LOUIS BOLK INSTITUTE

# The Healing Process

## Organ of Repair

Guus van der Bie MD
Tom Scheffers MD
Christina van Tellingen MD

BOLK'S COMPANIONS ON THE FUNDAMENTALS OF MEDICINE

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The Louis Bolk Institute has conducted scientific research to further the development of organic and sustainable agriculture, nutrition, and health care since 1976. Its basic tenet is that nature is the source of knowledge about life. The institute plays a pioneering role in its field by using experiential knowledge, by looking at questions that consider data as part of a greater whole, and through national and international collaboration. Through its groundbreaking research, the Institute seeks to contribute to a healthy future for people, animals, and the environment. For the Companions, the Institute works together with the Kingfisher Foundation.

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## About the authors

*Guus van der Bie MD* (1945) worked from 1967 to 1976 as a lecturer at the Department of Medical Anatomy and Embryology at Utrecht State University in the Netherlands. As a family physician since 1976, he has recognized the importance of phenomenology and Goethean science for understanding the human being in health and illness. Next to his practice he stayed involved in teaching medical students at Utrecht State University and physicians, and therapists. In 1998 he was one of the originators of *Renewal of Medical Education*, a project of the Louis Bolk Instituut to produce a complement to the current biomedical scientific approach of the human being.
Since 2004 he is a teacher of complementary medicine and Medical Humanities at the Medical School of Utrecht State University and teaches anthroposophic medicine at 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.

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*Christina van Tellingen MD* (1949) has been a family physician in California since 1982. From the beginning of her medical studies she has recognized the importance of a new approach to science for understanding the human being in health and disease. In her practice, she has found the phenomenological method of observation in systems biology of great value in understanding and treating patients. She has taught medical students and physicians in the United States, Canada, and Europe. Recently, she has been teaching medical students and physicians at the University of Witten/Herdecke, Germany at Herdecke. In 1998 she was one of the originators of *Renewal of Medical Education*, a project at the Louis Bolk Instituut to offer a compliment to the current biomedical scientific approach to the human being. She 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* aims 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

# *Acknowledgments*

This Companion was written at the Louis Bolk Instituut, Driebergen, Holland. It is a result of the stimulating exchange of ideas with K. Luske, another recently graduated young doctor, being trained now to become a family physician. Her research in the field of wound healing has given us the opportunity to study the most recent data in wound healing form a phenomenological point of view.

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Guus van der Bie MD
Tom Scheffers MD
Christina van Tellingen MD
Driebergen, September 2008.

# *Preface*

While preparing for a new series of the **BOLK**'S Companions that studies the practice of medicine, the idea developed to first thoroughly research the healing process itself and to describe it with the aid of phenomenology, a method of systems biology.

There proved to be an enormous volume of scientific literature on the healing process. It is easy to loose oneself in the countless details included in the descriptions of this process. It took quite an effort to maintain an overview and to be able to comprehend the process as a whole.

The phenomenological method of systems biology makes it possible to examine physiological and pathological processes in terms of the processes themselves. Collected data from the field of natural science can, with the aid of the phenomenological method, be classified and interpreted. When applied to the wound healing process, it results in a characterization of the various phases that can be differentiated in this process. This furnishes new insights into the presence of health and the origin of disease. It also offers possible leads for medical practice.

As such, this Companion forms a good basis for the new series of publications: **BOLK**'S Companions for the Practice of Medicine.

# 1. Introduction

## 1.1. Injury and the Effect of Damage

The human body is continually undergoing a process of injury, reaction, and recovery!
A wound (L. vulnus) is defined as a 'rupture of the natural cohesion of tissue, with the tendency to heal'. This definition makes it clear that the wound healing process begins the moment injury occurs.
What is curious about this definition is that it not only focuses on the actual damage, but that the following healing process is already included in the definition. Thus, the definition comprises both the physical event and the functional consequence for the organism as a physiological process. The tendency to heal belongs to the wound. The healthy body reacts to harmful influences with a healing process through which a new integrity is established and the damage is repaired. This self-healing ability is also called salutogenesis (salus = health and genesis = origin).

There is a separation that takes place when a wound occurs, since part of the organism looses its cohesion. Through the healing process, this part is again integrated into the full organism and the organism is made 'whole' again. When this occurs, the old situation is not restored; a *new situation* is created.

The wound healing process is crucial for the survival of every organism. What's more, if we were to imagine how we could go through life if our wounds would not heal (think about the innumerable microscopic injuries hidden deep within the body), we can only conclude that life would in no way be possible without the wound healing process.
Interestingly, the reverse is also true: without injury, damage, and tissue breakdown, life is also not possible. Without 'damaging' influences, organisms cannot develop into something new and, therefore, become vulnerable (Note: vulnerable comes from vulnus!). The recently developed hygiene hypothesis, for example, states that it is precisely through a regular 'damaging infectious stimulus' that the organism gains health and resistance. In

the studies that have led to this hypothesis, it also appeared that the more the immune system is activated by infectious stimuli, the better it develops its health-maintaining function. The healthy effect of repeated infections led to the pithy statement: "a little dirt does not hurt".
We must, however, differentiate here between the uncoordinated damage that results in *decay* (for example, the necrosis of a diabetic foot wound) and the coordinated *breakdown* that we see, for example, in apoptosis as in the forming of the fingers in embryology. During an entire lifetime, the organism is being broken down. This breakdown of tissues and cells is also an ordered process in time. This will be further developed in Chapter 6.4.

The balance between building up and breaking down in the organism is crucial for life. Injury and recovery are part of life; without both of these processes we would not be able to develop. This does not only have bearing on our body, but also applies to the course of our lives.

## 1.2. The Wound Healing Process of the Skin is a Manifestation of the Healing Process

In this Companion, the *wound healing* process of the skin will be the model for the general healing process. In the wound healing oprocess of the skin, the general healing process is, as it were, continually active and available 'in the background' as the underlying principle. Where there is a skin wound, the healing process occurs at this particular place 'in the foreground' in the form of the wound healing. The wound makes the healing process visible. Up until then, the healing process was only a potential process.

In general, wound healing is comparable for the various types of tissues. In scientific literature, wound healing of the skin is described as a model for or illustration of the general principles of wound healing in every tissue. The wound healing process of the skin can be observed directly and is immediately accessible for study. It has, therefore, been studied the most.

For the objective of this Companion, the description of the wound healing process of the skin is ideal because the process is best suited for phenomenological consideration. Sooner or later, everyone will accidentally cut his finger with a knife and cause a wound in the skin. He can then see and feel what happens during the wound healing process. The cut is an instructive example for describing the general phenomena of wound healing.

## 1.3. Phases of the Skin Wound Healing Process

How do we differentiate the various phases of the wound healing process of the skin? What criteria do we use in creating the phasing?
In the scientific literature, various classifications can be found for the phases of wound healing. All of these are determined by the chosen viewpoint. Traditionally, the wound healing process is divided into three phases: the inflammation phase, the proliferation phase, and the maturation phase.
Based on our systems biological phenomenological approach, we arrive at a description in four phases. The inflammation phase as it is described in most literature comprises two separate processes: hemostasis and the actual inflammation. We have separated these two processes, as have also a number of other authors, since these two processes appear to have an opposing dynamic.

## 1.4. Will the Coordination of the Healing Process be a Permanent Riddle?

Every phase of the healing process consists of complex interactions between cells and mediators which tend to and regulate the process. The extreme complexity of the processes demands perfect coordination. How and through what agent does this coordination take place? Who or what is the organizer? To date, no coordinating substance or center has been found for the healing process. A quote from Robbins

*Pathologic Basis of Disease* is compelling: 'The magic behind the seemingly precise orchestration of these events under normal conditions remains beyond our grasp...' (we will come back to this metaphor in chapter 7). It should be clear here that the coordination of this process must be understood from the organizational level of the organism as a whole and not just as the result of more cells and mediators.

## 1.5. The Further Content of the Companion

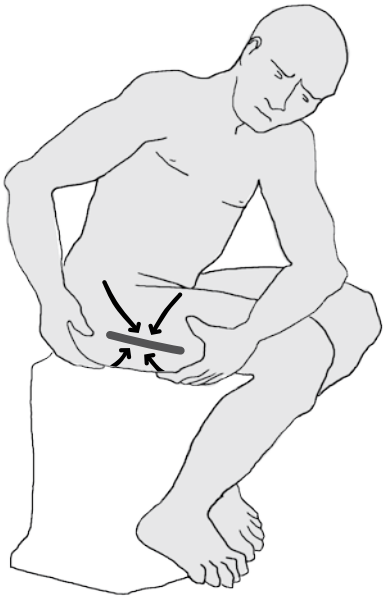
The four phases of the wound healing process of the skin will be discussed in Chapters 2 through 5. In each of these chapters we will discuss the following aspects:

- *Macroscopic visualization*: The description of the phase will be prefaced with what we ourselves can see and sense in a wound
- The *process* that belongs to this phase: A description of the processes that characterize the phase during a normally occurring cycle of wound healing
- *Summary* of these characteristics and a dynamic characterization
- The *healthy balance*: The extremes between which the healthy process occurs
- The *disturbed balance*: The diversion into two opposing disease groups. Here, pathology appears to be a good illustration of physiology
- Conclusion in completion of the phase in question

After the description of the four separate phases, we will describe the wound healing process as a whole in the form of an overview and it will become clear that, in the four different phases, four different 'worlds' are revealed. Subsequently, we will delve into what we could call the *Organ of Repair* and arrive, ultimately, (as promised) back at the above-mentioned metaphor from Robbins.

# 2. Hemostasis

## 2.1. Examination of the Wound, What Do We See?



To introduce the first phase of wound healing, we describe what happens immediately after there is a cut in the skin.

As soon as the skin is cut by a knife, it will bleed. If the cut is caused by a fairly sharp object, for example, a glass splinter or a surgical instrument, the pain sensation will even be missing at first. The appearance of blood is then the first sign that there must be a cut somewhere on the skin. After some searching, the person who has cut himself will be able to find the wound. If there is no arterial hemorrhaging involved, the bleeding will stop spontaneously after a fairly short time.

## 2.2. The Process

In well vascularized tissue, the primary reaction to the injury is to control the blood loss. At the same time, this provides a basic structure within which the wound healing process can take place. Stopping of the bleeding is called hemostasis. Literally translated, hemostasis means: blood standstill. Under normal circumstances, the bleeding always stops by itself even if the wound is still open. The duration of hemostasis consists of the period from the beginning of the bleeding after the injury until the bleeding has stopped. Hemostasis lasts anywhere from a few minutes to a maximum of an hour. A number of factors determine the duration of the bleeding, such as the amount of tissue destruction, the sharpness of the cutting object, the

skin temperature, the humidity of the air, and the place of the cut on the body.
Hemostasis is accomplished through:

- An activity of the blood vessels themselves (the vascular reaction)
- The effect of specific cells in the body (the cellular reaction)
- And by means of cellular signaling substances or mediators (the humoral reaction)

### 2.2.1. Vascular Reaction

The vascular reaction serves immediate hemostasis. When there is a wound, the smaller damaged blood vessels (arterioles) contract *reflexively* in two directions: by drawing back into the tissue (*retraction*) and by contraction of the blood vessel itself which closes the vessel (*reflexive vasoconstriction*). The reflex is partially determined by surrounding nerve tissue on the basis of local nerve products (the neurohumoral factors, such as endotheline), and partially determined by contraction of smooth muscular tissue. The muscle contraction occurs as a consequence of the influx of sodium into and the outflow of potassium from the muscle cell after it is damaged.

### 2.2.2. Cellular Rreaction

When the inner lining of the blood vessel (endothelium) becomes damaged, that results in the exposure of the connective tissue (collagen) around it to the circulating blood (collagen exposure). Part of the collagen, the extra-cellular matrix, activates the thrombocytes in the blood and is a strong stimulator of coagulation (thrombogenic). Subsequently, the coagulation cascade is triggered (see section 2.2.3.) in which a whole series of mediators are activated in a specific order. Together with the activated thrombocytes, this ultimately leads to the forming of a blood clot (thrombus) in the severed end of the blood vessel.
In hemostasis, one cell plays the lead: the thrombocyte.

