLOGY

Why write this new booklet on immunology when there are already so many excellent texts on the subject? This Companion is about questions such as: why is it that the immune system functions as one organ? What coordinates the immunological functions?
Here, an attempt is made to develop a viewpoint to answer these questions. By using a phenomenological approach, the factual knowledge obtained through reductionism is placed in a larger perspective.
The concept that is presented in this Companion is derived from the functioning of organisms, observed in the way that was introduced by Goethe in his phenomenological method.
This also includes the acquisition of insight into the holistic concept behind the immune system. Moreover, the organism as a whole can then be seen as an expression of the same concept.

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