Endocrinology

A methodological approach towards integrative understanding

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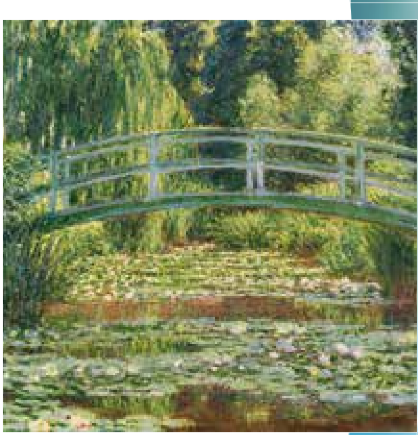

BOLK'S COMPANIONS
ON THE PRACTICE OF MEDICINE

LOUIS BOLK
INSTITUTE

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The Kingfisher Companion Group aspires to broaden the perspective of science by elucidating the context behind health and disease. To this aim, the foundation strives to pioneer investigative methods to complement and innovate conventional scientific views and research techniques. It examines the exploration of conscious-intuitive study in the research and practice of medicine such as the 4-step approach employed in the Bolk's series. The Kingfisher Foundation supports this development of new approaches for medical practice both logistically and financially.
The Kingfisher Companion Group works at the Louis Bolk Institute where scientific research to further the development of sustainable agriculture, nutrition, and healthcare has been conducted since 1976. The basic tenet of the Institute regarding the life sciences is that nature is the source of knowledge about life. Through its groundbreaking research, the institute seeks to contribute to a healthy future for people, animals, and the environment.

About Professor Louis Bolk

Louis Bolk (1866-1930) was a professor of anatomy and embryology at the University of Amsterdam. He developed and employed comparative scientific methods of investigation that conveyed new insights into his subjects. With the insights he gained, he was able to place his subjects into a meaningful context. To employ his method, he instructed his students to use the "macroscope" rather than the microscope!

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About the authors

Guus van der Bie MD (1945) worked as a lecturer at the Department of Medical Anatomy and Embryology at Utrecht State University, The Netherlands, from 1967 to1976. He was a family doctor from 1974 to 2008. As a retired family physician, he continued to educate physicians, therapists, and medical students at Utrecht State University and the University of Witten/Herdecke, Germany. At Utrecht State University, he coordinated education in Complementary and Alternative Medicine and he currently teaches Anthroposophical Medicine in Witten/Herdecke. He is a member of the Medical Section of the School of Spiritual Science at the Goetheanum in Dornach, Switzerland.

Ricardo Ghelman MD PhD (1963) has been a practicing pediatrician and family physician in Brazil since the late 1980s. From 1997 to 1999 he was trained at Pishwanton Center, Scotland in the use of Goethean phenomenological research. After earning his master's degree in Anatomy at São Paulo University in 2000, Brazil, he worked as a professor of Histology and Embryology. He concluded his doctorate thesis in the field of reproductive toxicology in the Department of Obstetrics at Federal University of São Paulo in 2003. From 2007 to 2014 he coordinated the Research Center of Anthroposophic Medicine in the same University, where he started his postdoctoral research in the Department of Neurology in 2014, focusing on the application of anthroposophic medication for the treatment of chronic pain.

Loes van den Heuvel (1976) graduated in 2001 cum laude as a physician from Erasmus University in Rotterdam, the Netherlands. Since 2006, she has worked as a family physician at the Utrecht Center for Physicians and Therapists, a healthcare model wherein clinicians and therapists integrate both conventional and anthroposophic approaches. She joined the Kingfisher Companions Group in 2010 and is a member of the Medical Section of the School of Spiritual Science at the Goetheanum in Dornach, Switzerland.

Kore Luske MD (1976) works as a family physician at the Physicians' and Therapists' Center Aquamarijn, Arnhem, The Netherlands. She joined the Kingfisher Companion Group in 2010 and in 2014, completed her education as an anthroposophical doctor. Ever since she was a student she has been inspired by the phenomenological research method, which has been the cornerstone of her recent research in endocrinology.
In addition to her work as a family physician, she also serves as a medical educator for medical students, nurses, and therapists.

About the Project

The project *Renewal of Medical Education* aims to produce Companions that complement medical study by demonstrating how the insights of current biomedical science can be broadened by the insights of inclusive thinking inherent to comparative science. Companion authors apply a scientific methodology that uses four consecutive steps to achieve an integrated understanding of wellness and disease. These steps are described in the foreword as the *4-step* approach. This approach seeks to recapture a coherent and comprehensive understanding of human nature and the environment after the segmentation that follows fact-finding research.

BOLK'S COMPANIONS FOR THE STUDY OF MEDICINE are designed to complement medical education, specifically as it relates to human facets of current biomedical sciences

BOLK'S COMPANIONS FOR THE PRACTICE OF MEDICINE contribute to a broader scientific basis for the clinical years of medical study and for developing the intuitive facets of medical practice.

BOLK'S COMPANIONS ON THE FUNDAMENTALS OF MEDICINE explore fundamental medical concepts and seek to broaden the medical paradigm.

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Guus van der Bie
Ricardo Ghelman
Loes van den Heuvel
Kore Luske

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Preface

As work on the Bolk's Companion series has progressed, it has gradually become clear that more thoroughness was warranted in the description of the *4-step* approach that we employ throughout the Companions in two areas in particular. First, we wanted to describe the approach more specifically than had previously been done.

Secondly, the authors of this Endocrinology Companion wanted to illustrate how the *4-step* approach may uncover an important link between the patient's physical symptoms and accompanying psychological phenomena. As such, this Companion intends to delve deeper to understand the interface between psyche and soma and bring to light concepts of psychosomatic medicine. Endocrinology, we found, lends itself particularly well to such exploration.

This Companion was created by integrating an in-depth description of the *4-step* approach and the specific insights that we found using this approach while exploring psychosomatic connections in endocrinology.

1. Introduction: Psychosomatics

by Loes van den Heuvel MD

Is there a direct link between somatic symptoms and mental phenomena? This is an important question in medicine given that somatic and mental symptoms often occur simultaneously in clinical practice.

Exercise: Observe the correlation between respiration and consciousness in yourself
Sit up straight with both feet on the ground. Observe your breathing. It may be helpful to close your eyes. Take about 30 seconds to do this.

Then observe a different breathing pattern. Breathe in deeply and exhale the extra air only partially. As you continue to breathe and retain this extra volume, your pulmonary residual volume is increased. What do you observe now? Has the movement pattern changed anywhere in your body? Do you notice a particular mood or emotion that accompanies this breath? Has your awareness changed? Take about a minute to examine any physical or emotional changes.

Change your breathing pattern once again.
Breathe out deeply and as you do so, allow your abdomen to move with the rhythm of the breath: filling with your inhalation and contracting with your exhalation. Continue this for about a minute and observe what changes take place in your body, conscious awareness, or in your mood.

The above exercise demonstrates that changing breathing patterns can have an effect on mental sensation and the question arises, how do physical processes relate to conscious awareness, psychic phenomena, and behavior?

This question is very relevant in the management of patients with endocrine disease. Changes in mood, consciousness, and behavior may be the first clue to underlying endocrine deregulation. Mental symptoms of physical disease impact the quality of life significantly.

This Companion uses the *4-step* approach to study the connection between the physiology and pathology of the endocrine system and mental phenomena and mood changes that accompany them.

In Chapter 2, the *4-step* approach as applied in this Companion is described briefly.

Chapters 3 and 4 cover the most common endocrine problems: thyroid disorders and diabetes. Each chapter begins with a case history and notes on the relevant (patho)physiology. The use of the *4-step* approach is explicit in Chapter 3; in Chapter 4, it is used implicitly in the case description.

In Chapter 5, the systemic nature of endocrine disease is addressed from a phenomenological, broad perspective.

Chapter 6 discusses the *4-step* approach in clinical practice more in depth and describes its added value.

Chapter 7 summarizes the conclusions of this Companion and discusses its possible significance for healthcare practice.

This Companion is an attempt to make a tangible and meaningful contribution to a bio-psycho-social approach to endocrine disease and to the overall humanization of medicine (Smith et al 2013).

2. ***Description of the*** *4-step* **Approach**
by Loes van den Heuvel MD

This chapter is an introduction to the 4-step approach. A more detailed account is laid out in Chapter 6.

Systematizing an approach to any human aspect is typically a dry and sterilizing process. As a counter-balance to that conception, we will introduce a technique that is hands-on and meaningful for practicing professionals. Both knowledge of the scientific basis of disease as well as clinical skills are essential when deciding on therapeutic measures. In theory, detailed guidelines, protocols, and decision trees are available to facilitate responsible decision-making, but the daily reality of clinical practice is often unique (Stolper 2011) and decision-making is in fact a much more dynamic and much less systematic process. Clinical competence has a sort of dual nature: factual knowledge and practical skills. The medical practitioner must be an expert at integrating both.

Can knowledge and skills be integrated into one single approach to systematize therapeutic decision-making and in the process, help clinicians to develop their clinical intuition? (Stolper 2011).

The *4-step* approach makes use of expertise, which encompasses both clinical knowledge and skill. It presents a qualitative picture of the symptoms, disease, and the patient. This may lead to a clinical solution for the patient that allows for better physical as well as emotional, and social functioning. This Companion uses the *4-step* approach to synthesize the strengths of scientific and experiential knowledge, which can be used to develop and foster fine-tuned therapeutic intuition.

2.1. Basic Orientation

The clinician's general orientation determines, to a large extent, the clinical questions he/she poses and thus, which answers he/she will or will not discover. This Companion uses the *4-step* approach to unite and extend the strength of scientific knowledge with the strength of experiential knowledge to facilitate the process of acquiring *skilled therapeutic intuition.* In order to reach this objective, the cultivation of *four basic attitudes* is required. These four basic attitudes are each a prerequisite for walking through one of the steps of the *4-step* approach.

- **The spectator attitude**

This attitude is analytic and necessary to clearly and precisely describe the facts and details of a patient's illness with the end goal of quantification of the disease process where possible. This attitude is necessary in the first step of defining the facts (see below).

- **The participating attitude**

The clinician processes the facts related to the patient and the disease and tries to find their intrinsic dynamic pattern in the second step. By inwardly processing the facts he/she becomes more intimate with the data. The participating attitude is crucial for the second step of the *4-step* approach in finding the underlying dynamic (disease) pattern of the facts.

- **The empathic attitude**

The clinician adds professional empathy to the observation of the dynamic patterns of the patient's disease. He/she attempts to describe his/her experience as it relates to the factual patterns of the second step. Thus, participating becomes empathizing: practicing this attitude is important in the third step of this approach.

- **The intuitive attitude**

This attitude is actually a process of *actively* "holding back." Creating openness may enable intuition to emerge which is essential for the fourth step of this approach. This attitude may lead the clinician to discover a picture of the initial disease impetus that is active on a deeper level in the presenting patient.

The *4-step* approach used in this Companion offers insight into four different levels of investigation, supported by the four above mentioned attitudes, in this case applied to endocrine research. The steps are:

1. Describing the **signs and symptoms**: investigating the disease phenomena as a conglomeration of facts, requiring the spectator attitude;
2. Examining the **dynamic pattern and context** of the signs and symptoms: endocrine processes work in a particular area of the body in specific dynamic interactions. Seemingly disparate phenomena reveal a dynamic relationship. The participating attitude is required in this step;
3. Recognizing and qualitatively characterizing **disease progression over time**: each disease has several stages that develop in space and time on the basis of the above dynamic pattern. The prerequisite for understanding this process is the empathic attitude;
4. Appreciating the **genesis of the disease** in the particular patient: an understanding emerges of the nature of the **pathogenic stimulus** based on what was perceived in previous steps. This provides insight into what might be therapeutically useful for the individual patient. It requires a skilled intuitive attitude.

The *4-step* approach may promote the conscious effort of physicians and therapists to develop an understanding of the context of disease processes on the basis of skilled empathic and intuitive abilities, thereby enhancing therapeutic potential. This Companion is an attempt towards a scientific approach to return details to their context. Examples of such context may be: the individual including their psychosomatic symptoms, the ecosystem, the organism or its subsystems.

In Chapters 3, 4, and 5, practical examples of these four steps are described and utilized in different ways; we use the analogy of music and its variations on the same theme to elucidate these four steps and their clinical applications. This is consistent with what our readers may experience in practice, wherein the approach varies based on the skills of the individual physician, the specific disease, and the context of the individual patient. Sometimes the process is more methodical; in other situations the steps are taken in a different order and/or simultaneously to achieve a similar result.

For the purpose of this Companion, we have chosen to first demonstrate the *4-step* in the approach of endocrine disease before describing the overall theory in greater depth in Chapter 6. Whereas the scientific basis of the *4-step* approach is outlined in the Companion Wholeness in Science (Van der Bie 2012), this Companion focuses on its practical application in the context of endocrinology. Readers are invited to “join in” with this approach. You can practice the *4-step* approach simply by reading the Companion and allowing “formal knowledge” and “experiential knowledge” to coalesce into a skilled therapeutic intuition.

3. *The Thyroid Hormone System*
by Loes van den Heuvel MD

This chapter approaches the thyroid hormone system as part of the whole human organism using the 4-step approach described in Chapters 2 and 6.