### The Primary Thrombus

At this stage of hemostasis, the primary thrombus is the first and provisional result. The primary thrombus is not very stable at this point and does not provide definitive prevention against a recurrence of the bleeding. For that, the next process is necessary by which the primary thrombus is reconstructed into a more stable clot: the secondary thrombus. This rebuilding takes place by means of the activity of mediators from the blood serum.

***Thrombocyte Aggregation***

*The thrombocytes circulating in the blood respond with a series of reactions to collagen exposure:*

1. *Thrombocyte adhesion: adhesion to the wall of the blood vessel*
2. *Thrombocyte activation: after adhesion to the endothelium, the thrombocyte undergoes a form change (expression of phospholipid complex) and secretes substances from its granulae:*
   *a. From the α-granula: fibrinogen, fibronectin, factor V, vWF, PF-4, PDGF, TGF-β*
   *b. From the δ-(dense) granula: ADP, ATP, $Ca^{2+}$, histamine, serotonin, adrenaline*
   *Moreover, $TxA_2$ and PAF are released which effectuate vasoconstriction, stimulation of the thrombocyte reactions, the release of other mediators, and further activation of the coagulation cascade.*
3. *Thrombocyte recrutation and thrombocyte aggregation: Under influence of $TxA_2$ and ADP, clotting of the thrombocytes (aggregation) to the exposed collagen and to each other takes place. At higher shear stress, this bonding occurs with the aid of the von Willebrand factor (vWF), a glycoprotein in the blood plasma that originates in the endothelial cells. vWF functions here as a sort of coupling protein that throws out anchors between thrombocyte and endothelial cell.*

## 2.2.3. Humoral Reaction and Production of Mediators

The constriction and retraction of blood vessels provides the first termination of bleeding.

The activation of thrombocytes results in the release of more mediators from their granulae, which further support the vasoconstriction. Alongside of that, an immediate production of thromboxane occurs that is secreted by the thrombocyte with the aid of the Cox-1 enzyme. The outcome is a further, *humorally mediated, vasoconstriction*. Further reactions of the thrombocytes stimulate the release of mediators of the coagulation cascade. The activated *coagulation cascade* in the blood serum ensures stabilization of the primary thrombus. Because of that, a secondary, fixed clot develops with the aid of thrombocyte contraction and fibrin forming.
De cascade itself consists of a series of conversions from inactive clotting factors (factor I-XIII), originating from the liver, into active clotting factors (enzymes). Phosphorus and Calcium play a role here.

### *The Coagulation Cascade*

*The coagulation cascade consists of two separate routes (with mutual interactions) that converge into a general route at the moment factor X is activated:*

- *The general route: From the activation of factor X, the general route ultimately culminates in the forming of thrombin*
- *The extrinsic route: Leads to initiation of the coagulation cascade. Activation through exposure of collagen, tissue factor (TF/factor III; a membrane bonded pro-coagulation factor synthesized by the endothelia), and the phospholipid complex*
- *The intrinsic route: Amplification of the coagulation cascade. Activation by factor XII. Also, stimulation of fibrinolysis occurs*

*Ultimately, through the interaction between the extrinsic and intrinsic routes of the coagulation cascade the regulating protein* thrombin *is formed.*

***Thrombin** fulfills a double role in its function as regulating protein. The thrombin effect results in both inhibition of the coagulation cascade, via activation of protein C and S, and in stimulation of the coagulation cascade, in particular through fibrin forming. Thrombin cleaves fibrinogen into soluble fibrin monomers, which then polymerize into insoluble fibrin polymers, and activation of factor XIII, which ensures mutual cross-linking of the polymers, so that an* insoluble *fibrin network is created. A stable blood clot is the result: the secondary thrombus. Alongside of that, thrombin stimulates the inflammation phase.*

**The Secondary Thrombus**

The thus created secondary thrombus forms a primary substance for the matrix, the basic structure within which the further processes of wound healing will occur. It forms a base for the secretion, accumulation, and concentration of mediators, for the adhesion and migration of the cells that are drawn in by this, and for the repair process.

In the thrombus itself, the secretion of a large number of mediators takes place. These ensure the initiation of the following phase of wound healing, the inflammation.

## 2.3. Summary of Hemostasis and Dynamic Perspective

In a state of health, the various tissues have clear relations to each other within the organism, but there is no arbitrary contact of various bodily substances or cells. A myriad of intervening membranes, collagen, and fluids order the contact that tissues have with each other. When there is a wound, this order is broken, the coherence falls apart and there is an uncommon contact between the various tissues and fluids of the organism.

At the *initial stage* of the wound healing, we find a chaotic mixing of tissues and cells.

The process of the hemostasis is set in motion the moment the injury occurs and blood and surrounding tissues come into *abnormal* contact with each other. In the first instance, hemostasis is a reflex reaction to the chaotic relationship of the bodily fluids and tissues that has developed. It calls a halt to the chaotization. In a *middle stage*, this halting of the chaotization and mixing of bodily tissues is directed by an organically orchestrated process. Cells and mediators become activated and the organism stops the chaotization and bleeding. The *end stage* of hemostasis leads to the forming and organizing of the secondary thrombus. Thus, the chaotization is halted and the beginning of a new order is created.

In hemostasis, **forces** are active with an **integrating** effect.

The phase of hemostasis consists of two sequences:

- Primary hemostasis: reflexive vasoconstriction and thrombocyte aggregation result in the forming of the primary, reversible clot

- Secondary hemostasis: local activation of the coagulation cascade results, with the aid of fibrin forming, in the forming of the secondary, irreversible clot

*Dynamically*, this process can be understood as calming, bringing to a stand still, and rejoining a chaotic dynamic. There are constricting blood vessels and a process of consolidation: thrombus forming. In order to view the situation dynamically, it is important to note that thrombus forming develops through an increasingly stronger bonding tendency of cells (among which are thrombocytes) and fibrous structures such as fibrin. The transition from the primary thrombus to a secondary thrombus, which ensures a definitive closing of the blood vessel, is an example of this.
The hemostasis is carried out locally and, in the chaos, there is stand still and tranquility.

*There is clearly a dynamic focused on one point that results in a stable and consolidated shape: the thrombus, where previously there was chaos.*

## 2.4. Hemostasis: the Healthy Balance

Under physiological conditions, the blood flows through the body in a dynamic fluid state. Under the influence of pathological stimuli, the latent, potential clotting ability of the blood becomes manifest (fig. 1).

Therefore, the homeostasis (state of equilibrium) of the blood comprises two continually active, alternating, and contrary functions in a mutually shifting balance:
- **Coagulation**: the solidifying of the blood in the form of the thrombus
- **Anticoagulation**: keeping the blood fluid

In the hemostasis phase, this equilibrium shifts physiologically in the direction of coagulation.

Hemostasis is, as we have described, shaped by three components:
1. The endothelium
   There is a balance between endothelial thrombotic and antithrombotic activity near the

vascular lining. Which process prevails is dependent upon the condition of the lining. When the continuity of the vascular lining is interrupted, thrombotic activity prevails.

2. The thrombocytes
   The function of thrombocytes balances between:
   - Stimulation of platelet aggregation ($TxA_2$)
   - Inhibition of platelet aggregation ($PGI_2$)

   During hemostasis, the $TxA_2$ activity dominates.

3. The coagulation cascade balances between
   - Activation: Stimulation of coagulation
   - Inhibition: After activation, the coagulation cascade must be halted and remain localized at the site of the wound. This inhibition occurs by means of thrombin

   During hemostasis of the wound healing process, coagulation processes dominate.

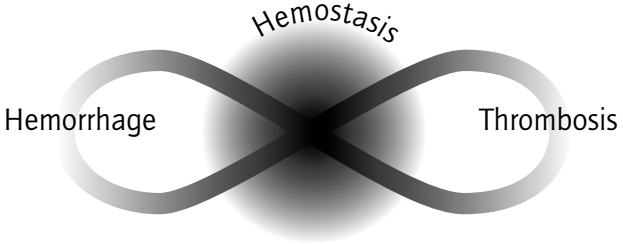



**Fig. 1. Healthy and disturbed balance in hemostasis**

## 2.5. Pathology: the Disturbed Balance

From the above, it is clear that pathological disorders develop from 'normal' processes that – either with respect to duration or to localization – no longer function normally. There are diseases that tend more to affecting the endothelium and diseases that tend more towards affecting the thrombocytes or the coagulation cascade.

### 2.5.1. Diseases which Involve Bleeding

From pathology, we know of a number of reasons for hemostasis to fail. These reasons include the elements that were discussed above for the different stages in hemostasis. We know about failure of hemostasis through diseases of the vascular wall (angiopathy), thrombocyte disorders, or a shortage of thrombocytes (thrombopathy or thrombocytopenia), and disorders of the coagulation cascade (such as hemophilia).

### 2.5.2. Diseases that Lead to Abnormal Clotting

The best known examples of pathological coagulation are, certainly, deep vein thrombosis of the legs and cerebral infarction. The reasons for the abnormal coagulation are often not well known and cannot easily be allocated to the previously differentiated elements of hemostasis.

HEALING PROCESS
Wound Healing Phase One: Hemostasis

| Pathogenesis<br>Dissolving characteristic | Salutogenesis<br>Normal course | Pathogenesis<br>Consolidating characteristic |
|---|---|---|
| Hemorrhage | Salvage of tissue<br>Integrity | Thrombosis |

**Table 2.1. Healthy balance and disturbed balance in hemostasis**

## 2.6. Conclusion: Hemostasis as Recovering Integrity

Every form of injury severs the integrity of the organism. Cuts, burns, injuries through freezing, invasion of bacteria or viruses, damage through chemicals or radioactive radiation all have the same consequence: the loss of integrity of the organism.

In the example that we have chosen – the cut – the organism would be destroyed by continued blood loss if there were no hemostasis. This is comparable for other types of trauma.

Hemostasis can therefore be seen as the primary reaction to injury resulting in a provisional recovery of the integrity of the organism. As such, hemostasis can be compared with the acute phase reaction of the innate immune system during infection (See **BOLK**'S Companions Immunology). The acute phase reaction also results in the provisional recovery of integrity. For the bleeding wound and for the immune reaction a whole range of physiological reactions is to follow, that ultimately leads to definitive recovery of the integrity.

Hemostasis leads to a (primary) **healing of the integrity** of the organism

# *3. Inflammation*

## 3.1. Examination of the Wound, What Do We See?

Let us return to the reality of the visible cut and, through careful observation, determine what happens after hemostasis. We can do this with wounds that have been surgically sutured as well as with wounds that heal without further treatment.

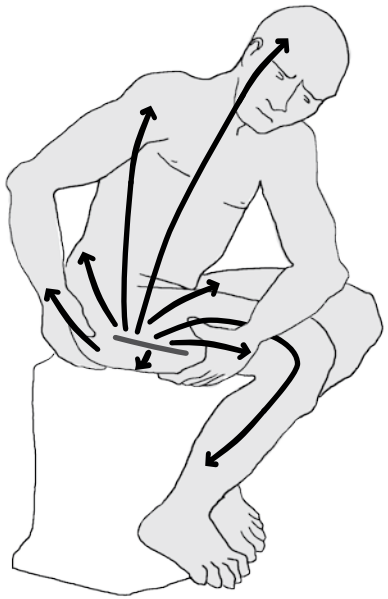
After the bleeding has stopped, a *swelling* around the wound occurs after a few hours – and certainly within a day. The skin surrounding the wound will display *redness* and will feel *warmer*, which can be determined by palpation. During this time, the wound will also start to *hurt*, often accompanied by a painful throbbing. The throbbing pain has the rhythm of the heartbeat. The inflamed organ or body part has considerably limited function.

Celsus (+/- 30 BC – 38 AD), a scientist in ancient Greece, was one of the first to describe these four physically visible or palpable characteristics of acute inflammation and called them the four cardinal symptoms:

- Warmth (Calor)
- Pain (Dolor)
- Swelling (Tumor)
- Redness (Rubor)

In the 19th century, Virchow added:

- Functio laesa (function loss/disturbed function)



## 3.2. The Process

In the literature, hemostasis and inflammation are often described as one phase. Because of the great

differences and the opposing dynamics of these two processes, we have decided, following a few other authors, to describe them as separate phases, each with its own characteristics. During the inflammation phase, the central task is 'clearing out' (phagocytosis = engulfing, see also box at the end of section 3.2.2.) of 'undesirable' material, such as cell debris and microorganisms. The removal of tissue is characteristic for the beginning of the process. Because this is the stage of breakdown (see also section 6.4.), destruction, and removal of tissue, we can view it as chiefly a catabolic phase. The organism literally clears the path for the later of growth of new tissue. This phase is actually the first active reaction of the organism as a whole to the tissue damage that has occurred. The inflammation phase of the wound healing process will actually appear to be characteristic of a complete activation of the organism by itself.

Just as in hemostasis, the inflammation is organized with the aid of a vascular, a cellular, and a humoral component. The inflammatory phase begins an hour to a day after the injury and runs until the commencement of the proliferation phase. (Chapter 4.).

### 3.2.1. Vascular Reaction

The second major phase of the wound healing process begins with a vascular reaction to support the inflammatory process on two levels. With the aid of enzymes in the endothelium, the secretion of various mediators occurs starting approximately one hour after the injury, including prostacyclin and leukotrienes, which, on the one hand, play an active role in the blood vessel dilatation (vasodilation) and, on the other hand, induce an increased permeability of the vascular wall.

#### Vasodilation

The vasodilation during the inflammation phase stands in complete contrast to the vasoconstriction of hemostasis. Through the caliber increase of the smallest arteries, there is an increased blood flow in the capillary vascular bed. This is the cause of both the redness (rubor) and the warmth (calor) that we can observe macroscopically. Moreover, the vasodilation also results in a slowing of the blood flow which ensures that new cells and mediators can reach the entire wound region.

The starting point in time and the duration of the vasodilation (minutes up to half an hour) is dependent upon the gravity of the injury.

**Permeability**

The permeability of the vascular wall is increased during this phase. Plasma and proteins leave the bloodstream to the intercellular space because of the increased permeability in the microcirculation. This process of the formation of exsudate enables an increase in the viscosity of the blood in the wound region, so that newly attracted cells and mediators can become well attached to the vascular endothelium and can ultimately pass from the blood vessel into the intercellular space.

The exsudate is visible as a swelling around the wound and can, if the epidermis is defective, be visible as serous fluid on the surface. Because later white blood cells (leukocytes) also leave the plasma and accumulate in the exsudate, the so-called infiltrate is formed, which is visible as a painful red swelling (dolor, rubor, and tumor) in the wound area.

***What Causes the Vascular Endothelium to become Permeable?***

***Fast temporary reaction:***

- *Reorganization of the cytoskeleton under the influence of cytokines and hypoxia resulting in endothelial retraction*
- *Expansion of the intercellular junctions as a consequence of endothelial cell contraction (under the influence of histamine, bradykinin, leukotrienes, substance P, and others). These substances are probably also responsible for the dolor in the wound healing process*

***Fast permanent reaction (hours):*** *Direct endothelial damage (direct endothelial trauma, oxygen radicals, or proteolytic enzymes) results in necrosis and the release of endothelial cells. This leads to increased permeability and to thrombus forming*

***Delayed permanent reaction*** *(starts after 2-12 hours): The mechanism of this reaction is unclear*

### 3.2.2. The Cellular Reaction

Now the reversal begins of the clotting of blood platelets in hemostasis. New cells, the leukocytes and the macrophages, are drawn in. They find their way locally through chemical attraction (chemotaxis, see box pg. 22). Both are phagocytosing cells. They phagocytose micro-organisms (bacteria, viruses, fungi, etc.), and cell remnants of the tissue.

In this phase, two types of cells are active: the leukocytes and the macrophages.

**The Leukocytes**

The leukocytes, in particular the neutrophiles, can be found in the bloodstream before the inflammation phase. In order to fulfill their role (phagocytosis) in the inflammation phase, they must first leave the bloodstream. The white blood cells depart from the blood vessel (venules) to the space between the body cells, the interstitium, through a number of steps. First, the white blood cells move to the vascular wall. They roll along the endothelium and attach themselves as a kind of pavement layer to the lining. Then, the white blood cells leave the blood vessel. This occurs with the aid of protrusions (pseudopodia) from the cell that could be seen as a sort of 'arms and legs.' In the regions of the endothelium which now have greater permeability, the white blood cell can work itself outwards through the endothelial junctions.
Once it has arrived in the interstitium, the white blood cells find their way, through chemotaxis, to the scene of the injury.

After phagocytosis, the leukocytes proceed with a self-organized process of dying, the so-called programmed cell death (apoptosis) (see also Section 6.4.) and are then themselves 'consumed' again by macrophages or removed via the lymphatic system.

### *How Leukocytes Migrate*

*The leukocytes go through various processes in order to get from the blood to the interstitial fluid:* ***Adhesion*** *is a process of margination; the leukocytes start to flow or roll along the lining of the blood vessel (peripheral orientation) and attach themselves to the lining (pavementing). This process develops through interactions of complementary adhesion molecules (receptors) on leukocytes and endothelial cells. Expression of these receptors is under the influence of mediators. Four classes of receptors are active: selectines, mucin-like glycoproteins, integrins, immunoglobulins.*

***Transmigration*** *through the endothelium (diapedesis) is the following step in the processes that the leukocyte undergoes on its way towards the interstitial fluid. The extravasation takes place in the same manner for all the cells involved in the inflammatory process. The sequence in time is dependent upon the induction of the involved adhesion molecules or chemotactical factors and cell apoptosis.*

*The leukocyte shifts itself with the aid of pseudopodia through the endothelial junctions (sometimes there is also intracellular migration through vacuoles) and then through the basal membrane (possibly with the aid of the enzyme collagenase) to the interstitial space. The neutrophiles arrive in this space after 6-24 hours, the monocytes/macrophages after 24-48 hours.*

***Migration*** *through the interstitium ultimately takes place under the influence of chemotaxis (see below).*

### The Monocytes and Macrophages

Via the blood, monocytes arrive at the place of injury and transform into macrophages. The presence of the macrophage is essential for wound healing. The macrophage phagocytoses all of the cells that have become apoptotic (lymphocytes as well as tissue cells) as well as other infectious cells that must be removed. The secretion of various mediators and nitrogen monoxide (NO) by the macrophages enable the transition to the proliferation phase at a later stage (see also the box in Section 3.5.2.).

### *Chemotaxis*

*Chemotaxis is a process of charming, recognition, and response. After the white blood cells leave from the bloodstream, they move through the tissue in the direction of a stimulus which has an magnetic effect on them. This involves:*

***Attraction**: by means of substances with a chemotactic effect. These substances are not diffusely distributed but always have a concentration gradient in the tissue that acts as a signpost for the cells that are sensitive to it. Immobilization of these substances is important for maintaining the chemotactic gradient.*

*These chemical substances can have various origins:*

- *From outside the organism (exogenous). These include, for example, bacterial products such as bacterial poisons (toxins)*
- *From inside (endogenous). These include the substances produced by the organism itself such as components of the complement system (C5a), leukotrienes (LTB4), and cytokines (chemokines)*

***Movement (locomotion)**: Locomotion takes place under the influence of contractile elements in and around the cells (generally actins), that contract under the influence of calcium. Calcium plays a role in all contraction of actin and myosin, visible both macroscopically in muscular action and microscopically in the contraction of these contractile elements. Calcium is, as such, an important substance involved in movement.*

**Direction:** *The direction is determined by the chemotactic gradient (and its variable composition) and through the variable receptor expression. Navigation takes place oriented along a chemical gradient.*

## Phagocytosis

The cells, once they have arrived at the wound or the source of infection, proceed to consume the cell debris and harmful micro-organisms through phagocytosis (fig. 2). That process once again proceeds in three steps:

- Recognition and bonding of microbes:
  The organism has the possibility to achieve a higher efficiency in this process by *coating* the piece of tissue to be removed. This occurs by means of signal substances

(opsonines) which attach themselves to the tissue to be removed so that this is more easily recognizable for the phagocytosing cells

- Engulfment, literally translated as *swallowing up*:
  This occurs through absorption into a vacuole, which evolves as it were around the material to be phagocytosed. That can lead to total enclosure in a phagosome

- Killing the microbe:
  Cytolysis and destruction or degradation of the engulfed material

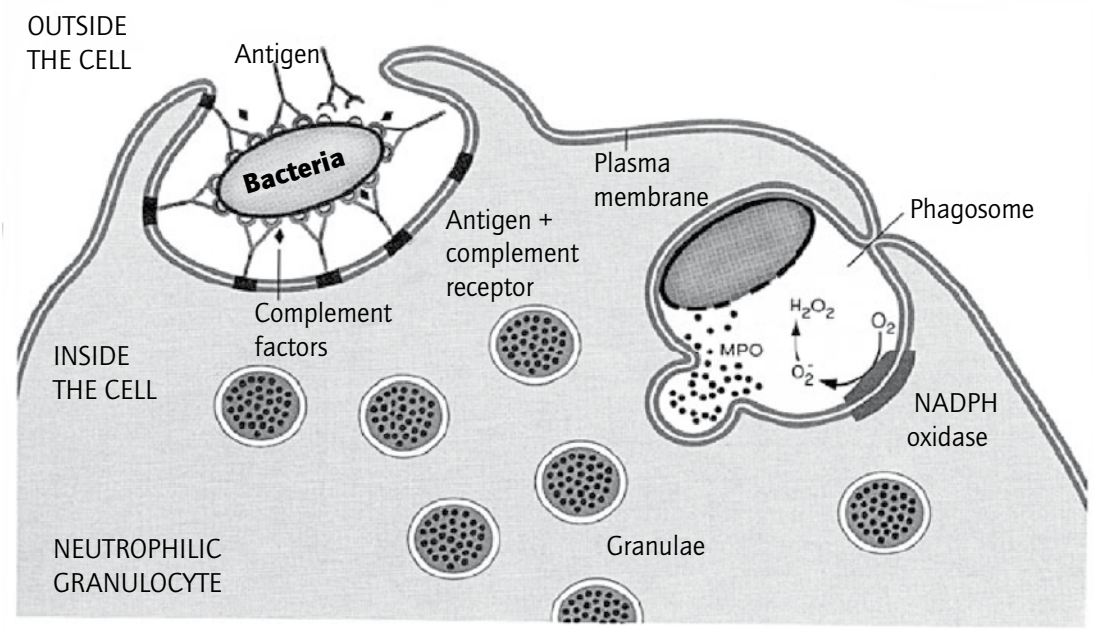



**Fig. 2 Phagocytosis of opsonized bacteria, engulfment, and cytolysis**

***Phagocytosis***

*The mechanism for killing pathogens and for degrading devoured material has two known forms:*

- ***Oxygen-dependent:***
  *Through the formation of oxygen metabolites by NADPH-oxidase such as $H_2O_2$ that are stored in lysosomes. Under the influence of myeloperoxidase (MPO) and in the presence of a halide such as Cl, this can be converted into HOCl. The $H_2O_2$-MPO-halide system is the most effective system. Other forms are: hydrolase, superoxide, hydroxyl radicals, and $O_2$-radicals*
- ***Oxygen independent:***
  *Through BPI (bactericidal permeability increasing protein), lysozyme, lactoferrin, major basic protein, defensines*

### 3.2.3. The Humoral Reaction

Mediators are important in the vascular and cellular reaction of the inflammation phase. During the humoral reaction, toxins and mediators are spread throughout the entire body. The consequence of the production of chemokines such as prostaglandines and leukotriens and adhesion molecules is the onrush of leukocytes and macrophages. Because of that, general symptoms that are not limited to the wound area may develop alongside the local symptoms. Particularly in larger injuries, the local symptoms may be accompanied by general symptoms. The person who is wounded can have a *fever, feel sick, have a loss of appetite, and experience general fatigue.* In extreme cases, the lymphatic vessels can become visible through an inflammatory reaction (*lymphangitis*). The body part with the wound, whether the arm, hand, or foot, has function loss. There is a *loss of strength* in the surrounding muscles. In more serious injuries, the wound region must even be given a complete rest. A sling, an immobilizing bandage, or even a splint may be necessary.