In practice, the four steps described in Chapters 2 and 6 are typically not executed sequentially, but rather simultaneously in twos or threes or even in a completely different order.

The purpose of this particular chapter is to demonstrate the *4-step* approach in a more abstract situation. As such, the steps are presented and used in sequential order by way of two case histories.

In contrast to applying general knowledge, this chapter describes facts and patterns of individual patients to ultimately arrive at an *individualized* therapy for the patient. Physicians must also use their *individual* clinical skills with this approach. By subsequently comparing the acquired insights to standard endocrine physiology more comprehensive and generally applicable insights come into view.

As a family physician, I regularly see patients with acute hypo- or hyperthyroidism or with a history of thyroid disease in my practice. Often, these patients take medication throughout their lives to keep their thyroid levels within normal range. Some patients wonder what they themselves can do to contribute to their health. Many patients have secondary and residual problems on a physical, emotional, or social level, despite having biochemically normal hormone readings.

This chapter examines how the *4-step* approach can lead to a scientifically founded *qualitative picture of the pathogenesis* of thyroid disease in individual patients that addresses not only somatic but also psychosomatic and psychosocial symptoms. This will inspire a better understanding in the reader of thyroid disorders and their wide spectrum of symptoms.

First, I will present the case history of a patient with **hypothyroidism** followed by a case report of a **hyperthyroid** patient. The emphasis will be on how patients themselves experience their complaints. Subsequently, the physiology and pathophysiology of the thyroid hormone system is described. We will conclude with individualized therapeutic recommendations.

3.1. History of a Patient with Hypothyroidism

3.1.1. First Step: Describing the Factual Signs and Symptoms

Sarah is a 25-year-old woman who uses thyroid replacement hormone for hypothyroidism. She has also been previously seen for pain in her knees and fatigue. She works as a group leader at a daycare center. When she enters the office, she appears small in stature and obese. I ask how her hypothyroidism has developed and about her complaints.

'I was a happy and slim girl in elementary school. In puberty, I suddenly increased in size. I was tired and lethargic. When I was 19 years old, blood tests showed that my thyroid levels were low but no medication was required or recommended.

The fatigue felt heavy, as if I had to lug a bag of potatoes around. I felt myself expanding. Despite the fatigue, I was glad to be active: rest did not improve my symptoms; I had no control over them. Initially, I took a dietary supplement that seemed to reduce my symptoms.

When I turned 22, I became depressed for a few months. At that point, I did not go to the doctor. During this time I was lethargic, fatigued, and could not persuade myself to do anything. I was

still working and was maintaining an outward façade, but I don't really know how I got through that time. From an early age my strategy has been to maintain a positive outward façade, even when I am suffering inside. I think the depression had to do with not living the life that I wanted to live or expressing what I really needed for myself.
After this episode, I made different choices and the depression resolved.

Later, other complaints developed: I lost my appetite, quickly felt full after eating, and after eating spinach my stool color did not turned green till three days later. Swallowing was also difficult. It felt like my throat was blocked and I also experienced trouble expressing my true feelings to other people.

The fatigue worsened and my limbs became heavier: I was slow, significantly overweight, and my knees hurt. I did not feel cold[1]. I slept soundly and was never awakened by noise at night, but then it would take an hour and three cups of coffee to wake up in the morning. During the day, it felt like there was a kind of fog between me and the outside world. Stimuli seemed weak or delayed. At work, it took longer before I reacted to something happening with the children. When there were too many stimuli, however, I noticed they did seem to affect me. I could not deal with them and would start scowling at my colleagues.

When blood tests showed that my thyroid levels were really low, I started on thyroid hormone. At first I had trouble falling asleep, but that disappeared. The medication eased a lot of my symptoms, except for being overweight.'

Sarah relates some of the classic signs and symptoms of hypothyroidism: fatigue, sluggishness, obesity, delayed intestinal passage, and depression. She had problems swallowing, speech problems, and a globus sensation[2] in her neck without the presence of a goiter. On exam, her voice was normal[3] as were pulse and blood pressure. She did not have myxedema and her body temperature was normal.

1 a customary symptom in hypothyroidism
2 a feeling as if something is stuck in the throat
3 had not become lower or cracking at the time

3.1.2. Second Step: Examining the Dynamic Pattern and Context of the Facts

Next, we will examine the *dynamic context* of the described signs and symptoms which requires an attitude of participation (2.1.).

Sarah describes the weight increase as "expanding." Her outer body circumference increases on all sides. Roundness predominates and details lose their shape.

She experiences internal stagnation manifesting as slower peristaltic movements in the upper GI, resulting in less food intake and a loss of appetite.

When she speaks about the lethargy before she started using thyroxine, she describes strain: she wants to move, but her body tends toward languish. She feels pulled between these two tendencies. A sluggish dense dynamic results. Fatigue is ever-present and does not remit no matter how much she sleeps or how much caffeine she uses. Her speech and swallowing change and her throat feels blocked.

During normal sleep, the body is given over to gravity. In Sarah, this process is intensified. She wakes up slowly. The sleep state is expanding as it were, at the expense of the waking state.
During the day, Sarah has delayed perception and reaction. Stimuli are delayed, but their effect is greater and her response suddenly becomes quite defensive. During her periods of depression, there is a discrepancy between her inner world and the outside world. The dynamic of her inner world is variable; in contrast, what comes to expression in the outside world—her façade—is less variable and not a reflection of her inner world. What she experiences in her inner world has little relationship with her appearance: she feels like something envelopes her.

Resume

The patient's story reveals the following dynamic patterns that have both physical and psychological facets:

- Sense of inner sluggishness and stagnation
- Increasing size, denseness
- Sense of inertia in the "exchange" between inside and outside; feeling enveloped

3.1.3. Third Step: Characterizing the Qualities of the Disease Process

The third step entails that I prepare for characterizing the *qualities* of the disease process by occupying myself with the dynamic context of the signs and symptoms (step 2) using a compassionate attitude (2.1.).

In the third step, I immerse myself in the process of increasing body size, at the same time feeling enveloped and experiencing qualities such as "expanding," "filling up," and "becoming heavy" as well as sluggishness, languish, and internal stagnation. My focus on the outside world is impeded and I experience being more introverted: inside I feel dreamy, sleepy, and slow, while simultaneously feeling at the mercy of what is coming towards me. It requires significantly more effort to ford the divide between my inner and outer worlds. When I attempt to bridge this divide, I feel like I lose my inner world. My inner world feels abandoned and I do not experience myself as whole. This inner qualitative experience is schematically represented in Table 3.1.

In scientific papers, *quantitative* concepts are definable in exact figures and unambiguous terms. *Qualitative* endeavors are much harder to describe and conceptualize. To fully conceptualize the quality of the patient's signs and symptoms, participation on the part of the reader is required. Grasping the qualitative aspects of disease appeals to the physician's individual skill of empathizing with the patient. My attempt to visualize this in drawing (or even better the reader's own drawing) attempts to generalize the experience of these qualities.

Table 3.1. Schematic Representation of the Qualitative Experience of Hypothyroidism

Signs and Symptoms	Dynamic Pattern	Disease Process
Increase in body weight, slow digestion, fatigue, globus symptoms, deepened sleep, slower reaction time, melancholy mood, outer appearance does not match inner state	Internal stagnation, increasing body size, stagnant exchange between inner and outer world	Increasing size, becoming full, being hampered to reach out, diffuse awareness, greater distance between inner and outer worlds, increased isolation of inner world

In section 3.3., the drawing below is compared to my drawing for the following case study. In these drawings, I attempt to show qualities in three areas: the inner world, the world outside, and the area in between.

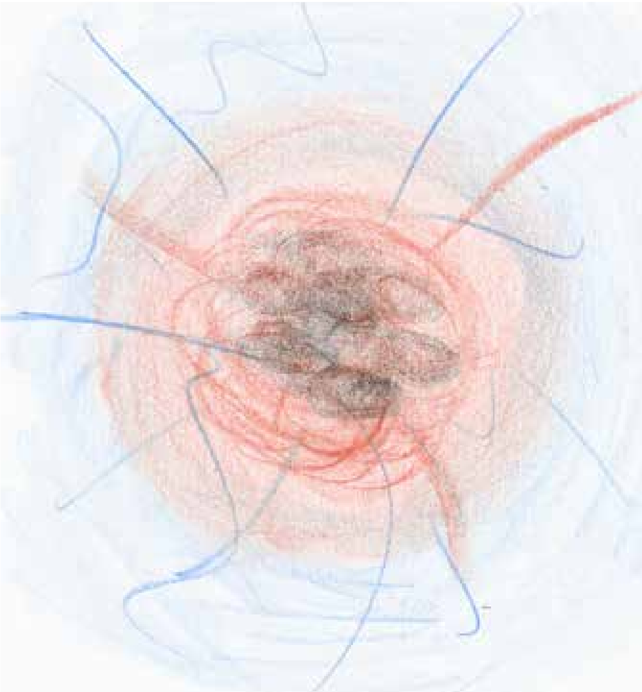


Figure 3.1. Pictorial Representation of Qualities of Hypothyroidism

The inner world of consciousness tends to become full, heavy, and dark. I have expressed this in the picture in dark gray and spherical structures. The outside world and the inside world are further apart from each other. The in-between area surrounds and conceals the inner world through its murky brown-grayish color. I have drawn the outside world in a misty blue. A number of outside stimuli (the lines in the drawing) do appear in the internal world and the inner world's response to them may be fierce. In general, there is a reduced interaction between the inside and outside.

Resume
Recognizing and characterizing the empathic experience of the individual patient's disease dynamics reveals *qualities of their disease process*: the experience of an expanding shell, congestion, struggle in reaching from the inside out, diffuse awareness, a greater distance to the outside world, and an inner world that feels abandoned.

3.1.4. Fourth Step: Qualitatively Identifying and Appreciating the Pathogenic Stimulus

In the fourth step we attempt to identify what the above mentioned qualities have in common. This may generate a picture of a person wishing to have a lively inner experience, open to the world, but who is inhibited in expressing herself. The inner and outer worlds do not function as a whole. This discrepancy is worsened by aggravating circumstances as the person gets caught in a body that tends to become denser.

One *qualitative* disease impetus in Sarah's case could be a reduced congruence between her inner and outer worlds on different levels. This may become a stimulus that triggers the *disease process* (that we identified in step 3), which primes the *dynamic disease pattern* we have described in step 2, and subsequently leads to specific *symptoms* that were described in step 1 (see also Chapter 6).

Table 3.2.

Disease Stimulus	Disease Process	Dynamic Pattern	Signs and Symptoms
Reduced congruence between inside and outside	Isolated inner world, becoming full, increasing size, diffuse awareness	Internal stagnation, increase in body size, stagnation in the exchange between inner and outer world	Increase in body weight, slow digestion, fatigue, globus symptoms, deepened sleep, slower reaction time not matching outer appearance

3.1.5. Concluding Remarks

The signs and symptoms of this patient with hypothyroidism articulate that the patient's inner world tends to shy away ever further from the outside world as the disease progresses. The distance between these worlds becomes amplified. Despite this distance, however, stimuli are experienced more intensely. This is a picture much like you see with macerated skin. The skin has a pathological watery thickening, there is a greater distance between inside and outside, but in effect, the skin's permeability is drastically increased, the barrier function severely disrupted. In a patient with hyperthyroidism, who will be described next, we also see a dynamic pattern resulting in a disrupted barrier function, but in a different manner (see section 3.2.5.).

Sarah perceived that her inner world was not in harmony with the outer world: she felt like she had not sufficiently shaped her life such that it could be coherent with her self-identity. When she began to make other choices, the quality changed and her depression decreased. During this period her hypothyroidism remained untreated.at a certain point, Sarah undertook her own measures to lessen her depression. Unfortunately, these were not sufficient to prevent further progression of her disease process. This does not imply that her change in behavior was inappropriate—indeed they may have contributed greatly to her emotional wellbeing and sense of self-efficacy. In hypertension, for example, stress reduction may be sufficient to decrease blood pressure to a safe and healthy level; other individuals may require additional measures, despite the fact that stress is a significant factor in the genesis of the disease.

Recognition of a disease impetus that generates the incongruence between inner and outer worlds may ascertain medical advice that enables the patient to develop or strengthen healthier qualities that counteract the disease process.

The therapeutic consequences for Sarah, based on this understanding, are described in paragraph 3.11.

The *4-step* approach as it was applied in this case history, not only examines disease patterns within the organism of the patient, it also identifies correlations between the patient and her social environment. If this is acknowledged and adequately assessed, it can offer direction to an individualized therapy for the patient.

3.2. A History of Hyperthyroidism

3.2.1. First Step: Describing Signs and Symptoms

Judith is 36 years old when she first experiences signs of thyroid deregulation. She is a happily employed physiotherapist working in a group practice. She follows additional training courses and teaches at a physiotherapy training program. In a brief time period, she develops various complaints such as diarrhea, increased heart rate, and shortness of breath. She visits her physician only after she herself treats a patient with a sports injury who has recently developed hyperthyroidism.