*Fever* is one of the signs that the entire organism is involved in the inflammation phase of the wound healing process. From the study of infectious disease, it is known that fever has

a positive effect on wound healing after infection. Here, it is a fascinating phenomenon that cold-blooded animals search for a warm spot when they are injured or have an infection.

The symptoms of the inflammation phase in the wound healing process are more intense when there is also a microbial infection.

The inflammation phase stops when the stimulus that led to the inflammation is removed. The mediators then disappear or are inactivated by an active process of inhibition.

### 3.3. Summary of the Inflammation Phase and Dynamic perspective

The phenomena of the inflammation phase of the wound healing process occur in an 'organized chaos.' Many variables modify this process, such as the type and seriousness of the wound, the type and location of the tissue, and the reactive ability of the host.
At the *initial stage* of inflammation, the local vasodilation and increased permeability of the vessels ensure better accessibility to the wound region. Because of this, in a *middle phase*, the cells coming from the entire organism, the leukocytes and the macrophages, move from the blood vessels to the wound region and fulfill their task there: opsonizing of cell remains and micro-organisms. At the *final stage*, the phagocytotic cells are then again cleaned up by macrophages and removed via the lymph stream. If the opsonizing or apoptosis do not go smoothly, general symptoms can occur during this stage, such as fever and lymphangitis.

Along with the inflammation, there is a systemic reaction in the organism. This reaction is, in terms of the dynamics, clearly opposite to the dynamic of hemostasis that remains local. Instead of a consolidating dynamic (clotting) that is focused on one point, we now come across a process of motion – through the activation of cells and mediators – that expands itself to the periphery of the organism.

In the inflammation phase, **interactive forces** are in effect that restore the connection of the wound region to the rest of the organism.

The result is, therefore, not a relatively stable situation such as the thrombus, but precisely a dynamic and labile equilibrium: the inflammation. In this phase, tissue is dissolved and space is created within which in the following phase of the wound healing process (the proliferation phase) new tissue can be deposited.

*In the inflammation phase, there is a clearly active expanding dynamic out to the periphery of the organism, which restores the interaction of the wound area with the entire organism as a whole and which results in a labile equilibrium.*

## 3.4. Inflammation: the Healthy Balance

The concept of inflammation comes from 'inflammare', that means 'to set on fire'. After the blood has been brought to a standstill in hemostasis, there is an inflaming, a kindling process – in short, a process that sets things in motion!
The 'fire' must not, however, destroy everything, but must be regulated. In the inflammatory phase, we can therefore discern a balance between **'warming up'** and **'cooling down'** (fig. 3).

There are three possible outcomes of the inflammation process:

- Neutralization of the stimulus and, in the following two phases, complete recovery leading to a return to the normal situation
- Forming of an acute infectious process such as an abscess or an empyema in which the inflammatory products are brought together in the body in a newly formed cavity (abscess) or a previously existing cavity (empyema)
- Transition from an acute to a chronic inflammation

## 3.5. Pathology: the Disturbed Balance

The role of infection in the inflammation phase is an essential element for understanding the pathology of this phase.

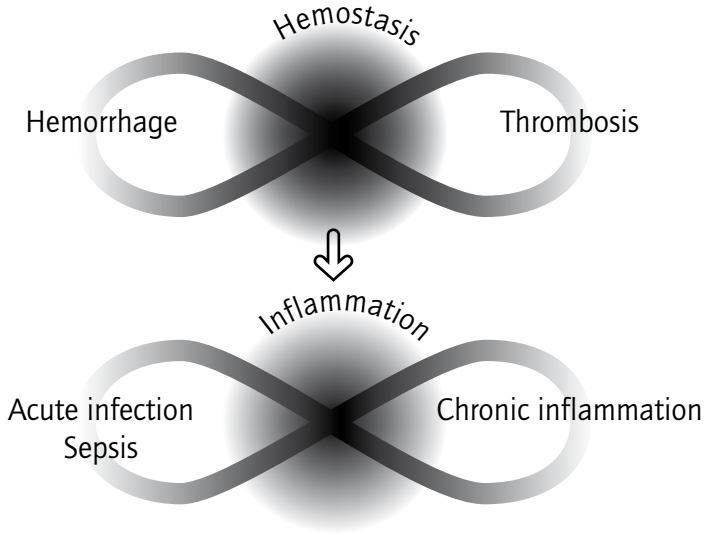



**Fig. 3. Healthy and disturbed balance in inflammation**

### 3.5.1. Infection

A wound is generally perceived as macroscopic tissue damage, but actually, every discontinuity of tissue in the airways, the urinary tract, the intestinal wall, or the skin can be considered a wound. Frequently, the chemical substances secreted by the body itself can induce a quick recovery of the barrier function and, thus prevent infection.
When there are, nonetheless, micro-organisms present that can multiply, then the wound becomes infected. Toxic products from the leukocytes can also become active extracellularly, and lead to an increase in inflammatory stimuli. This is an important cause of additional tissue damage. An infected wound is considered to be a complicated wound. When the wound is infected, there is an enhanced inflammation phase. The overly activated inflammatory process is, in fact, damaging and can divert into tissue destruction or allergic reactions. It can also lead to chronic infections.

### 3.5.2. Acute Infection and Sepsis

An unrestrained 'warming up' of the inflammatory reaction in a wound infection can result in a sepsis with tissue destruction in the entire organism. Thus, a local cellulitis, can expand into a flegmone and further into a generalized toxic infectious picture. The organism is then flooded with toxic products released by the uninhibited inflammatory process that has been caused by the infection. This toxic situation can lead to shock (toxic shock) and, in extreme situations, to death through a total physiological system collapse.

### 3.5.3. The Chronic Inflammation

The transition from acute to chronic inflammation occurs when the acute inflammatory reaction cannot be successfully completed. This may be the result of a persistent stimulus or through a disturbance of the normal healing process. Examples of illnesses in which chronic inflammation play a role are: rheumatoid arthritis, arteriosclerosis, tuberculosis, and chronic lung diseases. The characteristic of these diseases is that there is, at the same time, active inflammation and tissue destruction, alongside healing attempts in the form of fibrosis.

The most important symptoms are:

- Persistent infection, particularly in connection with micro-organisms with a low toxicity; they cause a delayed allergic reaction. The inflammation then often has the form of a granulomatous reaction, such as in tuberculosis
- Extended exposure to endogenous or exogenous toxins, for example in arteriosclerosis
- Auto-immune reactions against the body's own tissue, such that an auto-antigen related vicious circle develops, such as in rheumatoid arthritis or Systemic Lupus Erythematodes. The inflammation can then behave as a chronic process from the very beginning

### *Monocytes/Macrophages in Chronic Inflammation*

*The macrophage is the central cell in chronic inflammation. In the inflammation phase, monocytes from the blood transform to tissue macrophages. In chronic inflammation, the macrophage accumulation in the tissues remains high as a consequence of:*

- *Recrutation: permanent recrutation of monocytes through permanent production of chemokines and adhesion molecules*
- *Proliferation: local proliferation of macrophages*
- *Immobilization of macrophages*

*As a consequence of incorrect activation of the macrophages* ***by mediators,*** *the secretion of numerous biologically active substances takes place which, when produced in an uncontrolled manner, result in tissue destruction and fibrosis. As described above, this is characteristic for chronic inflammation. The various mechanisms of release of cell products and cell necrosis such that progressive tissue damage can repeatedly activate the inflammation cascade, can explain why acute and chronic inflammation frequently occur together.*

We can summarize the pathology of the inflammation phase as follows:

HEALING PROCESS
Wound Healing Phase Two: Inflammation

| Pathogenesis<br>Dissolving characteristic | Salutogenesis<br>Normal course | Pathogenesis<br>Consolidating characteristic |
|---|---|---|
| Acute infection<br>Sepsis | Tissue clearing<br>Activity and interaction | Chronic inflammation |

**Table 3.1. Healthy balance and disturbed balance in inflammation**

## 3.6. Conclusion

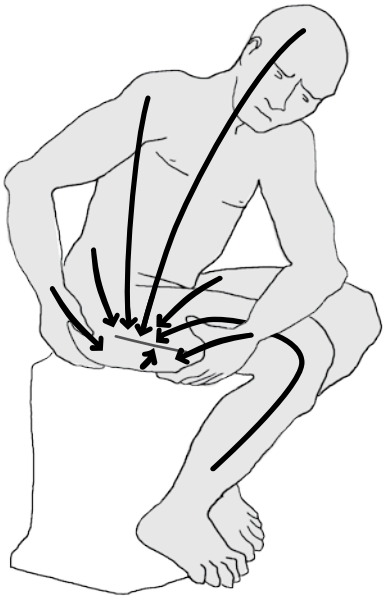
In the inflammation phase, the entire organism becomes involved in the wound healing process. What started as a local activity in hemostasis, is now a generalized activity that, beside specific reactions also summons aspecific reactions such as fever and a general feeling of ill health. In the local reaction, there was little interaction between the organism as a whole and the region of the wound or infection. The inflammation phase in the wound healing process now heals the severed communication between local and general process. The important consequence of the inflammation phase is the reintegration of the local process in the context of the organism, the cleaning up and clearing out of the wound, and the removal of all material that would hinder or complicate further wound healing.

Inflammation leads to a healing of the **interaction** between local and general reactions of the organism

# *4. Proliferation*

## 4.1. Examination of the Wound: What Do We See?

After the bleeding has stopped and the inflammation symptoms have decreased, we see new tissue developing in the wound. When the wound is not sutured, we see this tissue as a pale substance with small red dots that look granular. This is the red granulation tissue, full of many small blood vessels, that is formed in a skin defect during wound healing. The granulation tissue is often soft, pale, and edematous and it bleeds easily. This tissue fills up the open space in the wound. If the wound has been surgically sutured, ther is much less tissue and the new tissue will, therefore, be much less noticeable.



At the same time, starting from the edge of the wound, a thin layer of epidermis (epithelium) is formed, moving inward over the wound surface. When wound healing is successful, this epithelium covers the entire wound and, thus, again protects the organism against environmental influences, dehydration, and heat loss.

For the first few weeks, the area of the wound remains vulnerable and sensitive, but after a month, the skin is perfectly closed, pale, and strong.

## 4.2. The Process

After removal of the damaged tissue and elimination of a possibly present infectious pathogen,

the genuine wound healing process can now begin by means of proliferation of new tissue. In the proliferation phase, we can also differentiate among vascular, cellular, and humoral components. This phase generally lasts from a few days to three months after the injury.

### 4.2.1. Vascular Reaction

A good blood supply is essential for this phase of wound healing. The existing blood vessels ensure the formation of new offshoots, a process that is called neovascularization.

***Neovascularization***

*The process of neovascularisation relies on the interactions between growth factors such as VEGF (from the keratinocyte and the macrophage) and angiopoietin on endothelial cells and on extracellular matrix. The release of NO, that is formed under the influence of hypoxia from eNOS in the endothelial cell, is an additional stimulus.*

The development of new blood vessels progresses via a number of steps:

- Migration of the inner lining of the blood vessel (endothelial cells) in the direction of the stimulus that generates angiogenesis
- Increase of endothelial cells, just behind the front of the migrating cells
- Maturation and remodeling of endothelial cells
- Recruiting of periendothelial cells: cells that form the tissue surrounding the endothelium

### 4.2.2. Cellular Reaction

During the proliferation phase, cell replication takes place such that new tissue develops, the so-called wound-healing *matrix*. Characteristic for this phase is the *formation of new tissue*. It is, therefore, an anabolic phase.