She energetically enters the office, but once seated it becomes noticeable that she is short of breath and appears exhausted. Her heart rate is 120/minute with a blood pressure of 124/84 mm Hg. Following a blood test, it becomes clear that her TSH levels are less than 0.02 mU/L (reference values: 0.30 to 4.00 mU/L) and free T_4 levels are 49 pmol/L (ref:. 11-25 pmol/L) in the presence of TSH receptor antibodies (21 IU/ml; ref <1 IU/ml).
Judith chooses not to initiate the suggested β-blockers or antithyroid medications immediately. In the subsequent period, she continues to work, but her symptoms worsen. Only when she takes adequate rest by taking a leave from work and starting art therapy and movement exercises (eurythmy) do her symptoms slowly improve. Her hormone levels also improve: free T_4 drops to 23 pmol/L and TSH receptor antibodies to 6 IU/ml. The TSH level remains immeasurably low.

After this period of illness, she relates her experience of her symptoms and how she had dealt with them:

'I looked different: I lost 7 kg of weight in a jiffy! My colleagues noticed that my face was sunken in. My skin was thinner and more yellow in color. I was suffering from a watery diarrhea roughly twice a day. My sister noticed that my voice was higher in pitch, as if I were nervous. Personally, I noticed a feeling of high tension in my body. I felt as if my breathing was too high in the chest. My resting heart rate increased. When I went running, I was not able to run even a hundred meters before I was completely out of breath and my heart rate was even higher afterwards. I continued to exhaust myself by maintaining my prior level of activity and my condition further deteriorated: I was tired, exhausted, and pooped.

I have continued to sleep well. It took maybe a little longer to fall asleep after a busy day. I had more trouble really relaxing because of my audible heartbeat. My husband commented that sometimes my breathing was quick, short, and shallow while I was sleeping. I woke up in the morning feeling tired. My knees would especially feel tired and even a bit sore. And as soon as I woke up, I got very hot in bed and would throw off the covers. Only after cooling down, would I be able to fall asleep again.

Everything that came from my external environment came fiercer and louder at me. I was not especially sensitive to noise or light, but I noticed that people seemed too close to me. What they said and were carrying emotionally seemed to have a greater impact. I was more quickly emotional at that time. I experienced more pressure, not necessarily appropriate to the situation or how I usually feel: I found my reactions to be quite odd! I noticed that I really could not communicate well with others or establish a connection with them. The hyperthyroidism made me feel less myself, as if I were lifted out of myself. The outside world seemed too close.

I was always psychologically stable. I felt highly capable and able to take on the world even when I was very busy or experiencing stress. I could relax and enjoy myself after being highly productive. During this illness, however, I began to feel that my body could no longer calm down and stress was constantly present. Eventually I became angry and did not want to have anything to do with patients: I could no longer be compassionate. I worked because others needed me, but I experienced no pleasure in it—not because I was depressed, but due to feelings of exhaustion and burnout.'

3.2.2. Second Step: Examining the Dynamic Pattern and Facts in Context

In order to find the dynamic disease patterns, we will elaborate upon Judith's symptoms similarly to how we did this in the previous case history, addressing the areas of body shape, digestion, energy, speech, sleep, the patient's experience of her inner and outer worlds, and of her mood.

Weight loss triggers the body to become narrower and more elongated; the body boundary moves inwards in a centripetal, concentrating gesture. The inner world of the body literally comes closer to the outer world as the underlying structures of bone, muscle, and tendon become more pronounced. The body shape pulls in and sticks out. The concave and convex shapes of the surface area alternate with each other more strongly, the surface comes out in sharp relief.

Bowel movement goes from the inside to the outside. In diarrhea there is increased motility: stool and water are less retained and there is a centrifugal, outgoing dynamic.
In general, the body's activity is increased. The accelerated heart rate increases the momentum of the blood and respiration is more superficial, as if "lifted." The dynamic thrust of the body is from the inside out, centrifugally. Eventually, Judith's metabolism creates a burning up from within.
The vocal cords are more taut and tense. The voice is higher and appears to carry further. The sound movements in the air are narrowed and vibrate faster.
When sleeping, Judith's body still has accelerated activity, lifted and tense, and her consciousness remains focused, a condition typical of the waking state.

Judith feels as if lifted out of herself and the space between her and the outside world has become smaller and narrowed. There seems to be more activity as well as more exchange at the interface between the inner and outer worlds.

Healthy, rhythmic alternation between tension and relaxation has changed to a sustained tautness. There is a kind of rigidity and hardness in both her physical and emotional realms. Judith is exhausted and feels internal emptiness. An angry mood is accompanied by repulsion and pushing away. This results in a decreased ability to reach out and connect her inner world with the world outside, as in empathizing with others.

Resume

The symptoms in Judith's story may be seen as a dynamic pattern of concentration and hardening in the body. Inside she feels empty, there is increased motility in general, particularly at the interface between the inner and outer world, including a centrifugal dynamic from the inside out.

3.2.3. Third Step: Characterizing the Qualities of the Disease Process

The third step attempts to recognize the *qualities* of the patients illness on the basis of the dynamic pattern of signs and symptoms.

As I do this third step as described in section 3.1.3., I become aware of a sense of raw vulnerability to the outside world, as if I were skinless, being alert and focused on the environment. I become aware of the experience of an involuntary relinquishing of myself to the outside. It almost feels like turning inside out. I sense being put under pressure by myself and reaching out too far beyond myself. Inside, I become aware of turmoil, excitement, and something akin to fleeing. It takes effort to focus on my inner self, as if I cannot quite get home.

It becomes clear that it takes all of my attention to hold myself together and I cannot concern myself with my own inner world or what is important to others. I feel empty inside and lose my inner focus.

I experience myself at the mercy of this situation.

Table 3.3. Summary of Hyperthyroid Symptoms

Signs and Symptoms	Dynamic Pattern	Disease Process
Decreased body weight, rapid digestion, exhaustion, high-pitched voice, restless sleep, heightened responsiveness, tense mood	Concentration and hardening of the physique, internal depletion, increased movements, centrifugal dynamics: from the inside out	Being unprotected, losing inner base, alert awareness of outside world, active and reacting

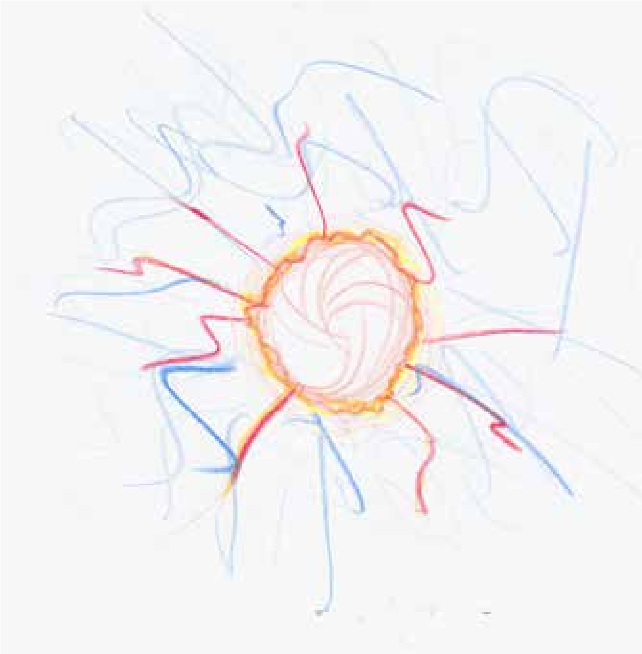


Figure 3.2. Pictorial Representation of Qualities of Hyperthyroidism

The inner world of consciousness becomes empty and has been moved to the periphery in terms of the spiraling orange lines; it becomes unprotected. I drew the narrowed margin between inner and outer world as lighting up in red and yellow: there is much tension and action represented by the red lines extending outward. The outer world I drew as clear and rich in various stimuli with a reduced exchange with the inner world.

Resume

By employing an empathetic attitude (2.1.) in looking at the disease dynamic, I can characterize the disease process as a sense of being unprotected, which is accompanied by a loss of inner basis, a heightened awareness, and greater sensitivity towards the external world.

3.2.4. Fourth Step: Qualitatively Identifying and Appreciating the Pathogenic Stimulus

Attempting to identify in the fourth step what the above mentioned qualities have in common may yield a picture of a person who is committed to actively participate and function in the outer world, but who ends up feeling at the mercy of it, burning up from the inside out, leaving her empty.

One important qualitative pathogenic stimulus in Judith’s case could be summarized as an excessive focus on the outside world due to a decreased barrier function.

Table 3.4.

Disease Stimulus	Disease Process	Dynamic Pattern	Signs and Symptoms
Excessive focus on the external world	Being unprotected, losing one's inner basis, alert awareness of the outside world	Concentration and hardening of the body, becoming depleted inside, more mobility, centrifugal dynamic: from the inside out	Decrease of body weight, rapid digestion, exhaustion, high-pitched voice, restless sleep, more responsive, tense mood

3.2.5. Concluding Remarks

In this patient with hyperthyroidism inner and outer worlds move closer together. In the margin between them there is increased tension while the outer world breaches more forcefully into the inner world.

The barrier function is disrupted here too, but in a different way than in hypothyroidism. Employing the analogy of the skin, hyperthyroidism is more a picture of parchment skin, hardened but thinner and more permeable to external influence.

This patient did not suffer from thyroid ophthalmopathy[4]. However, Grave's ophthalmopathy exhibits similar qualities to those we recognized in Judith's situation: turning inside out with an increased awareness of the outside world. This characteristic hyperthyroid quality may be reflected in an individual patient in all its different forms, but this need not be so.

Recognizing a particular quality as a pathogenic stimulus of the disease—such as an excessive focus on the outside world that ultimately expresses itself in symptoms of hyperthyroidism—is like identifying a characteristic disease clue (see also the Companion "Wholeness in Science", Van der Bie 2012). Besides the usual diagnostic method based on symptom scores, it is valuable to

4 another characteristic symptom of hyperthyroidism, in which the lid gap becomes wider and the eyes come forward

identify such other clues for the genesis of disease and develop this as a conscious skill to increase therapeutic options. The *4-step* approach augments clinical competence. Other examples of skills recognizing disease related clues which are esteemed in clinical practice are the "gut feeling" and "skilled medical intuition" (Stolper 2011).

Table 3.5. Diagnostic Process

Disease Stimulus	Disease Process	Dynamic Pattern	Signs and Symptoms
↑			↑
pattern recognition			symptom scores

Disease stimuli come to expression in individual patients in a way that is typical for ***this*** particular patient. Recognizing and identifying disease stimuli ***qualitatively*** can be a diagnostic tool, revealing the connection between seemingly disparate symptoms. The *4-step* approach may thus expose the connection between different manifestations of the same disease.

In section 3.11., specific therapeutic recommendations will be described for Judith.

3.3. Hypothyroidism and Hyperthyroidism Compared

Fatigue is a common symptom reported by patients with many different diseases. However, the fatigue described by the patient with hypothyroidism is quite different from the fatigue of the hyperthyroid patient. Sensing the quality of the dynamic aspects of fatigue in each case as we worked out above (the second and third step of the *4-step* approach) and naming its distinguishing qualities can help specify vague or general complaints.

Fatigue indeed can be present in many forms. Many diseases other than thyroid disease are accompanied by their own particular form of fatigue. When the diagnostician asks targeted questions, the distinguishing disease characteristics of the fatigue may be identified and further explored to help detect diseases at an earlier stage. In addition, patients with fatigue that is insufficiently explained by physical problems (such as chronic fatigue syndrome (CFS), (Prins et al 2006) may benefit from specifying the qualities of the fatigue when selecting specific advice and therapeutic measures.

Describing the unique qualities of thyroid disease in individual patients reveals that the distinguishing characteristics apply to both physical and psychological phenomena (see the descriptions in sections 3.1. and 3.2.). Working with characteristic disease qualities can form the basis for a targeted treatment in which the patient is approached from a bio-psycho-social model (Smith et al 2013).

> The *4-step* approach leads to an understanding of symptomatology in terms of distinguishing disease qualities that can specify a general or misunderstood complaint. Diagnosis and treatment formulated via qualitative terms, constitute a valuable, complementary instrument in a bio-psycho-social approach to the patient.

The figure below gives a pictorial representation of the qualities of a healthy, euthyroid state as compared to hypo- and hyperthyroid conditions.

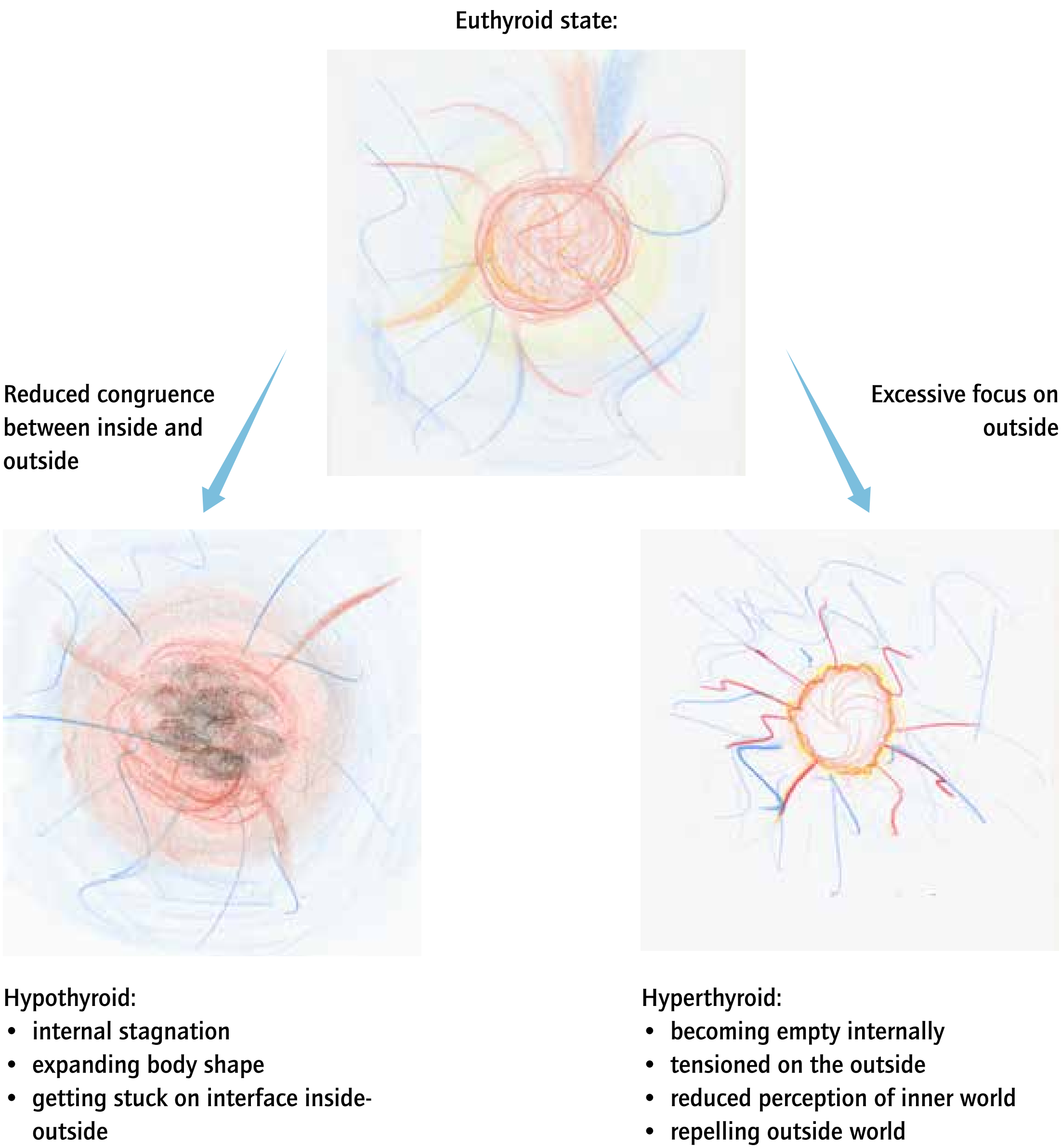


Figure 3.3. Pictorial Representation of the Distinguishing Qualities in Normal Thyroid Function as Compared to Hypo- and Hyperthyroid Conditions

Everyone has times of “increased focus on the outside world” and of “diminished connection between the inner and outer world.” This remains within healthy boundaries as long as it fits the situation and the person in question can recuperate from the temporary imbalance when necessary. Health is a dynamic balance between polarities. When the dynamic balance falters and a person becomes more or less fixated in one of the two polar states, disease makes its appearance. This is what we see in, for example, thyroid disease. The Companion The Healing Process (Van der Bie et al 2008) discusses how human self-healing abilities are in fact the capability to maintain and restore a balance between polar processes. In a healthy individual, the healing process itself goes through different polar stages but never remains stagnant in one or the other polarity.

The steps identifying the pathogenic stimulus of disease qualitatively as described in this chapter provide insight into the impetus that compromised the healthy balance in thyroid function. It also provides insight into the qualities that can be developed in the pursuit of returning to health, which is associated with increased adaptation regulation and improved self-management.

The idea of individualized diagnostics and treatment based on disease qualities is in line with Huber’s definition of health, which is the ability to adapt and self-manage one’s physical, mental, and social state (Huber et al 2011; Huber 2014).

3.4. Physiology of the Thyroid Hormone System

In previous sections, we attributed specific distinguishing qualities to thyroid symptoms in the clinical scenarios of two individual patients (3.1. and 3.2.) by means of the *4-step* approach.

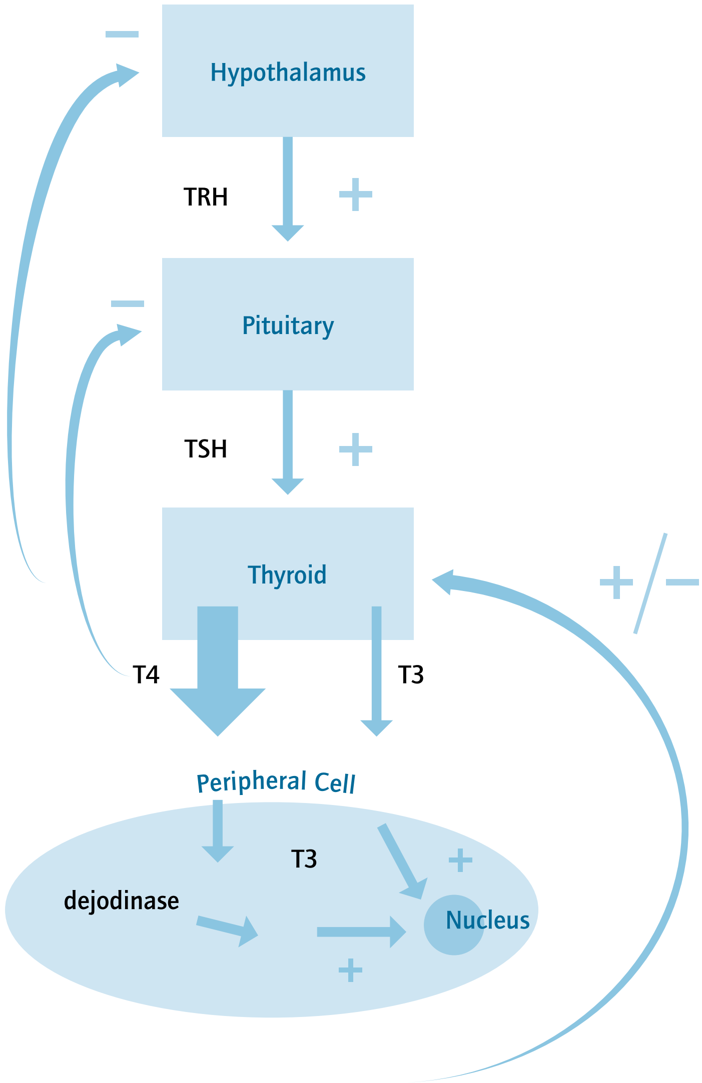
In this next section, we will demonstrate how a qualitative approach can also be applied to physiological thyroid processes in healthy human individuals. The objective is to characterize the thyroid hormone organization as a whole and come to a qualitative understanding of it. Again we are asked to embrace a specific orientation, a different basic attitude at each particular step as we use the *4-step* approach (section 2.1. and Chapter 6). In the description of thyroid physiology we have, however, opted for not explicitly describing all four steps. The first step, which is gathering the facts, will be addressed in detail. Subsequently we will attempt to summarize the essence of steps 2, 3, and 4 together. Then we will compare characteristic qualities of the healthy thyroid hormone system to the pathophysiology, and will investigate further insights for therapy that may follow from this comparison.

The sources used in this chapter are textbooks of (patho)physiology, internal medicine, and endocrinology (Cotran et al 1994; Hall 2011; Fauci et al 2008; Gardner and Shoback 2007). Basic knowledge of endocrinology and in particular of the thyroid gland is presupposed in this section. The physiology in this section will nonetheless be described in some detail to enable the reader to participate fully in the process of the first step of the *4-step* approach: the description of the facts.

The thyroid hormone system includes different parts, each with its own function in the context of the whole organism. It is precisely these different processes within a single coherent organization that enable the body to function in a healthy manner. The organization of this system into subsystems will be described "top-down:" from the hypothalamus to the pituitary gland, the thyroid, iodine physiology, and via the blood to the peripheral cells. Each subsystem is characterized in comparison to previous and following subsystems. Next, we will turn to a broader view, attempting to characterize the system as a whole.

3.4.1. Hypothalamus

The hypothalamus releases Thyrotropin Releasing Hormone (TRH) to the pituitary gland. The hypothalamus has neuronal connections to the limbic system, and affects autonomic function such as heart rate, digestion, vasocontraction, and vasodilation and many other hormone systems. The hypothalamus is actually positioned between the nervous and endocrine systems. This intermediate position is also reflected in the properties of TRH. The TRH-molecule is a hormone made up of just three peptides and as such is larger than neurotransmitter molecules, but smaller in size than most other hormones. TRH is delivered to the pituitary gland in brief pulses and has a half-life of a few minutes, which is longer than neurotransmitters' half-lives, but shorter than most hormones. Further, TRH has a very short distance to travel from its origin in the hypothalamus through the hypothalamic-pituitary portal system. It reaches its target organ even before it would get into the systemic circulation. This is longer than neurotransmitters travel but both shorter and more focused than the transport of other hormones through the blood.



Legend:

TRH = Thyrotropin Releasing Hormone

TSH = Thyroid Stimulating Hormone

T4 = Thyroxine

T3 = Triiodothyronine

\+ = Stimulant

– = Inhibitory activity

Figure 3.4. Simplified Schematic Portrayal of the Thyroid Hormone System

3.4.2. Pituitary Gland

The feedback system of thyroid hormone metabolism is complex. The release of Thyroid Stimulating Hormone (TSH) by the pituitary gland is regulated both from top-down and from bottom-up, each having its own regulatory system (see figure 3.4.).

Top-down regulation comes from the hypothalamus through TRH secretion, which stimulates a basic level of TSH release. In times of stress or serious disease, TRH levels increase rapidly and override the baseline production of TSH to upregulate the system.

Bottom-up regulation employs varying hormone levels. Small changes in circulating thyroid hormone levels (mostly free T_4) within physiological limits result in a substantial change in TSH response to TRH. Other hormones, such as cortisol, also affect its release. This regulation from the periphery is the most important physiological determinant of TSH concentration in a healthy state, the most significant factor being the unbound inactive thyroid hormone (free T_4) level. The aim of TSH regulation is a steady blood level of free T_4. It is important to realize that the benchmark for pituitary activity is not the level of active thyroid hormone (free T_3) nor the amount of thyroid hormone in peripheral tissue.

The half-life of TSH is fifty minutes. TSH can be found throughout the circulatory system. Its target organ is the thyroid gland.

3.4.3. Thyroid Gland

The thyroid gland produces a large reserve of the inactive pro-pro-hormone thyroglobulin, which contains about 130-140 molecules of the amino acid tyrosine. This is stored extracellularly along with iodine as a thick colloidal liquid, ensconced by thyroid cells. Iodinated thyroglobulin is taken up into the cells by endocytosis and then mostly cleaved to the inactive pro-hormone T_4. Only 5% is split to become the active hormone T_3. T_4 contains two tyrosine residues and four iodides; T_3 contains three iodides. The half-life of T_3 is one day and one week for T_4, which is considerably longer than the half-life of TSH. The thyroid provides for an extracellular reserve of pro-pro-

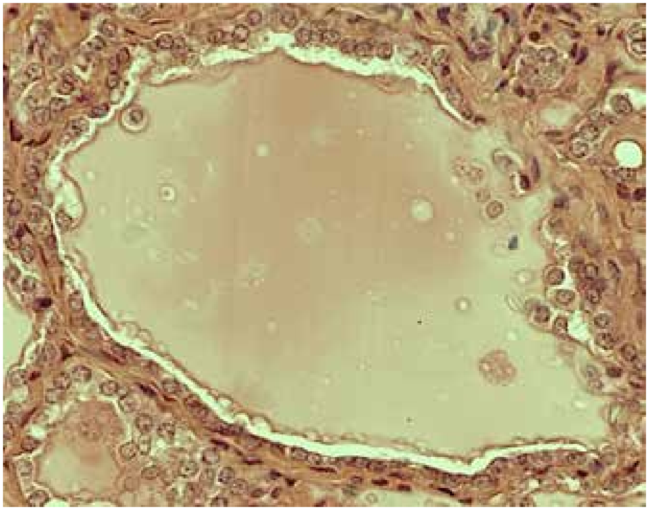


Figure 3.5. Histological image of a thyroid gland follicle, enlarged 20x (www.histology.med.umich.edu; January 2015)

hormone thyroglobulin in the thyroid follicles, and an extracellular stock of the pro-hormone T_4 in the blood. It produces mainly inactive substances which through the incorporation of iodine gain the potential to become active elsewhere.

TSH does not only directly affect the release of T_4, but also has more diverse and slower effects on metabolic processes that precede T_4 production and release, such as stimulation of the endocytosis of thyroglobulin, of protein synthesis, and of growth of the thyroid gland. Next to its response to pituitary stimulation, the thyroid gland also gives off thyroid hormone on its own, albeit at a low basal rate. Thyroid activity is not only regulated by TSH, but also by iodine, local growth factors, and autonomic innervation.