*Three* cells play a leading role in this phase:
• The *vascular endothelial cell* plays a role in the new growth of blood vessels (angioneogenesis), as has been discussed in neovascularization
• The *fibroblast*, a specific connective tissue cell, plays a role in the formation of connective tissue (fibroplasia), the development of granulation tissue, and matrix formation
• The *epithelial cell* (keratinocyte) of the epidermis plays a role in covering the wound (epithelization)
Beside these three cells, the macrophage continues to play an important role in regulating the process and in taking on the functions that the leukocyte fulfilled during the inflammation phase.

First, *granulation tissue* develops through the proliferation of vascular endothelial cells and fibroblasts (day 3-5). Granulation tissue is a tissue type that is characteristic for wound healing.

**Fibroplasia and Matrix Formation**
The human body is capable of replacing the cells that have been damaged or killed through trauma or inflammation. A wound actually always sets two polar processes in motion: tissue breakdown (as in cell apoptosis), on the one hand, and tissue recovery (as in cell replication), on the other.
Tissue recovery consists of the combination of two processes depending upon the degree of the damage:
- Regeneration (normal tissue): Tissue recovery dominates in regeneration through proliferation of the parenchyma cells that are already present. The precondition for regeneration is the presence of an intact basal membrane, which functions as an underlying and supportive framework. Regeneration generally leaves no macroscopic sign of injury
- Fibrosis (scar tissue): The breakdown of normal tissue dominates in fibrosis through the collagen secretion of *fibroblasts*. Destruction of the basal membrane on top of the destruction of parenchyma cells leads to fibrosis. This results in a permanently visible scar

Both processes make use of comparable biological mechanisms which include cell proliferation, cell differentiation, and interactions between cell and matrix.

In this phase, the deposition of fibroblasts, consisting of fibrin and fibronectin, forms the next, provisional matrix that will fill up the wound.

### *Fibroplasia*

*Fibroplasia originates from:*

- ***Fibroblast migration and proliferation***
  *Due to an increased vascular permeability (also under influence of VEGF and angiogenesis) the deposit of plasma proteins (fibrin and fibronectin) occurs. These form a temporary framework for endothelial cells and fibroblasts. The fibroblast is influenced by growth factors (including TGF-β, PDGF, EGF, FGF) and cytokines (IL-1, TNF-α). TGF-β is important because, beside migration and proliferation, it also stimulates the synthesis of fibronectin and collagen. The expression of TGF-β is increased in a number of chronic diseases*
- ***Deposition of extracellular matrix***
  *From day 3-5 to a number of weeks after the injury (depending upon the size of the wound), the deposition of extracellular matrix takes place under the influence of the same mediators (+ IL-4). The net matrix accumulation is dependent upon the balance between matrix synthesis and matrix degradation. Collagen type III is first oriented vertically along the incision, then an increased bridging of the tissue cleft is formed*

*This leads to the formation of a provisional matrix (see also box Provisional matrix).*

## Epithelization

Through the injury, the skin is damaged and open to the environment. Through epithelization, the skin is closed again and a protective barrier is formed against the loss of fluids and heat and against the invasion of microorganisms.

The epithelization is dependent upon the condition of the basal membrane of the epidermis. When there is an intact basal membrane, *cell migration* can take place and then the epithelization will occur quickly. When the basal membrane is severed, *cell proliferation* (new formation) must take place. The epithelization process is controlled by the macrophage.

***Epithelization***

*The macrophage stimulates the fibroblast, by means of IL-1 and TNF-α, to secrete KGF-(1)-2 and IL-6. These then prompt, together with EGF and TGF-α, the keratinocyte to migration, proliferation, and differentiation; so that a new epithelial layer is developed. Alongside of that, the keratinocyte starts to produce VEGF, IL-6, and NO. These last two substances function as auto-stimulation for the keratinocyte and ensure a form of positive feedback such that the keratinocyte itself warrants the maintenance of the epithelization process. Macrophage and fibroblast are, therefore, only necessary for the initiation of this process. Epithelization lasts, on average, approximately a week.*

### 4.2.3. Humoral Reaction

The humoral reaction of the proliferation phase progresses with the aid of several humoral factors for processes such as further matrix formation out of the secondary thrombus, and epithelization.
The macrophage has, once again, an initiating role through the secretion of various signaling substances and growth factors. These stimulate fibroblasts to develop further:

- Outside of the wound region, fibroblasts are urged towards migration, activation, proliferation, and synthesis of a second type of matrix, the provisional matrix

***Provisional Matrix***

*The second type of matrix consists of proteoglycans, fibronectin and pro-TGF-β. Through proteases, pro-TGF-β, originating from the macrophage and from the fibroblast itself, cleaves to TGF-β. This then stimulates the fibroblast to synthesize collagen type III.*

- Inside the wound region, the fibroblasts present in the wound region transform themselves into myofibroblasts. These are, literally translated, muscle-connective tissue cells. Due to the fact that these cells can develop contractile activity, the edges of the wound are pulled towards each other (wound contraction)

***Myofibroblasts***

*The transformation of fibroblasts to myofibroblasts is under the influence of TGF-β in the fibroblasts and gives a change of the fibroblast phenotype in the direction of α smooth musclular tissue with an actin phenotype. The myofibroblasts are bonded, with the aid of integrins, with the fibronectin in the matrix and can thus ensure wound contraction.*

**Renewed Deposition of Collagen: The Definitive Matrix**

Gradually, the collagen type III, a temporary form of collagen, is replaced up to a total of 90% by collagen type I under the influence of humoral factors. Collagen type I creates the *definitive matrix*. This process occurs under the influence of TFG-β with a peak concentration on day 7-14 of wound healing. Just as earlier in the proliferation phase, collagen synthesis at this stage is greater than collagen degradation.

In this process, there are structural changes of the collagen fibers such as cross-linking and later also an increase in the fiber size. Because of this, the strength of the matrix increases quickly. After a week, the matrix strength is only 10% compared to normal skin, after 4-5 weeks, it is 70-80% and, at around 3 months, a plateau phase of 80% is attained. The matrix strength will never reach 100% due to an increased hydroxylation and glycosylation of the lysine residues in the collagen.

## 4.3. Summary of the Proliferation Phase and Dynamic Perspective

The proliferation phase is an anabolic phase. In the proliferation phase, new formation of wound tissue is central. In the space of the wound that had been cleared during the

inflammation phase, starting from the base and the edges of the wound, tissue can grow in to fill up the defect from the injury with new tissue. This process of tissue growth is quite localized. Although the entire organism was activated during the inflammation phase, now the accent lies once again on the local effects of new formation of tissue and blood vessels. The growth factors circulating in the blood also have a chiefly local effect in matrix formation. The three central cells in this phase are the angioblast, the fibroblast, and the epithelial cell.

At the *initial stage*, young, cell-rich, vascular-rich connective tissue, granulation tissue, is developed. The angioblast causes new blood vessels to grow to optimize the metabolic process in the wound region. During the *middle stage*, tissue develops that is rich in collagen type III, secreted by the fibroblasts and this tissue forms the provisional matrix. The fibroblast is a cell that ensures the connection between the metabolic aspects, on the one hand, and the ingrowing epithelium on the other. The epithelium can be seen as a cover that protects the organism from the outside world and that, in keratinization and the daily flaking off of horn cells, represents a form of death process. In the *final stage* of proliferation, a true differentiation is realized since the more general collagen type III is replaced by the stronger and more specialized collagen type I. This ensures the formation of the definitive matrix. In the literature this last phase is often seen as a part of the maturation phase. We have placed it here because of its proliferative dynamic.

In the proliferation phase, anabolic **growth-promoting forces** are active. The new tissue growth occurs in a localized, damp environment. During this phase, damp applications can further promote wound healing.

As a result, matrix tissue is developed in the wound that becomes the basis of the processes of the following phase in wound healing, the maturation phase.

*There is an anabolic dynamic in the proliferation phase that results in the formation of new matrix in the defect of the wound region.*

## 4.4. Proliferation: the Healthy Balance

The proliferation phase is, just as hemostasis and inflammation, a process in equilibrium. On the one hand, there is growth and new formation of tissue, on the other hand, there is decomposition (see section 6.4.) of material which ensures the correct amount of matrix tissue in the wound defect. Growth stimulation and growth inhibition follow each other in a balanced sequence. This is all about the balance between **growth (proliferation)** and **specialization (differentiation)** that is coupled with growth inhibition (fig. 4).

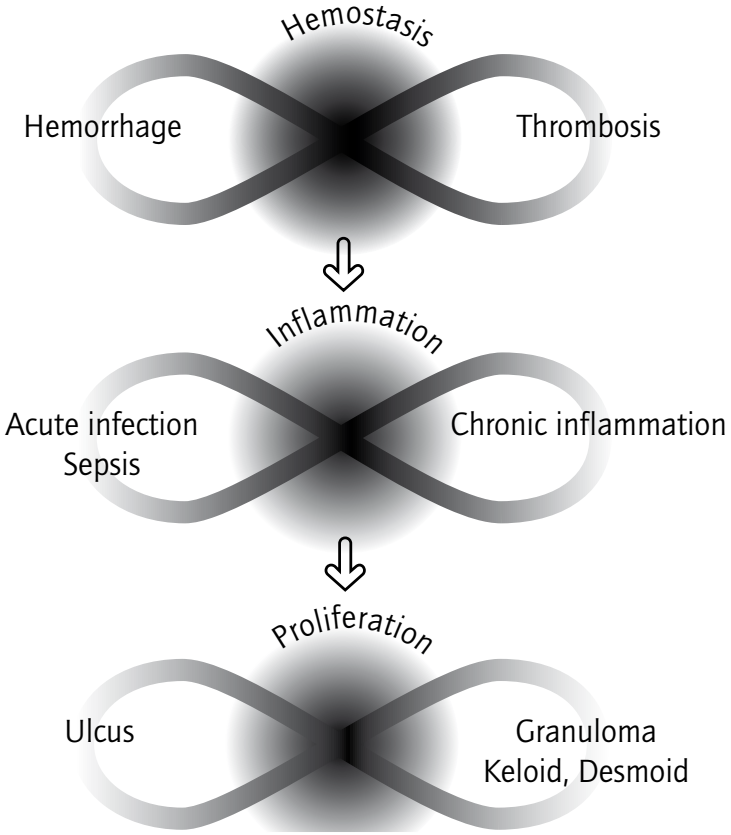



**Fig. 4. Healthy and disturbed balance in proliferation**

## 4.5. Pathology: The Disturbed Balance

Do we know examples from pathology in which the proliferation phase does not develop or, conversely, overdevelops? The disturbed balance of proliferation can diverge to the not-actively healing wound in the form of the ulcus, or to excessive production of wound tissue, the granuloma.

### 4.5.1. Ulcus: the Wound that cannot Proliferate

Two specific types of wounds fill patients and doctors with terror because it takes an exceedingly long time for these wounds to heal, namely the 'diabetic ulcer' and 'the bedsore'. Both wounds are qualified as ulcers, and sometimes they never heal.
The definition of an ulcus says it all: "an ulcus is a wound that displays no tendency to heal". In an ulcer, all characteristics of the inflammation phase are still present. An ulcus is extremely pain sensitive, the surrounding area is red and somewhat swollen and warm. But it never receives the impulse for proliferation. The wound healing process remains stranded in its development in the inflammation phase. The central question in treating an ulcus is, therefore: how can we give the healing process a new impulse?

### 4.5.2. The Granuloma: Uninhibited Proliferation

The word granuloma is quite a graphic description: it indicates that, in the wound, something develops that maintains a continued neovascularisation process. The granuloma is an example of an uninhibited proliferation process. Milder forms of an extended proliferation lead, in the maturation phase, to thickened and often consolidated scars.
Other examples of excessive proliferation are keloid and desmoid tumor growth.