3.4.4. The Blood

The blood carries two forms of thyroid hormone, T_3 and T_4, which are mostly bound to three types of protein:

- Thyroxine binding globulin (TBG) has a high affinity for both hormones and contributes 70-80% of T_3 and T_4 transport capacity;

- Transthyretin (TTR) has a low affinity for the hormones, it transmits 10% of the T_4 and has a role in the delivery of thyroid hormone (T_4) to the central nervous system;
- Albumin also has low affinity for both hormones and contributes 30% to T_3 and 10% to T_4 transport.

The concentration of free thyroid hormone (FT_3 and FT_4) is much smaller than the bound fractions. When a person is called euthyroid, or hypo- or hyperthyroid, the prefix references the concentration of free hormone in the blood. The bound fractions are relatively larger, but, as far as we know, of less clinical relevance. The properties of the bound fractions are different from those of the free fractions. Binding of the hormone in the blood ensures a slower clearance and enables the blood to accommodate a larger supply of thyroid hormone. T_3 in bound form is unavailable for the cell, however, dissociation from the binding protein immediately renders it available
Protein binding can also buffer changes in thyroid hormone levels that result from either thyroid gland production "from above" or from conversion or production by the peripheral cells "from below" (see section 3.4.6.).

TBG has a high affinity for thyroid hormone, and as such, its hormone release-rate is slow. Albumin and TTR have low affinity, thus releasing the hormone quicker. The different binding capacities of these proteins in the circulation ensure an abundant and yet equal distribution of thyroid hormone throughout the body.

3.4.5. Iodine

Iodine is a "small" elemental molecule. In humans, it can only be concentrated in the thyroid gland by incorporating it into thyroglobulin. Iodine is highly specific for the thyroid hormone system. This is in contrast to, for example, the tyrosine-part of thyroid hormone, which is also a component of catecholamine and different proteins. Iodine bestows a high specificity on thyroid hormone since the presence of either three (T_3) or four (T_4) iodine-ions determines whether the hormone is active or not. In peripheral cells, iodine's removal activates the pro-hormone T_4 to T_3 or transforms it into rT_3, which is irreversibly inactive. The thyroid gland provides the basis for the activity of peripheral cells by incorporating iodine into the hormone.

Iodine is clearly an important and even distinguishing element of thyroid hormones as well as of the thyroid hormone system, and determines their functional activity.

Besides TSH, iodine is an important regulator of thyroid hormone production, employing autoregulation for its activity. TSH has little influence on iodine autoregulation. Iodine autoregulation is biphasic: when iodine intake increases, thyroid hormone synthesis initially increases; an even greater iodine intake will conversely reduce thyroid hormone synthesis. In addition, iodine influences the production ratio of T_4 and T_3. With low iodine intake, the thyroid gland produces relatively more T_3 so that the active hormone level is maintained as much as possible. Regulation by iodine is thus much more focused on active hormone production, whereas regulation by TSH is aimed at inactive hormone levels in the serum.

Iodine reaches the thyroid gland from both the digestive tract and via the peripheral cells where iodine is released by the conversion of T_4 to T_3, rT_3 (the permanently inactive form), and T_2. Thyroid hormone production may thus be affected by the activity of peripheral cells "bottom up." This regulation can only be slightly modified by the pituitary gland from "top down."

3.4.6. Peripheral Cells

Peripheral cells have two distinct roles in the thyroid hormone system: systemic and local.

Some tissues, particularly liver and kidneys have a systemic role in the activation and deactivation of T_4 by means of deiodinase. These tissues are the site of active thyroid hormone T_3 production for the whole body and are also responsible for a major part of the conversion of T_4 to the irreversibly inactive rT_3. The ratio of T_3-/rT_3-production of these tissues may vary. These tissues therefore play an important role in regulating serum levels of T_4 and T_3.

In addition, all peripheral cells are end organs for thyroid hormones, which, via transcription (switching on of genes) stimulate glucose, protein, and fat metabolism. In addition, thyroid hormones stimulate physiologic processes such as breathing that are coupled to the metabolic processes. Some of the effect appears relatively quickly, however, it may take several weeks before the maximal effect is reached.

Deiodinase and thyroid hormone receptors are essential for the activity of thyroid hormones.

- Intracellular deiodinase may rapidly and directly change the biological activity of inactive T_4 on site to active T_3 or inactive rT_3. Thus the amount of available active thyroid hormone is locally regulated in the cell itself.
- Cell metabolism in turn affects the activity of deiodinase: the final result affects its own local process. Regulation of deiodinases by the hypothalamus, pituitary, or thyroid seem limited, except for providing for T_4 as substrate.
- Thyroid hormone receptors on the cell have a ten times greater affinity for T_3 than T_4. This binding capacity affects the activity of the hormone and is linked to the free fraction of hormone in the serum. Direct regulation by the pituitary or hypothalamus has not been described.

At the peripheral cell level, local control mechanisms are employed: they are influenced by the final local effect and by the circulating free hormone fraction. The peripheral cells could thus be considered a “peripheral center” of the thyroid hormone system with significant systemic and local activities.

3.4.7. Summary

Reflecting on thyroid hormone physiology from the hypothalamus down to the level of the peripheral cells, we may notice how the quality of physiologic activity changes with varying levels. The hypothalamus has a *dynamic* similar to the neuronal signal, which acts as a sort of “central” center. The peripheral cells together form a locally and systemically synchronized “peripheral center.” It may strike us how important the dynamic feature of synchronization with qualified input is at all levels of thyroid hormone system activity, even though at each level the synchronization may be effectuated in a differently way.

3.5. Health and Disease in Relation to (Patho)Physiology

Using the above descriptions, we can begin to form an initial *qualitative impression* of physiologic thyroid hormone system processes. Thyroid gland physiology appears to be organized as a chain reaction extending from central to peripheral, from neural to metabolic regions. The whole system is characterized by a precise synchronization between all levels, made possible by various forms of buffering. The result is a very complex regulation system, which, in health, ensures the availability of active thyroid hormone in intracellular tissues in the short, medium, and long term.

If we "zoom in" on specific properties of the chain reaction, but still regarding the system qualitatively, the thyroid itself appears to take in a "middle position" between the more neurally inclined part of thyroid physiology and its more metabolism inclined part. Thyroid physiology responds to both impulses "from top-down" and "from bottom-up."

Healthy thyroid function includes autonomous trends: most people have an autonomously functioning nodule that usually does not cause any problems. It is precisely this very active, autonomy-prone organ that has the function to physiologically integrate the whole organism by supplying it with thyroid hormone. These two polar qualities of the thyroid must be kept in balance to maintain a healthy situation.

Health in the thyroid hormone system means the ability to mediate between and integrate all of the polar (sub-)processes.

What happens when the thyroid hormone system becomes out of balance (figure 3.6.)? In primary hyper- or hypothyroidism, the thyroid gland no longer functions in a synchronized manner with the other parts of the system; rather it either forces an excess of thyroid hormone on peripheral cells or deprives them of it. In either case, the buffering or control mechanisms from "top down" and "bottom up" are no longer sufficient. The thyroid gland, which usually has a supporting role in the thyroid hormone system, dominates the whole system in producing too much or too little. As a result, the peripheral cells can no longer synchronize the local and systemic thyroid hormone needs. Disease emerges when the capability to mediate between and integrate fails.

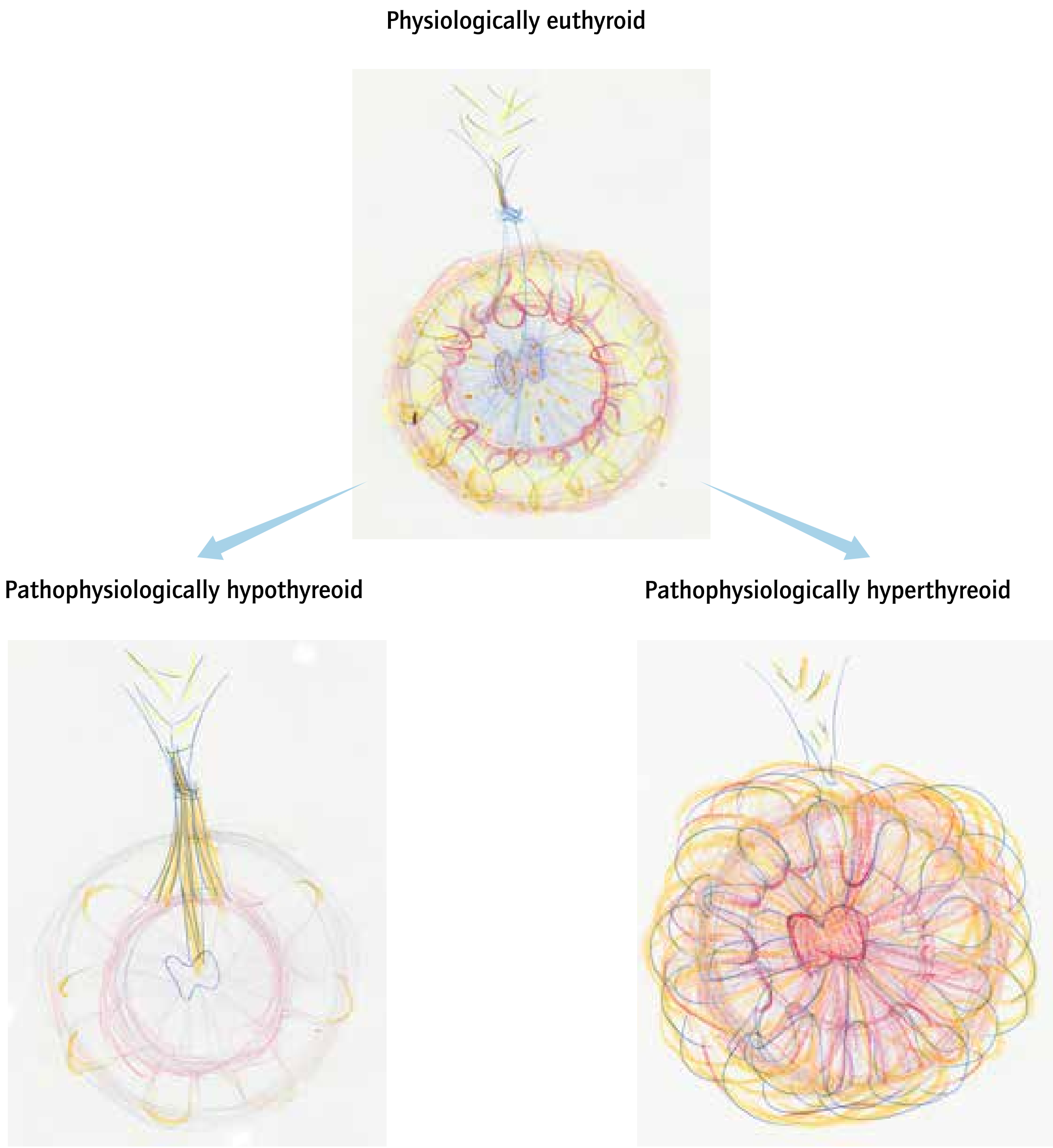


Figure 3.6. Pictorial Image of Pathophysiological Effects

In the most common forms of hypothyroidism and hyperthyroidism, autoimmune processes play a role. In autoimmune processes, the thyroid is no longer recognized as part of the organism. Consequentially, the organ is antagonized by the immune system.

Health and Disease: (Patho)Physiology in Clinical Setting

In (patho)physiological descriptions the organization of the thyroid hormone system comes first. In clinical descriptions the physical and psychological signs and symptoms predominate. When thyroid hormone is insufficiently available to bodily and mental processes, material processes appear to become dominant. Internal stagnation, heaviness, and consolidation take place both in body and mental processes: biochemically, there is too much anabolism. At the same time that the body becomes heavy, dense, and less accessible, psychologically, the inner world becomes less accessible to the outer world and vice-versa.

When thyroid hormone becomes too dominant in body and mental processes, both burn up and break-down predominates.

As described in physiology, thyroid hormone activity is aligned with the need for local and systemic metabolism. The term “synchronization” also applies to what was said in the two case studies, but now in connection with the relation of inner and outer worlds. The balance here is sought between perception of stimuli and impulses, their inner processing, and the ability to give adequate expression to them in the outer world. To this end, a healthy combination of anabolism and catabolism (break-down) is one of the conditions. The thyroid hormone system plays a key role in this balance.

Resume

For healthy functioning of the thyroid hormone system, each subsystem must fulfill its specific role in the context of the system as a whole.

Within the thyroid, physiologically polar qualities exist: autonomous organic processes take place next to processes that are closely synchronized with organs and tissues throughout the body. The

thyroid hormone system disintegrates when thyroid disease occurs, and the thyroid loses its key function of integrating and synchronizing the anabolic and catabolic metabolism in the whole organism.
Equally essential to the healthy function of the thyroid hormone system is the ability to take into account both stimuli that come from inside the body and psyche as well as what comes from the outer world in the form of impulses and incentives. This hormone system is essential for the healthy processing of these perceptions from inside and the outer world.

3.6. Therapeutic Consequences

Expounding on the *4-step* approach raises the practical question whether this new way of comprehending thyroid disease could also contribute to early disease detection and prevention, or could provide ideas to halt disease progression at an earlier stage.