HEALING PROCESS
Wound Healing Phase Three: Proliferation

| Pathogenesis<br>Dissolving characteristic | Salutogenesis<br>Normal course | Pathogenesis<br>Consolidating characteristic |
|---|---|---|
| Ulcus | Tissue formation<br>Growth | Granuloma<br>Keloid, Desmoid |

**Table 4.1. Healthy balance and disturbed balance in proliferation**

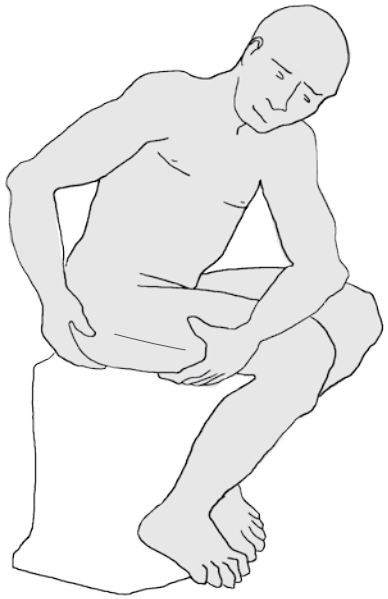
## 4.6. Conclusion

Growth and new formation of tissue are characteristic for the proliferation phase. After the provisional recovery of the integrity of the organism by means of hemostasis and recovery of the interaction with the rest of the organism in the inflammation phase, the first tissue recovery occurs in the proliferation phase. The matrix tissue that develops still has a primarily vital vegetative character and is not yet completely differentiated, but functions as a substrate upon which, at a later time, the definitive recovery of the physical boundaries of the organism can occur.

The proliferation phase leads to **tissue healing**

# *5. Maturation*

## 5.1. Examination of the Wound, What Do We See?



After the wound space is completely filled up with granulation tissue, the scar is generally still red and pain sensitive. Gradually, the scar becomes paler and the epithelium thicker. Through shrinkage of the granulation tissue, the edges of the wound are continually drawn closer together. When the wound healing works well, only a thin line on the skin remains where the cut was. With this, the healing of the wound is, in a practical sense, completed. Nonetheless, there is still activity in the wound area. Although hardly visible, an important change is taking place: the stress lines in the skin are restored.

## 5.2. The Process

Improvement of the collagen in the scar to the greatest possible perfection is characteristic for the maturation phase (maturatio = ripening). This development determines the transition of a temporary matrix to a definitive matrix. In the collagen, a remodeling takes place with a continuous resorption and redeposition of collagen, changing the structure and the quality of the matrix. The process moves forward from a temporary structure to a definitive structure, from temporary to definitive tissue, and from an orientation of the collagen fibers parallel to the wound edges to an orientation along lines along which mechanical load occurs, the so-called stress lines. The mechanical forces working on the tissue determine the ultimate form it will take. This phase actually lasts up to a year after the injury.

### 5.2.1. Vascular Reaction

During the maturation phase, the blood vessels from the granulation tissue regress further. For the duration of the transformation of scar tissue, there is, therefore, a generalized reduction of blood vessels, so that, ultimately, there is a white scar in which there are no more blood vessels present.

### 5.2.2. Cellular Reaction

No later than six weeks after the injury, long after the wound is visibly closed, the proliferation supported by collagen *synthesis* has stopped and the transformation of the scar begins under the influence of physical-mechanical *stretch and strain*. A 'mechanical phase' dawns under the influence of a continuously changing mechanical load. With the aid of the isometric contraction of the fibroblasts that can create muscle fiber, the myofibroblasts (see 4.2.3.), there is an equilibrium between the internal and external load. Subsequently, fibroblast apoptosis occurs resulting in a normal looking scar.

### 5.2.3. Mechanical Reaction of Humoral Reaction

In this phase, humoral factors play a subordinate role. Their function is assumed by the mechanical stretch and strain that is exerted on the tissue in daily life. These now provide the impulse for the final transition. The typical original skin lines on, for example, the fingertips, return.

## 5.3. Summary of the Maturation Phase and Dynamic Perspective

During maturation, there is a definitive restructuring of the tissue formed thus far.

At an *initial stage*, the blood vessels and fibroblast activity are reduced so that the

scar assumes its definitive pallor and thin form. During the *middle phase*, the collagen is structured along the stress lines working upon it in the affected region, so that the original skin lines again become visible. Another beautiful example of this sub phase of wound healing is seen in bone healing after a fracture. Ultimately, the mechanical use of the skeleton provides the final refinement to the new bone formation. There is, therefore, a change in scar structure during maturation. In the *final stage*, the entire wound healing process settles down and is closed off definitively.
For the maturation phase, **physical forces of stretch and strain** are characteristic. The more active processes, such as inflammation and proliferation, come to a complete stop through *self-regulating inhibition*. Apoptosis, in the sense of programmed cell death (see 6.4.), plays a leading role here.

The result of the maturation phase breathes the atmosphere of processes that come to rest. This state of calm also expresses itself in the way that the scar region assimilates into the archetypal form of the organism as a whole!

*The dynamic in the maturation phase has the characteristic of cutting down, completion, and rest and results in retrieval of the authentic form of the organism. All of the metabolic processes activated by the injury have again come to a halt.*

## 5.4. Maturation: the Healthy Balance

There is also an equilibrium during remodeling. Of central importance is the equilibrium between the healing wound that **takes on its own shape** and the **total form** of the organism. During tissue remodeling, the equilibrium now shifts in favor of tissue breakdown and apoptosis. This facilitates the reintegration and readjustment of the specific shape of the scar that arises through the wound healing process to the form and the functions of the body region in question. The so-called 'restitutio ad integrum', literally translated, the 'recovery to the undamaged state' allows the scar to adapt itself to the total form of the organism by means of resorption (breakdown processes, see 6.4.) and differentiation

(modeling processes). The modeling of tissue in this phase is primarily determined through mechanical forces and no longer through growth.

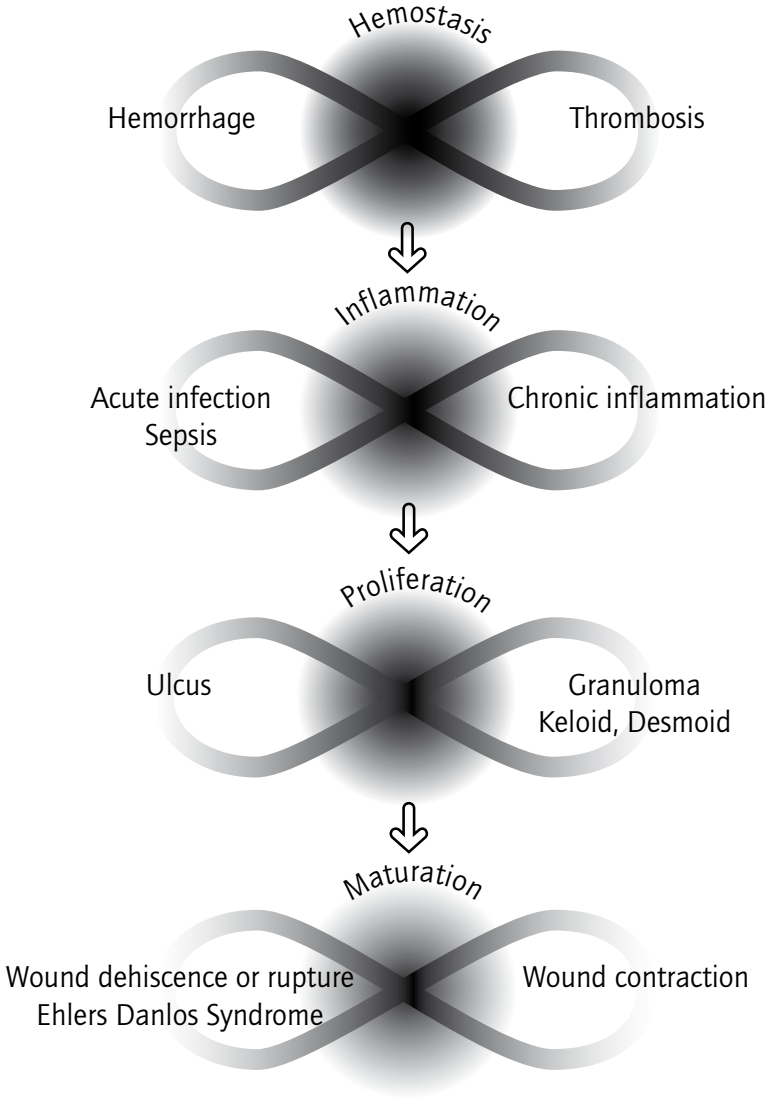



**Fig. 5 Healthy and disturbed balance in maturation**

## 5.5. Pathology: the Disturbed Balance

### 5.5.1. Ehlers Danlos: Disturbed Collagen Formation

The Ehlers Danlos syndrome includes several diseases that each have a different type of congenital collagen defect. In all cases, an inferior type of collagen is formed that leads to problems particularly in the wound healing process. Too little collagen synthesis results in a decrease in scar strength. Therefore, a rather broad scar develops after a cut. In this broad scar, a connective tissue arises that is thin, shiny, and often wrinkled. The edges of the wound remain far apart and the new collagen is vulnerable and has little tensile strength. When patients with the Ehlers Danlos syndrome undergo joint surgery, they may sustain permanent dysfunction and instability of the involved joint. Since the scar contains inferior connective tissue, the original form of the organism does not return properly. Then the scar tissue's own shape remains present because of a dissolving tendency in the pathology.

### 5.5.2 Wound Contraction

Excessive wound contraction leads to a physical deformity characterized by skin retraction and functional limitations. Here, too, the organism's original form is not optimally restored. An abnormal scar formation remains due to too much consolidating tendency.

HEALING PROCESS
Wound Healing Phase Four: Maturation

| Pathogenesis<br>Dissolving characteristic | Salutogenesis<br>Normal course | Pathogenesis<br>Consolidating characteristic |
|---|---|---|
| Wound dehiscence or rupture<br>Ehlers Danlos Syndrome | Integration into the form of the organism | Wound contraction |

**Table 5.1. Healthy balance and disturbed balance in maturation**

## 5.6. Conclusion

It is characteristic for the maturation phase that physical-mechanical forces play a role in the remodeling. The specialized shape of the scar in the wound healing process is thus integrated into the total form and function of the organism. Metabolic processes, growth, and new formation of tissue dominated previous phases. In these processes mechanical forces would function disruptively. Wound healing in the first three phases benefits, in particular, from rest and protection from mechanical influences. Many medical procedures from the initial phase of the recovery are based on immobilizing and mechanically disconnecting the affected area through bandaging, swaddling, taping, a sling, or a plaster cast.
Maturation occurs exclusively with the aid of the mechanical forces. If you have broken your leg and want to recuperate completely after sufficient tissue recovery has taken place, you will have to apply mechanical load to the leg.

Two elements stand out at the completion of the wound healing process:
- a permanent recovery occurs of the physical form of the organism and
- the affected area is reintegrated in the functionality of the organism

This can be justifiably called 'restitutio ad integrum'.

The maturation phase leads to **recovery of the physical form and reintegration** of the affected area into the organism's whole

# *6. Synopsis*

## 6.1. The Healing Process

The integrity of the human body is maintained through continuous self-regulation, as is the integrity of every other organism. Health or integrity of organisms cannot be seen as a stable situation, but is a continuously re-acquired and actively maintained condition of physiological equilibrium (homeostasis).

## 6.2. Different Types of Wound Healing as Manifestation of the Healing Process

The various types of attacks that the human body is subjected to summon various types of reactions from the organism. When harmed, the damaged tissue itself initiates a response in the form of a specific and fitting *healing process*. We can, therefore, distinguish among healing processes as a reaction to cuts or burns, or to wounds caused by radiation, or the immune response to a viral or bacterial infection. The various reactions are different *wound healing processes*, which are specific manifestations of the general healing process.

These different wound healing processes usually make use of mechanisms which involve various types of cells and factors (mediators) dissolved in body fluids. It is evident that the same cells and mediators are active in the various types of wound healing process (such as the healing of a skin wound or the immunological immune response). The different wound healing processes, therefore, appear to 'use' the same 'available material'. This denotes a mutual connection and a common origin of these processes.

The relation of the general healing process and the various wound healing processes can also be traced back to evolution. Early in evolution, there was one general physiological healing process that slowly differentiated itself into more specific and ultimately highly complex constituent processes. Thus, the healing process in the amoeba still manifests

itself as one whole while, in humans, the general healing process has differentiated itself into specialized wound healing processes. The general healing process as an entity has developed into a variety of processes.