Until recently, the common way to describe thyroid problems was based on the presumption of a top-down-regulated system. On closer examination, the different regulatory mechanisms reveal the importance of bottom-up-regulation as well as the various peripheral adaptation mechanisms for a healthy function of the whole system. Practicing physicians may witness pathophysiological problems resulting from this (Abdalla et al 2014, Gereben et al 2008). A familiar way of describing the patients that suffer from this is "*hypo but not happy*," which refers to patients with hypothyroidism that seem to be adequately supplemented with thyroid hormone according to their serum levels but who still suffer from refractory symptoms (Wartofsky 2013, Wiersinga et al 2012, Wiersinga 2014). One possible explanation for this phenomenon could be that T_4 is inadequately converted to T_3 in the periphery.

The manner in which the system is regulated from the periphery happens in a completely different way than the top-down-regulation that relies on central control, as evidenced by the physiological qualities described earlier. Current pharmacological agents have a dominant central steering effect matching the centralized top-down management. It could be valuable to develop drugs and other therapeutic interventions that address peripheral regulation. It seems important to start looking for drugs that allow or improve rapid local adaptation to both local and overall need.

Further exploration of the patients and their cases discussed in sections 3.1. (Sarah) and 3.2. (Judith) exposes the important role of psychosomatic dynamics in the manifestation of thyroid problems. The thyroid seems to be important in maintaining a healthy balance between the inner and outer worlds, acting as a "shield" (Greek θύρεός, thureós, also etymologically related to "door" or "gate"). A healthy functioning "shield" may be indispensable for a healthy function of the inner world. The *4-step* approach shows both on an individual level and in relation to disease which qualities must specifically be developed to promote health and well-being: in *this* disease, at *this* stage, and/or in *this* patient. Depending on the disease process and individual potential, medicinal treatment for the excess or deficit of thyroid hormone is needed to support the development of such qualities.

There is ample choice of therapeutic interventions that could strengthen these qualities, both focused on psychological processes as well as on physical needs. The range varies from body related psychotherapy, drama therapy, art therapy, haptotherapy, and psychosomatic physiotherapy to different complementary therapies. Below is a selection of anthroposophic therapies.

For Sarah it is important to focus therapy on becoming more mobile inwardly and to promote exchange between the inner and the outer world (section 3.1.4.). This is supported by rhythmic massage, which will bring a flowing "airy" quality to her relatively dense, heavy body. With this treatment she noticed that her mood became less heavy. Anthroposophical speech therapy may also be helpful in actively strengthening her (inner) voice, emphasizing not only self-expression, but strengthened connection to her own core.

For Judith it is important to work on relaxation, less focus on the outside world, and more awareness of the experience of the inner world (section 3.2.4.) as well as staying with it. She particularly enjoyed art therapy, which was also relaxing for her. It supported her staying connected to herself while remaining active. The therapist's aim was to establish a connection to the materials, in this case charcoal and paper, and to Judith's inner response to working with light and darkness. This nourished Judith's inner world. She also worked with therapeutic eurythmy on her ability to balance inner and outer experience. One of the ways this can be practiced is by bringing first the arms and then the legs in an left and right alternating movement forwards, which causes a balanced inbreathing and exhaling (called the "M-movement").

Based on a qualitative diagnosis describing the (dys)balance in terms of qualities, therapeutic goals may be formulated to support both psychological skills and the physical organism to promote individual health.

Resume
The thyroid hormone system is active in the organic alignment between and synchronization of local and systemic metabolic demands and in the need to balance inner and outer worlds.
When treating patients with thyroid disease, bio-psycho-social aspects can be strengthened by means of therapeutic interventions that target these specific qualities.

> The *4-step* approach allows us to use individualized therapeutic interventions that promote health *qualitatively* in addition to regular medication.

3.7. Conclusion

This chapter expanded upon the experiences of two patients and on the physiology of the thyroid hormone system by means of the *4-step* approach. The coherence between the biological, psychological, and social aspects, which are part of an organic whole, emerged through this process in qualitative terms. The healthy person as well as the sick individual appears in a meaningful context with this approach. In thyroid disease, synchronization of metabolic processes as well as the synchronization of the person's inner world with the social surroundings, appears disturbed. The peripheral cells cannot function adequately to satisfy both local and systemic needs, and the thyroid gland dominates the system through over- or underproduction. The hypothyroid patient relates a discrepancy in experiencing her inner and outer worlds, in which her inner world has become heavy and sluggish. She seems caught in an introverted and stagnant process. The hyperthyroid patient experiences an overly awake and excessive orientation to the outer world. She cannot seem to escape this and feels as if she is inwardly drained. A healthy thyroid function has a key role (“gate keeper” function) in the interplay between anabolic and catabolic metabolism which supports our perception, digestion, and expression of impulses in body and psyche.

Using this insight and recognizing specific qualitative changes in patients when they occur can be an additional diagnostic tool and provide guidelines for individualized additional therapy. The patient is stimulated to self-manage her own life, physically, mentally, and socially.

This insight may prompt an evolution in the medical treatment of thyroid disorders to a more effective health-promoting modality.

4. *Diabetes Mellitus*

by Kore Luske MD

4.1. Introduction

In the previous chapter, the *4-step* approach was systematically introduced and explained. This chapter also makes use of this approach. To reiterate, the *4-step* approach proceeds as follows:

- research of the factual signs and symptoms of the disease process (first step)
- examination of the dynamic patterns and context of the facts (second step)
- recognition and qualitative characterization of the dynamic patterns from the perspective of an empathic understanding (third step)
- appreciation and identification of the qualitative pathogenic stimulus of the disease from the perspective of skilled intuitive understanding in an effort to arrive at an individualized treatment for the particular patient (fourth step)

The four individual steps are actually taken from what we do in daily practice. The practitioner in daily practice will, however, often skip one or the other step and may or may not come back to it later, depending on the presentation of the patient and the practitioner's personal skills and competence. The phenomena of having a "gut feeling" and "skilled intuition" (Stolper 2011) are good examples of proceeding directly to the fourth step of intuitively grasping the essence of the patient's situation. In this chapter, we will employ the *4-step* approach as it is often used in practice rather than systematically apply it. Systematic use in specific situations will nonetheless aid practitioners in developing and expanding skilled intuition. Methodical clues in grey text blocks will enable the reader to recognize the individual steps.

To integrate the *4-step* process with clinical practice, we will study one patient with diabetes mellitus type 1 (DM1) and another with type 2 (DM2). From the signs and symptoms, lab work, and histological and pathophysiological data, the dynamic pattern in diabetes mellitus is described and characterized. The third part of this chapter compares DM1 and DM2 to obtain a perspective on general disease characteristics of these disorders; from this, suggestions may evolve for additional support, advice, and therapeutic possibilities.

As we continue to explore diabetes, it is helpful to establish diametric themes such as consciousness/metabolism and anabolism/catabolism; this will prove effective in visualizing dynamic disease concepts. Another diametric theme is that of the organism's center/periphery; presenting the blood stream as "intermediary" between them.

In the text, additional background information on DM for interested readers appears in italicized gray boxes, sometimes accompanied by illustrations.

4.2. Diabetes Mellitus type 1 (DM1), from Patient History to General Overview

4.2.1. DM1, Case Presentation Janine

Janine is a tall, thin woman with light blue eyes and thin blond medium length hair. She is 53 years old and she looks tired and somewhat haggard.

Once, when Janine was driving her car, she suddenly noticed her vision was blurred. She had never experienced this before. Because her daughter has DM1 and DM is common in her family, she immediately thought of diabetes. That evening, she measured her own blood glucose with her daughter's blood glucose meter at 34 mmol/L. Repeating the test yielded the same result and she realized she probably had diabetes, too. She contacted the GP who was on call that evening.
Further inquiry reveals that Janine has more symptoms that are indicative of diabetes mellitus. During the previous months, she reports increased thirst and urination. She has also lost about two kilograms of weight and complains of extreme fatigue that has been present for quite some time. She describes this tiredness as feeling like a blanket of weariness about her that differs from the more typical, healthy post-exertion fatigue she experienced in the past.

Janine has always been on the thin side. She says that she must be careful to not lose too much weight in periods of stress and overload. Yet, her two kilos weight loss went unnoticed until now.

At physical examination, we see an alert, thin woman with a regular pulse of 56/min and a somewhat elevated blood pressure of 160/105 mm Hg, which later normalizes. She has a low normal body temperature at 36°C. Otherwise the exam is normal.

At 26-years old she was found to have auto-immune hyperthyroidism, otherwise known as Graves' disease, for which she was treated with iodine-131 (radioactive iodine). Over the course of the following years, she developed hypothyroidism, which has since been treated with thyroid hormone.

4.2.2. Symptoms in DM1

Symptoms that may occur in DM1 are polydipsia[5], polyuria[6], glucosuria[7], weight loss with increased appetite, and fatigue.

Janine exhibited most of these symptoms. She also experienced blurred vision, which can occur with rapid changes in blood glucose level. The first symptoms in patients with DM1 usually appear quite suddenly and may develop rapidly. Yet the underlying disease process has long been present without the patient's awareness.

Sometimes an acute illness or surgery triggers the first appearance of DM1, which coincides with a greater chance of developing keto-acidosis[8]. Ketoacidosis is associated with symptoms of abdominal pain, nausea, vomiting, shortness of breath, a fruity odor on the breath (acetone odor), confusion, and mental fog. Eventually, the patient may slip into a coma with Kussmaul breathing[9]. Without medical intervention, these patients will eventually die.

---

5 excessive thirst that leads to more than normal drinking
6 excessive urine production
7 urine containing glucose
8 a type of metabolic acidosis in which uncontrolled amounts of ketones are produced and the body acidifies
9 fast and deep respiration; the body attempts to counteract acidification by breathing out more carbon dioxide

DM1 can occur at any age, but most commonly, it appears at a young age, with a peak incidence at puberty. The probability of another auto-immune disease such as celiac disease[10], thyroid disease, Addison's disease[11], and vitiligo[12] is much greater in patients with DM1. These other diseases may have already appeared prior to diagnosing DM1. Graves' disease as auto immune disorder in Janine's medical history is therefore significant.

DM1 symptoms can be classified as either metabolic or mental (including sensory) changes. Perception is closely related to consciousness, which is illustrated by the difference in perception in sleeping and waking. In a dormant state when consciousness is temporarily reduced, there is no perception of the outside world via the senses. However, someone may wake up from a sound sleep and regain consciousness through a sensory perception. On the other hand, metabolic processes take place almost entirely unconsciously; they do not require mental awareness.

> Classifying makes it easier to order the various symptoms into typical patterns. A classification of the facts (disease symptoms) aids to arrange them correctly.

DM1 causes profound *metabolic changes*. There is a loss of water and glucose in the urine and the patient loses weight despite (extra) food intake. In keto-acidosis, the loss further extends to ketones. Fatty acids are broken down to ketones and excreted in the urine as well as exhaled in the form of volatile acetone. The uptake of nutrition in the intestine decreases sharply and abdominal pain and vomiting are often present. Even though the organism is very good at retaining water and energy in a healthy state, at the onset of DM1, it loses its ability to facilitate anabolic metabolism and falls into a catabolic state. The body seems to disperse (urinary excretion) and dissipate (elimination in breathing). Janine's blood pressure is increased, but this seemed to normalize later, indicating that it was probably stress-related.

10 gluten allergy
11 adrenal insufficiency
12 a skin condition in which patches of hypopigmentation occur

Co-morbidities[13] in DM1 point to the immune system's tendency to regard parts of the body as non-self, to be disposed of and broken down.

Table 4.1.

Category	Symptoms
Physical signs and symptoms	• Thirst, polydipsia, polyuria, and glycosuria • Signs of dehydration, tachycardia, hypotension • Weight loss and increased appetite • Abdominal pain, nausea, and vomiting (ketoacidosis) • Acetone odor on the breath (ketosis) • Fast, deep breathing (ketoacidosis) • Weight normal or underweight
Changes in consciousness and perception	• Blurred vision • Fatigue • Confusion • Decreased consciousness • Coma (ketoacidosis)
General changes	• Acute course (and therefore as yet no chronic complications) • More often occurring at a young age
Comorbidities	• Auto-immune disorders such as celiac disease (gluten allergy), autoimmune thyroid disorders, Addison's disease, and vitiligo

In figure 4.1., the above description is summarized with arrows.

13 disorders that often occur together and that are often associated with one another

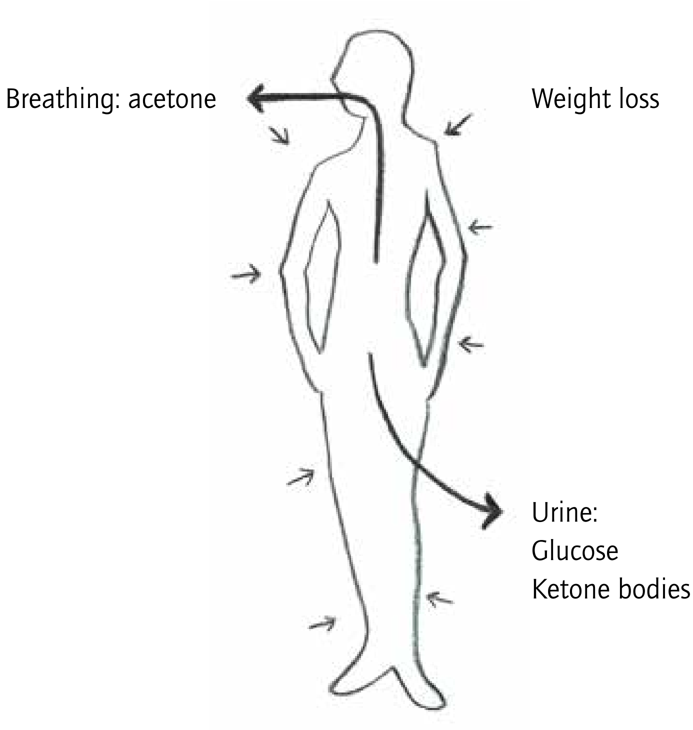


Figure 4.1. Dynamic Display of Metabolic Changes Induced by DM1

In the above text, *dynamic* aspects of the metabolic changes in DM1 are indicated with expressions like "to lose," "breakdown," "excretion," "to disperse," "to dissipate," "to eliminate." This dynamic classification aids in exposing the disease process and discerning how the clinical picture develops.

The impairment in contacting and consciously connecting with the environment affects both the *mind and the senses*. This impairment may begin as blurred vision, one of Janine's symptoms, but, when left untreated, will eventually end in coma and possibly death. The *dynamic* description of the changes in consciousness may be summarized as loosing contact with the world.

It is harder to describe consciousness and perception dynamically since conscious awareness does not manifest itself physically. The effect of a present, absent, or decreased awareness can be inferred from certain externally visible phenomena and behavior such as open eyes or an appropriate response to stimuli, for example. To come to a dynamic description of awareness and perception, a participating or sympathetic basic attitude is important (see section 2.1.).
The symptom "blurred vision," for example, is easy to imagine, especially for people who wear glasses or contact lenses. What happens to your awareness and your presence when your vision is blurred?

In summary, the symptoms of DM1 can be seen as the result of catabolic metabolism through which the body seems to disappear, to waste away, and to dissipate. Consciousness and perception seem to retreat from contact with the world.

4.2.3. Janine's Blood Tests

Lab work is done to determine Janine's DM1diagnosis.

On admission, Janine has a serum glucose of 25.3 mmol/L (reference non fasting value is 2.7 to 11 mmol/L). C-peptide is low at 0.15 nmol/L (reference 0.26 to 0.62 nmol/L). Serum C-peptide is dependent on the organism's insulin production (see further in section 4.2.4.).

Renal function is normal, but Janine is hyponatremicwith a sodium concentration of 129 mmol/L (reference 135-145 mmol/L). With NaCl infusion this normalizes within a few hours. Blood gas values are normal.

In the following section we will explore Janine's symptomology.

4.2.4. Laboratory Research in DM1

Today, a DM1 diagnosis is always confirmed with laboratory tests. In advanced disease, pathology is easy to spot: there are extremely high glucose levels in the serum and low insulin production. Insulin production can be determined by measuring the C-peptide. C-peptide (or connecting peptide) is a small protein that is released when proinsulin is converted to insulin. The pancreas therefore secretes C-peptide in the same quantity that it secretes insulin (see figure 4.2.).

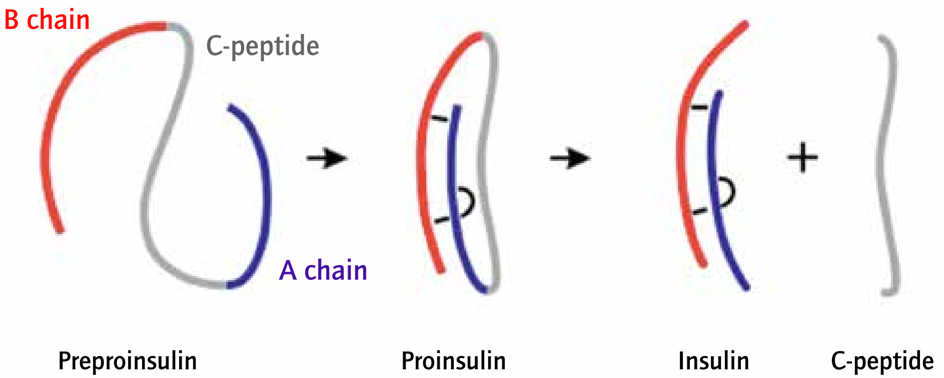


Figure 4.2. : The production of insulin is accompanied by simultaneous release of C-peptide. Source: http://www.diabetesadvocates.net/Complications.html

Metabolic changes can be investigated by blood gas analysis and by measuring the ketone body concentration in urine. Osmotic changes often reveal themselves through an ion deficiency (sodium, potassium, magnesium) and renal impairment due to dehydration.

Janine's lab work shows a lack of insulin production via a low C-peptide value and the high glucose level. Osmotic diuresis triggers hyponatremia. Janine's blood gas values are normal indicating no acidosis.

Laboratory tests can be classified into several categories: organ-specific (in this case, the pancreas), metabolic changes, and osmotic changes.

Table 4.2.

Category	Laboratory findings
Organ: endocrine pancreas	• very high blood sugar • low C-peptide
Metabolic changes	• very high glucose level in the blood • ketonuria • acidosis
Osmotic changes (secondary to metabolic changes)	• hyponatremia • renal impairment

Resume

DM1 laboratory tests show contrasting metabolic values: high blood glucose levels combined with a catabolic state of the organism (ketonuria and acidosis), which include osmotic changes.

> Laboratory changes reflect the dynamic of the signs and symptoms of DM1 pathophysiology of a catabolic metabolism.

Is it possible to also recognize the DM1 disease process in histology and physiology? The following paragraphs explore this possibility.

4.2.5. DM1 and Histological Changes in the Pancreas

To be able to interpret pathological changes, we will first briefly explore normal pancreas anatomy and histology before describing its typical histological changes in DM1.

The pancreas is a retroperitoneal organ that lies behind the stomach (figure 4.3.). It consists of exocrine and endocrine tissue.

The *endocrine part* is composed of the islets of Langerhans. The islets secrete hormones that are important for regulation of the organism's metabolism. The main pancreatic hormones are insulin (produced by the β-cells in the islets) and glucagon (produced by the islets' α-cells)
The *exocrine portion* produces pancreatic juices that contain many digestive enzymes that are necessary for nutrient breakdown in the gut.

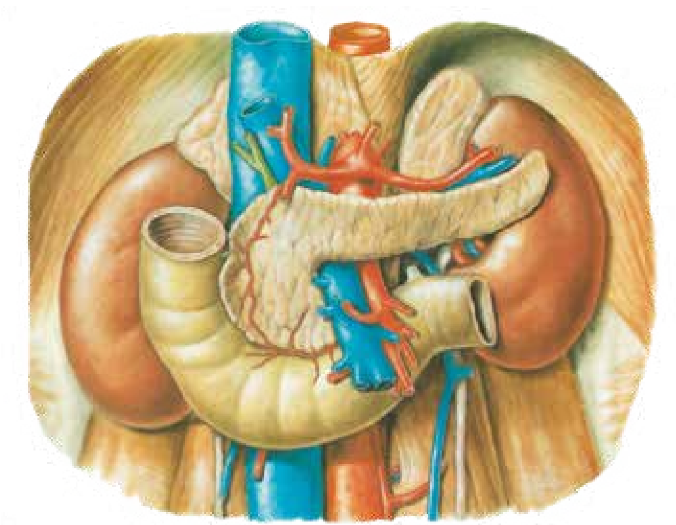


Figure 4.3. Retroperitoneal Organs and Vessels in the Upper Abdomen, ventral view.
Source: Putz et al 1995

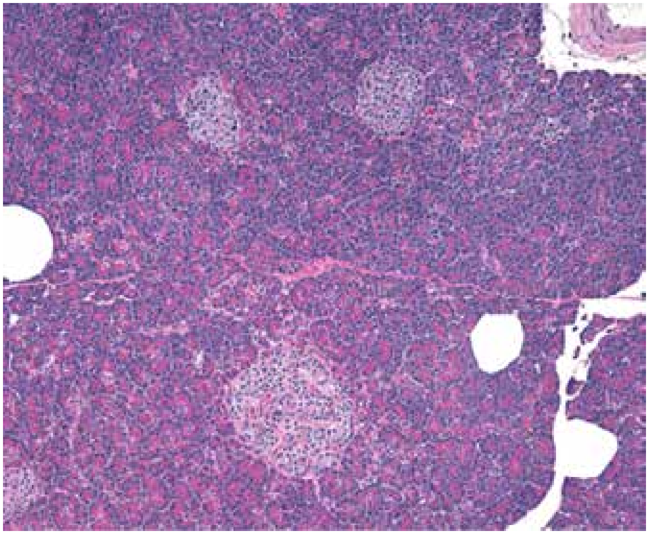


Figure 4.4. Slice of Human Pancreatic Tissue.
Hormone producing islets of different size are visible surrounded by exocrine tissue. Source: Treuting, 2012

DM1 is a disease characterized by the a failure of insulin production by the pancreas. Insuline production failure is typically due to autoimmune destruction of β-cells mediated by activated T-cells and macrophages. The islets of Langerhans are infiltrated by lymphocytes in an inflammatory process: insulinitis. In the end, β-cells disappear by apoptosis[14]. All other types of islet cells remain intact. When all the islet β-cells have disappeared, the lymphocytes vanish and the islets almost look as they did before. The exact trigger for the autoimmune process is unclear. Genetic, environmental, and immunological factors probably all play a role.

A small portion of DM1 patients shows no evidence of autoimmune destruction and the exact mechanism by which β-cells vanish remains unknown.

Before DM1 manifests clinically, there is a time period when the number of β-cells declines. The rate of this decline varies from months to many years. Symptoms only occur when an absolute insulin deficiency occurs or when approximately 70-80% of the β-cells are gone.

14 programmed cell death

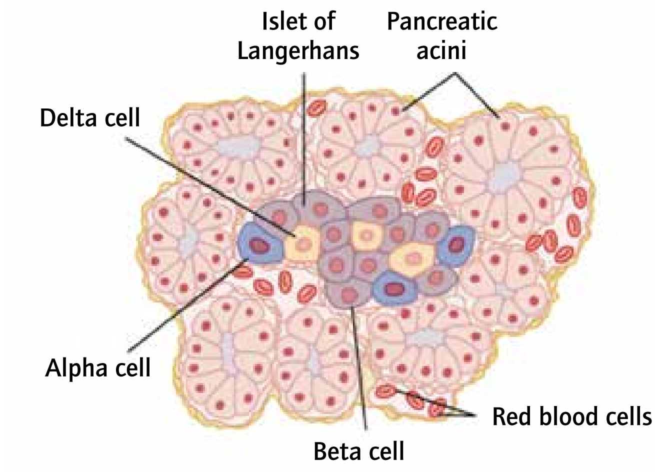


Figure 4.5. Schematic Cross-section of Pancreas Tissue. In the middle, an islet of Langerhans (endocrine tissue) surrounded by exocrine tissue. Source: Hall 2010

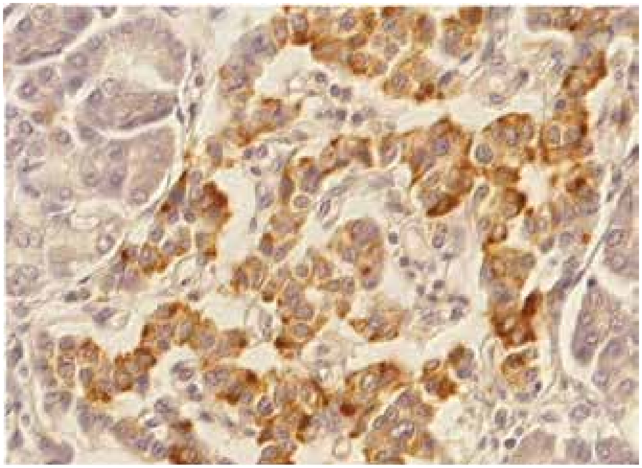


Figure 4.6. Normal islet of Langerhans; insulin is colored brown. Source: In 't Veld 2011

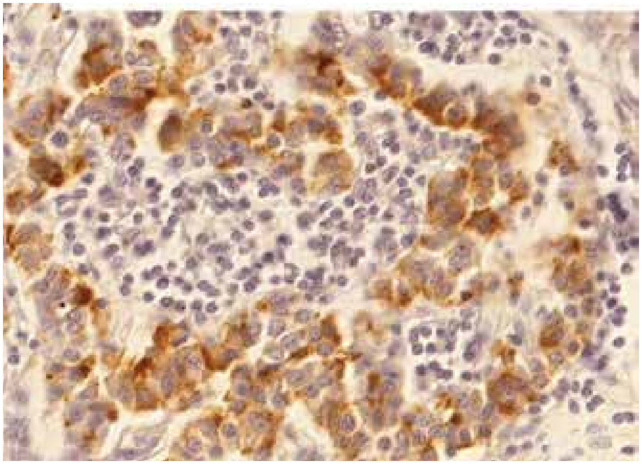


Figure 4.7. Insulinitis of an islet of Langerhans. Insulin is colored brown. An infiltration of purple stained lymphocytes becomes visible. Source: In 't Veld 2011

> Histology shows disease processes at a microscopic level.
>
> Describing pancreas histology and its changes in DM1 unveils many additional interesting facts. Some of these facts point to dynamic aspects of the disease process, such as the infiltration of lymphocytes, loss of β-cells, and other chronic inflammatory insignia.