**Summary**: every type of wound healing process can ultimately be understood as a variation of the original, universal healing process. The *healing process* is understood to be the general, central process that has various, specific manifestations in the different wound healing processes.

## 6.3. Characteristics of the Healing Process

We can learn about the concept of the universal healing process in humans by studying the common characteristics that are displayed in the various wound healing processes.

### Phasing

Every process takes time. Between the beginning and the end state of the process, a number of transformations take place that follow each other orderly. Thus, each specific wound healing process (and, therefore, also the healing process) proceeds in an ordered sequence through a number of *phases*.

We have seen that each phase has itself a *definite course in time*. Each phase consists of a start up process (initial stage), a central process (middle stage) and an end stage (result). From the start, the process builds up (stimulation and positive feedback play a role here). Then there is a plateau phase, followed by a slow extinguishing of the process (inhibition and negative feedback play a role here). These three sectional stages could be described in musical terms as crescendo, forte and decrescendo. Within the healing process, therefore, there is development which occurs *in phases*. The word 'phase' comes from the Greek 'phasis,' which means 'manifestation.' Each phase of the healing process is, taken in itself, yet again a process and has, itself, different stages.

The various phases of the healing process cannot be disconnected from each other. There

are, in fact, only flowing transitions and overlapping in time. Nonetheless, the phases differentiate themselves from each other on the basis of certain characteristic elements. The division into phases occurs on the basis of the description of such characteristic elements and their passage in time. We found four such phases in the healing process.

The healing process has its own *intrinsic rhythm in time.* The factor time plays an important role in every process. It seems that the healing process cannot be shortened by increasing the tempo. It can, however, be lengthened by slowing the tempo down. Each phase in the process has a minimum duration. Tempo differences are also dependent upon the type of damaged tissue (liver tissue heals faster than nerve tissue) and the place in the organism (for example, facial skin versus tibia skin). The tempo variation is, therefore, dependent upon spatial organization. The speed of the healing process is, of course, also dependent upon the general state of health of the person in question.

Each phase has, ultimately, its own characteristic developmental *task* in the process as a whole. It is not until one phase has been successfully completed that the next phase in the process can begin (fig. 6).

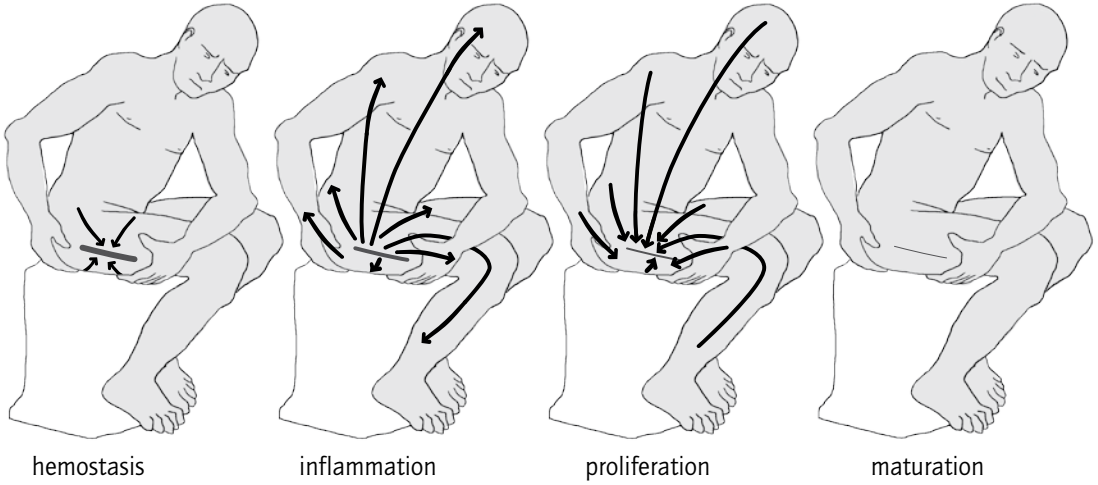



**Fig. 6. Dynamic differentiation subsequent phases**

## Balance

Every process is played out between two polar opposites; it balances, as it were, between two extremes. The opposites in tandem facilitate a development through the process that occurs between them. Thus, each process or phase is in a dynamic state of equilibrium.

In physiology, the state of equilibrium is also called homeostasis. This balance is an unstable condition and can topple in one of two directions. Two situations could then arise:

- **Physiological shift:** A temporary shift of the equilibrium can be necessary if, for a short time, a specific situation is desired. An example is: The blood is kept in a constant fluid state and balances between bleeding and clotting. As we know, when there is a bleeding wound the equilibrium shifts in the direction of coagulation.

- **Pathological diversion**: Under certain circumstances, the coordination of the healing process can fail or the healing process itself can become disrupted. The process derails in one of the extremes, which becomes dominant, and deteriorates into a *pathological* process. Then the involved phase of the wound healing no longer plays its role in the healing process (principle of salutogenesis), but starts to take part in a disease process (principle of the pathogenesis). The phase in question can, ultimately, become stuck in one of the two above-named extremes between which the process is played out. At that point, there is no longer a process, but rather a stable situation stranded in one extreme of the polarity. As soon as this is the case, we speak of *disease*.
  At that point, the developmental task of a specific phase can no longer be implemented. The stranded condition must be put back in motion and become a process again.
  We have described that, based on the two directions in which a phase can become diverted, we can differentiate, for each phase, between two types of pathology that result in two types of illness.

## Two Types of Illness

The two directions in which the balance of the healing process can shift have opposing, polar characteristics. One pole has a dissolving characteristic, the other pole a consolidating characteristic.

The central question in the treatment of disease is then clearly: how can we give the stranded healing process a new impulse and get it moving?

*Example of infection:* In acute infections, the inflammation phase in the healing process supports recovery (salutogenetic principle). There are, however, inflammatory processes that are no longer part of the normal self limiting wound healing process. Based on the two directions in which the inflammatory process can become derailed, we can differentiate between:

- The *acute* infection: When the healing process becomes acutely complicated by an infection, this may even lead to a sepsis. This is an extreme example of a disease state that diverges from the normal healing process toward the dissolving and expanding polarity (see 3.5.2.)
- The *chronic* infection: When an inflammatory process becomes chronic, unnoticed and continuous dormant inflammatory processes may arise which can be made visible through blood testing. If these inflammatory processes continue for a longer period of time, or if they increase in intensity, there is a chance of permanent tissue damage and of chronic degenerative disease, which diverge from the normal healing process towards the consolidating and contracting polarity. One clear example of this is rheumatoid arthritis

An increasing number of studies show that the process of chronic inflammation is also at the root of chronic diseases for which the inflammation is less apparent, such as arteriosclerosis, adipositas, and diabetes mellitus. To an increasing degree, the inflammatory process, as such, is being recognized as the common underlying cause of degenerative diseases.

HEALING PROCESS

Example: Wound healing process in infection

Example: Inflammatory phase

| Pathogenesis: Dissolving characteristic | Normal course (salutogenesis) | Pathogenesis: Consolidating characteristic |
|---|---|---|
| Acute clinical picture<br>Sepsis | Self limiting process<br>Recovery | Chronic clinical picture<br>Degenerative disease |

**Table 6.1: Summary of the described phenomena with acute and chronic infection as examples.**

## 6.4. Remodeling and Continual Renewal

The processes of breakdown, decay, and rebuilding described in the previous chapters do not only occur incidentally after injury. Within the boundaries of normal, healthy physiology, the organism is continually being broken down, decomposed, and reconstructed.
By *breakdown* we denote systematic decomposition, which is in contrast to decay, a form of decomposition that is not systematic. The systematic breakdown is characterized by the fact that the broken down elements are not lost but are made available for reuse. *Decay*, on the other hand, is a process by which the decomposed elements cannot be reused in the organism and must be disposed of.

### Necrosis (Decay)

During true decay, *necrosis*, there is an unfocused and non-systematic destruction of cells and tissues. We see this, for example, after extensive bruising or other injury in which a great deal of tissue dies off and must be disposed of.

### Apoptosis (Breakdown)

The breakdown of tissues and cells in apoptosis is an ordered sequential process. Apoptosis is a process of programmed cell death. 'Expert knowledge' of the structures to be broken down and rebuilt is essential in this process. In construction, a good demolition contractor is able to recover the maximum amount of recyclable material for reuse. A

systematic breakdown of body cells and tissues and the recycling of freed cell substances are characteristic of apoptosis. The definition of the word *breakdown*, as is used above, must, therefore, be taken literally as the opposite of rebuilding and forms a true contrast to decay. The impulse for apoptosis comes from the organism itself, the impulse for decay generally comes from outside the organism.
A clear example of what we mean here can be seen when we look once again at what happens daily within the skeleton. Our skeleton is continually being broken down – not only after a fracture – by bone-dissolving cells, the osteoclasts. At the same time, the bone is also being rebuilt again by bone-producing cells, the osteoblasts. These processes take place under the influence of the mechanical forces which the skeleton is subjected to. A spatial structure of thin bone spicules is formed as a consequence of these mechanical forces. This is a process comparable to the formation of stress lines in the skin.

What is extraordinary about the physiological breakdown and rebuilding is that no scar tissue is formed. Nonetheless, there is an on-going replacement of the body's own, well-differentiated tissue. Interestingly, fetal wounds also do not leave a scar.

In the wound healing process when tissue elements must be disposed of there is also breakdown through apoptosis. This casts a special light on the wound healing process. In this respect, wound healing is related to the physiological recovery processes described above and, as such, forms *part of the normal physiology of the organism.*

It may have become clear that the ancient Greek phrase 'panta rhei' (everything flows, Heraclite, 500 B.C.) enables the correct approach to the organic world (see **BOLK**'s Companion Biochemistry, section 2.1.). This also clarifies how the organism breaks down and rebuilds in a healthy equilibrium within the context of *self-regulation.*

## 6.5. Self-Regulation as an Organic Function

*Self-regulation* is perhaps the most typical vital function of organisms which pervades everything, which creates and steers differentiated processes, and ensures that they are in tune with one another. Self-regulation forms the basis of the integrity of the organism. How does self-regulation function and how is it maintained?

A dynamic conceptual method that includes graphic and phenomenological elements can give the discerning ability that matches organic systems. The phenomenological approach in systems biology offers a method to gain insight into this. The objective of this Companion is to provide such a phenomenological description of the wound healing process and its self-regulating ability. Below, we will summarize the four phases of the wound healing process in the light of self-regulation.

**Wound Healing as a Self-Regulating Process**

We have discussed and characterized, in detail, the phases of the wound healing process. The result of the phases in wound healing are:

| | |
|---|---|
| *Thrombus forming:* | recovery of the integrity of the organism |
| *Inflammation:* | recovery of the interaction of the wound region with the rest of the organism |
| *Proliferation:* | recovery of lost tissue in the wound area |
| *Maturation:* | recovery of the original form of the organism |

The activities in wound healing develop from the acute process to save the **integrity** of the organism in general to a gradual recovery of the authentic physical form of the organism. That means that the organism, during thrombus formation, first ensures its own existence and only then instigates other processes such as inflammation, proliferation, and maturation to repair the specific damage that has been incurred through the injury.

These later phases become increasingly more specific:

- Inflammation focuses on reinstalling the interaction of the wound region to its environment. The immune system and nervous system activate processes throughout the entire organism in this phase. These are **interactive** reflexive functions analogous to the reflex of the nervous system. The nervous system is an organ system that is characteristic for animal life (see also **BOLK**'s Companion Immunology). Recognition and digestion of the material to be removed play an important role here
- The proliferation phase is concerned with the production of tissue continuity through growth and regeneration, a characteristic **vegetative** process
- The maturation phase is the most specific when, under the influence of **physical mechanical forces**, the specialized tissue configuration, adapted to the region where the wound is situated, is restored.

The phases of wound healing are, thus, related. They are also connected with each other by the circumstance that processes of the previous phase always initiate the following phase. At the same time, the original impulse for healing is already present in undamaged tissue and normal physiological processes. When wound healing is initiated, the continuously present equilibrium in the tissues is temporarily diverted by the substances that are released through the injury. The balance between growth and breakdown is tipped and breakdown gains the upper hand at first until, through the self-regulated process of wound healing, the integrity of the organism is restored.
The role of the equilibrium in the various phases has been discussed:

- In hemostasis, the balance between clotting and bleeding in the blood is temporarily shifted in the direction of clotting
- In inflammation, the equilibrium between 'warming up' and 'cooling down' is temporarily shifted in the direction of warming up (inflammare = to set on fire)
- In the proliferation phase, the equilibrium between growth and differentiation is temporarily shifted in the direction of growth
- In the maturation phase, the equilibrium between the specialized shape of the scar and the authentic form of the organism as a whole is definitively shifted in the direction of the integration of the specialized shape of the scar into the physical form of the organism

The healing process reestablishes the integrity of the organism in changing circumstances and makes possible a continuous renewal of the organism to adapt to new situations.

*The coordination of the phases of the wound healing process and the described shifting dynamic equilibrium make it clear that the healing process is part of self-regulation in the human organism.*

# *7. The 'Organ of Repair' and the Metaphor*

## 7.1. The 'Organ of Repair'

The established sequence of events that occur in an organism after an injury form, as has emerged from section 6.4 and 6.5, a closed cycle. The sequence of hemostasis, inflammation, proliferation, and maturation is an essential condition for the successful completion of the healing process. The cycle of healing and repair is self-regulating.

Now, we would like to return to the question in the introduction concerning the coordination of the healing process (see 1.4.). After all, the healing process, in the manifestation of the various wound healing processes as described in section 6.2., appears to progress in a completely coordinated manner. This coordination falls within t*he self-regulating ability of the organism* and is, as such, a typical phenomenon of life. The healing process is ultimate proof of the organic unity and organizational level of the organism.
Which forces are active here?

## 7.2. Integrating Forces

We have seen that the wound healing process begins with recovery of the integrity of the organism as a whole and ends with recovery of the integrity of the form and functionality of the organism. Starting with hemostasis, the *integrating forces* immediately set the stage for the healing process and initiate the following phases chronologically. Because the activity of the two interim phases, inflammation and proliferation, is in tune with the activity of the environment of the injured tissue, these phases are also permeated with integrating forces.
We could say that, in coordinating the healing process, the *integrating forces preserve the self-regulation of the organism.*

In the healing process, the integrating forces work in a manner comparable to regulating forces in an independently functioning organ, such as the liver. In this sense, we could

also call the healing process an 'Organ of Repair'. This 'Organ of Repair' initiates and coordinates all of the essential functions and forces. In a functional sense, it unites process development, coordination, and a flexible changeability and has, as such, the following characteristic qualities:

- An integrating and coordinating function in the healing process and
- A capacity for metamorphosis that is expressed in the differentiated healing processes

There is no known physical coordination center for the healing process or 'center for self-regulation'. Neither is there a known physical central regulating mediator that provides direction to the course of the process. When we bear in mind that, moreover, the healing reaction in each phase is – in time, space, and intensity – precisely attuned to the place, the nature, and the severity of the injury, then the entire process, in all its modulations, becomes transparent as an *organic phenomenon: the Organ of Repair.*

## 7.3. Phenomenology of the 'Organ of Repair'

What does the organ of repair look like?
Its form is changeable in time, as is described at the beginning of the chapters on hemostasis, inflammation, proliferation, and maturation. Initially, only a primary thrombus is visible, then the secondary thrombus, then come the phenomena of rubor, calor, dolor, and tumor, then granulation tissue becomes visible and, finally, the scar tissue contracts so that it becomes (nearly) invisible.
Alongside of this, during each phase of the activity of the organ of repair, there are both breakdown and rebuilding processes going on.

We can provide insight into the processes in an organ of repair in the following manner:
Each phase lasts increasingly longer than the previous one: hemostasis takes anywhere from a couple of minutes to an hour. Inflammation takes days, proliferation takes months, and maturation takes up to approximately a year after the injury. The phases also flow into each other and exist, in part, simultaneously (fig. 7).

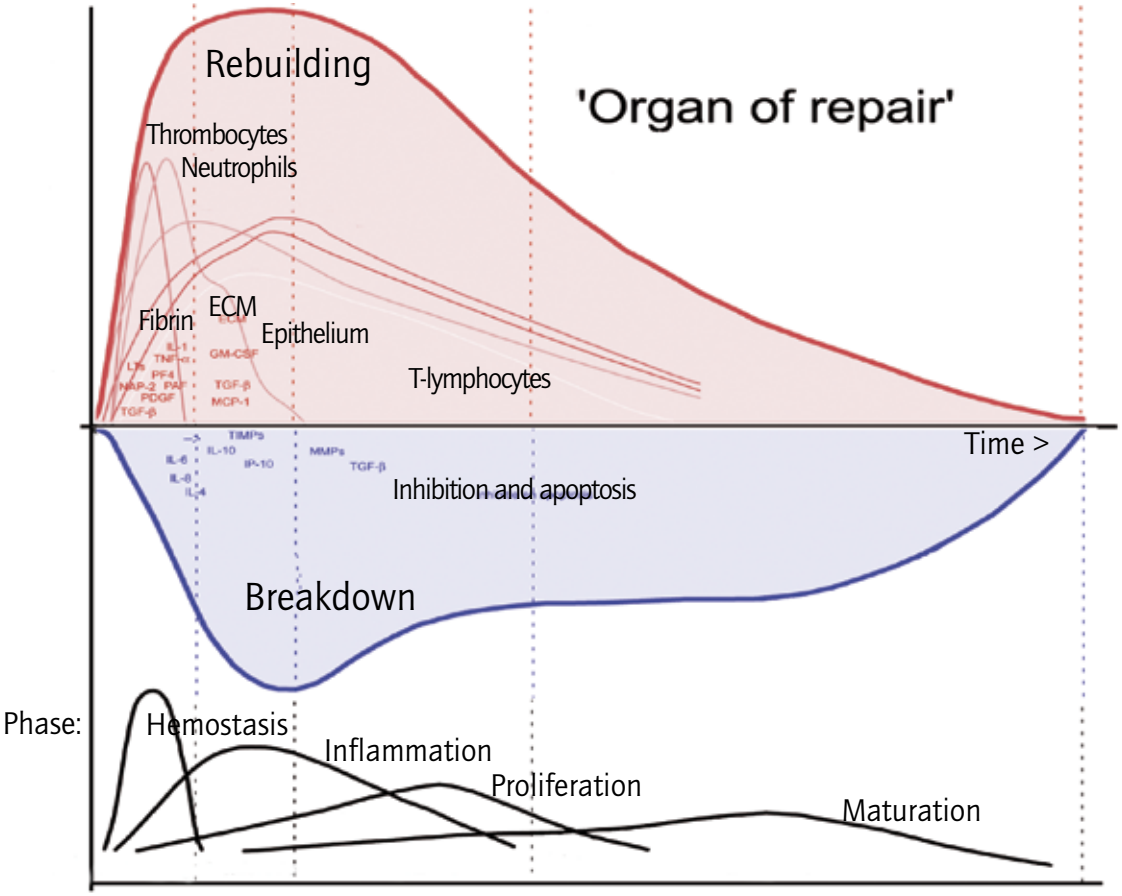



**Fig. 7. The 'Organ of Repair'**

## 7.4. Gaining Insight by Means of a Metaphor

The multiform and multiple interaction among cells, mediators, organs, neurotransmitters, immunological factors, and tissues stimulates the natural inclination of authors of scientific works to use the metaphor as a didactic tool. A metaphor appears in the literature wherever the definition fails. It can play an important role as a didactic tool in providing insight into (patho)physiological processes. Judging by the great number of authors that have intuitively understood this and have used the metaphor of orchestration for the wound healing process, this appears to be a pertinent metaphor in the field. The concept of the 'orchestrated functions' is a typical outcome of a systems biology approach. The study of natural processes seems to hand us, as a matter of course, this method of observation.

Robbins writes:
*'The magic behind the seemingly precise orchestration of these events under normal conditions remains beyond our grasp...'*

The metaphor of the orchestration allows the reader to experience a process that is structured in time, can be subdivided into various phases, and in which the musical theme and its metamorphoses are leading. And, it also shows that a composer (the self regulation of the organism) and a conductor (the organ of repair) were essential for recreating the musical composition. Finally, metaphors help the reader learn to 'think organically'!

## 7.5. Further Reading on the Practical Application of the Organ of Repair Presented in this Companion Recommended

After the first edition of this Companion, the concept of the Healing Process as described above was further developed. In two subsequent Bolk's Companions for the Practice of Medicine, we demonstrated how this concept can be applied and aids the understanding and classification of disease and its therapeutic consequences. (See the Bolk's Companions 'Respiratory System Disorders and Therapy, from a New Dynamic

Viewpoint' – Tellingen 2009 - and 'Depressive Disorders, An Integral Psychiatric Approach' – Gerven 2010).

In addition, an article will be published that describes the healing process as it relates to the fourfold view that is known in anthroposophical spiritual science and anthroposophical medicine. (Wie wirkt Heilung? Das „Heilungsorgan" als übersinnliche Organisation des Heilprozesses und als Grundlage zum Verständnis von Gesundheit, Krankheit und Therapie. How does Healing work? The Organ of Repair as Invisible Organization of the Healing Process and as the Basis for Understanding Health, Disease, and Therapeutics. Scheffers submitted).

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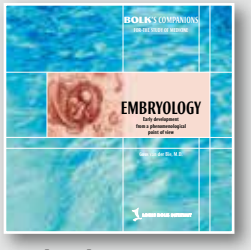


**Embryology**
**Early Development from a Phenomenological Point of View**

Guus van der Bie, M.D.
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**

Christina van Tellingen, M.D.
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.

# BOLK'S COMPANIONS FOR THE STUDY OF MEDICINE

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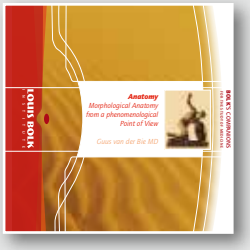



**Anatomy**
**Morphological Anatomy from a Phenomenological Point-of View**

Guus van der Bie, M.D.
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**

Christina van Tellingen, M.D.
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.


**Immunology**
**Self and Non-self from a Phenomenological Point of View**

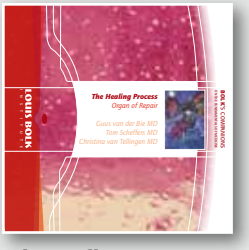
Guus van der Bie MD
Publicationnumber GVO 05

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.


**Pharmacology**
**Selected Topics from a Phenomenological Point of View**

Christina van Tellingen MD
Publicationnumber GVO 06

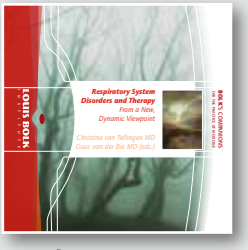
Pharmacology gives us insight into the way organic processes change when foreign compounds are introduced into the organism. Pharmacology is a changeable subject, depending on the needs and knowledge of the time. Can we find an inner coherence in the manifold ways compounds influence organisms? What 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
Christina van Tellingen MD
Publicationnumber GVO 07

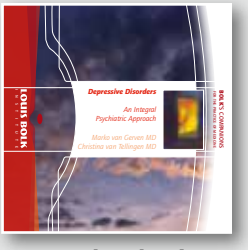
After finalizing the series BOLK'S Companions for the Study of Medicine for the moment, this module on The Healing Process introduces a new series of BOLK'S Companions that studies the Practice of Medicine. In it, we research the healing process itself. There proved to be an enormous volume of scientific 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

Christina 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
Christina 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.

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# The Healing Process

## Organ of Repair

After finalizing the series **BOLK**'S Companions for the Study of Medicine, this module on The Healing Process introduces a new series of **BOLK**'S Companions that studies the Fundamentals and 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. We collected the data and, with the aid of phenomenological method, classified and interpreted them. 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.