In DM1 there is (usually) a chronic inflammatory response that is specifically directed against the β-cells of the pancreas. To understand this dynamic we may liken it to the physiologic healing process. The physiological healing process has a sequence of different phases:

1. the acute phase: hemostasis and the acute-phase reaction;
2. the inflammatory phase: pathogens, foreign material, and damaged and dead tissue are attacked and destroyed;

3. the proliferative phase: tissue repair and growth of connective tissue takes place;
4. the maturation phase: the new tissue is integrated into the whole of the organism (Van der Bie et al 2008).

When compared to the physiological healing process, the DM1 disease process could be characterized as a stagnation in the second, inflammatory phase. The β-cells are attacked by the immune system and destroyed as if they no longer belong to the organism. The consolidation in the second phase of the healing process eventually leads to a permanent change.

> The progression of the inflammatory process in DM1 may be compared to the inflammatory phases of physiologic healing. Comparing a disease process with a physiologic (healing) process can upgrade the characterization of the disease process and may offer ideas for therapeutic action.

Resume

Pancreas histology of DM1 shows a chronic inflammatory process that eventually specifically destroys the β-cells of the pancreas.

4.2.6. The Role of Insulin in Metabolism

To understand the metabolic shift that occurs in DM1, it is important to know and understand the normal role of insulin in metabolism.

When pancreatic β-cells function normally, insulin production is mainly determined by the serum glucose levels. The higher the glucose level, the more insulin the pancreas produces. In the pancreatic β-cell, glycolysis[15] is coupled to the production of insulin. This feedback loop is shown in figure 4.8.

15 the metabolic breakdown of glucose to release energy

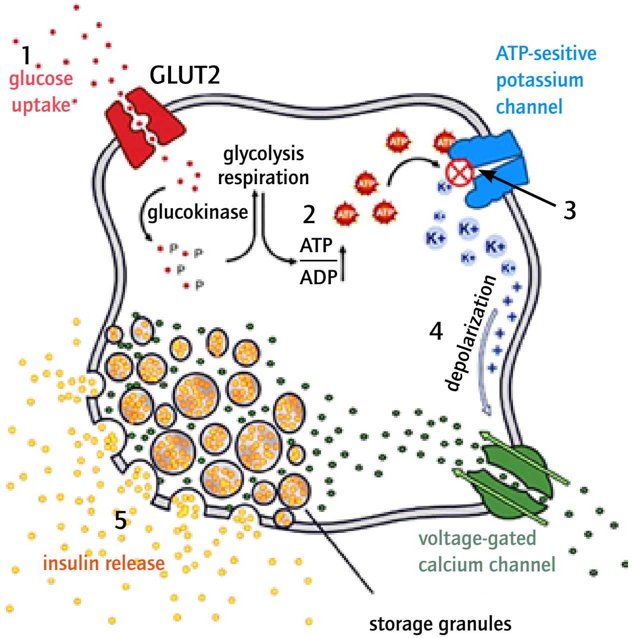


Figure 4.8. Schematic diagram of the coupling of the serum glucose level to insulin secretion from the pancreatic β-cell: (1) glucose enters the β–cell via the GLUT-2 transporter; (2) glycolysis provides ATP; (3) ATP-increase inactivates potassium; (4) the cell depolarizes, calcium channels are opened, and (5) insulin is secreted. Source: Beta Cell Biology Consortium, www.betacell.org 2004

In addition, hormones produced by entero-endocrine cells in the intestinal wall influence insulin production. Entero-endocrine cells secrete (incretin) hormones in response to specific bowel content. This signals the pancreas to prepare for the nutrients that will appear later in the blood. A full stomach and small intestine stimulate insulin secretion. Conversely, as the stomach and small intestine empty, insulin secretion is inhibited. For more specific information see the gray printed italic text block.

Moreover, conscious processes and perception (stress, smell, and the like), affect insulin secretion via the autonomic nervous system. Sympathetic stimulation with norepinephrine provides a net inhibition of insulin secretion. Parasympathetic stimulation (relaxation) results in stimulation of insulin secretion.

The pancreas as part of the gastro-entero-pancreatic system (GEP)

The entero-endocrine cells of the gastrointestinal tract together with the pancreas endocrine system are the largest endocrine system in the body: the "gastro-entero-pancreatic system" (GEP). This GEP is a system of intense communication, with feed forward and feedback communication by for example incretins. GEP, in reaction to food in the intestine, controls the digestion, absorption, and processing of nutrients as well as communication with various organs and tissues in the body. GEP is entirely focused on the successful integration of nutrition from the intestine into the body. The islets of Langerhans are the only part of GEP not in direct anatomic contact with the intestinal lumen. During embryonic development, we see how small groups of entero-endocrine cells detach from the intestinal wall and migrate to develop into islets in the pancreas. The same type of development is seen phylogenetically in the invertebrates (chordata). They have pancreas-like structures which develop from groups of insulin-producing cells near the bile duct into a real organ. This organ has exocrine and endocrine functions, such as can be found in the mammals.

All body cells are affected by insulin. Generally, insulin stimulates amino acid uptake and protein synthesis and inhibits protein breakdown. Additionally, insulin stimulates DNA synthesis and cell division and inhibits apoptosis.

Liver, muscle, and lipid cells in the body are largely dependent on insulin for glucose uptake from the blood. Fat and muscle cells make up a large part of the body. This accounts for a total of about 40% of insulin-dependent glucose uptake from the blood (see also section 4.4.4.).

The effect of insulin on liver and muscle cells includes stimulation of glucose uptake, glycogen synthesis, lipogenesis with the formation of fat droplets, and protein synthesis. The effect of insulin on fat cells consists glucose and fatty acid uptake and lipogenesis.

In other words, insulin supplies energy and promotes its storage (in the form of glycogen and fat) and encourages recovery (protein synthesis): it has an anabolic effect.

In fat and muscle tissue, insulin is necessary for energy creation and storage. Muscle tissue enables physical action and the ability to actually change things in the outside world. Adipose tissue is important for the storage of energy and enables humans to be active for longer time periods without the need for caloric intake. Adipose tissue moreover contributes significantly to the outer body shape of the human being. This renders insulin an important link in the human being's physical expression in the world.

The above information on insulin may enable us to reformulate and articulate its role in the organism: this is the **third step** of the *4-step* approach. The anabolic effect of insulin has a profound impact on how the human being expresses him- or herself in the world.

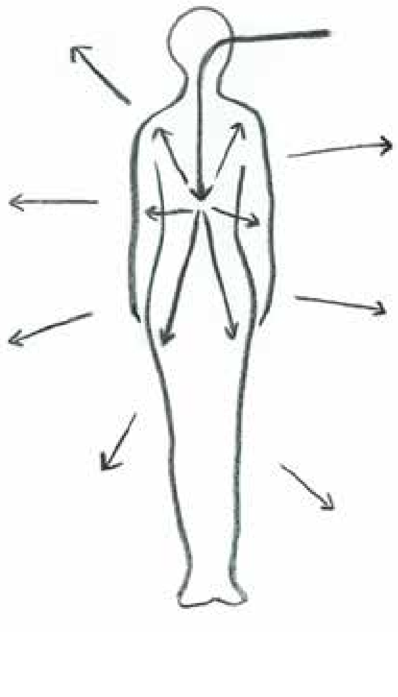


Figure 4.9. Pictorial representation of the dynamics of insulin activity. Insulin allows for the absorption of nutrients and the ability to express oneself physically in the outside world. The large arrow that goes from outside through the mouth towards the middle of the body indicates the food that is taken up in the intestines.

Resume

Insulin is an anabolic hormone, it generally stimulates anabolic processes and growth, and it is of great importance for the regulation of the serum glucose level. Insulin is a central link in the energy supply to fatty tissue and muscles, and is therefore significant for humans in being able to express themselves in the world.

4.2.7. Metabolic Changes in DM1

DM1 occurs when there is a significant shortage of insulin. The body changes to a catabolic state of extreme fasting, despite the excess of glucose ("starvation in the midst of plenty"). There is not enough insulin available for glucose uptake in insulin-dependent tissues (liver, muscle, and adipose tissue). The liver produces glucose from glycogen stored in hepatocytes, and ketones (as glucose substitute) via fatty acid oxidation. As muscle cells deplete their glycogen stores, they move to the consumption of fatty acids and ketones. Fat cells give off free fatty acids which the liver partially converts to ketones. This creates an over-production of ketones. Ketones are acidic and can cause ketoacidosis.

The energy supply stream that is normally present in the blood becomes disconnected from the insulin-dependent cells in the body that need the energy.

Secondary to the metabolic changes, osmotic changes also occur. Normally, all glucose present in the proximal renal tubule can be reabsorbed from the primary urine, but when the serum glucose level reaches a certain limit, the kidney can no longer recover glucose from the filtrate and it is excreted in the urine. The excess glucose in the filtrate creates an increased osmolality in the distal tubule causing water to move into the lumen and be excreted in the urine. This osmotic diuresis causes a loss of water from the blood and a watery glucose-containing urine. The serum has a high osmotic value due to the high glucose level that hinders the reabsorption of a variety of ions, such as sodium. This causes a loss of minerals.

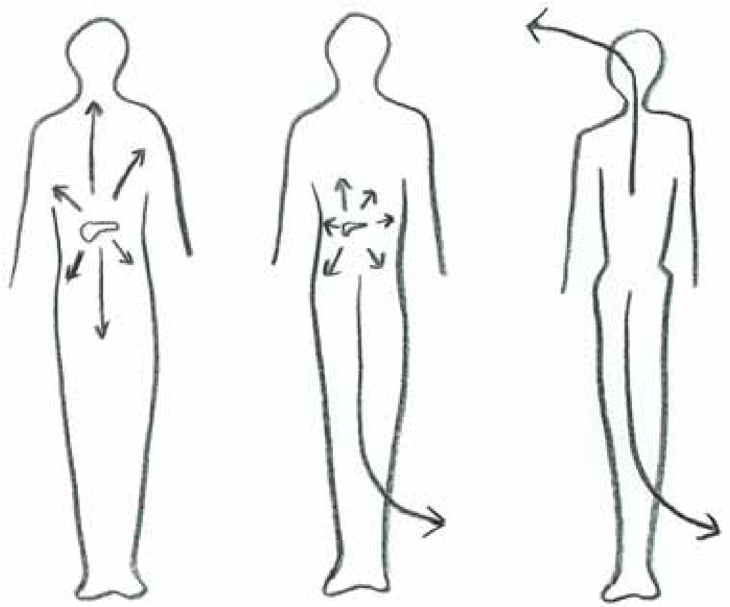


Figure 4.10. Metabolic Changes in DM1. Left: sufficient production of insulin by the pancreas. Middle: insufficient production of insulin, and loss of glucose in the urine. Right: near absence of insulin production with weight loss, loss of glucose and ketones in the urine, and loss of ketones via respiration.

Resume of DM1

DM1 symptoms show the body in a catabolic state. It seems to disappear, to waste away, and to dissipate. Conscious awareness and perception retreat from the outer world.

Laboratory examination reveals a metabolic contrast between the high serum glucose level and the catabolic state in the peripheral cells accompanied by ketonuria, acidosis, and osmotic changes.

Histology shows a chronic inflammatory process in which specifically the β-cells of the pancreas are destroyed.

Insulin stimulates the nutrition phase of the organism and generally promotes anabolism and growth. It is of great importance for regulating the serum glucose level. Insulin is an important link in the energy supply to muscle and fatty tissue, and subsequently in the person's capability to physically express himself in the world.

Anabolic metabolism, growth, and energy supply to the periphery are deficient in DM1; the organism is in a catabolic state despite the fact that there is abundant glucose in the blood. Secondary to the lack of anabolic capability, the body loses the ability to retain water and minerals.

4.3. Diabetes Mellitus Type 2 (DM2), from Patient History to Pathophysiology

4.3.1. DM2; Case Presentation John

John is a 55-year-old heavy balding man with short gray hair. He seems moderately taken care of and somewhat fatigued; he has a pale, gray complexion.

He presents to the clinic complaining of thirst and dry lips over the past three weeks. He must constantly visit the toilet and urinates large quantities. He sleeps poorly at night since he wakes up thirsty every hour and a half, goes to the fridge to get something to drink, and then to the toilet to urinate. He also suffers from penile inflammation making urination painful. He feels tired which he attributes to poor sleep.

After further inquiry, he appears to have felt depressed for some time, has little desire to be active, and sees little purpose in his life. He lives by himself, is jobless, and often sits in front of the television when home. Out of a sense of duty, he goes grocery shopping for his mother once a week. The only thing that he looks forward to is his weekly meeting with his son.

At physical examination, we see an obese man with a waist circumference of 123 cm. His pulse is regular at 88/minute and his blood pressure is slightly raised at 150/88 mm Hg.

The penis glans is red around the urethral opening with some white spots that have a sharp border consistent with a fungal infection.

Physical examination was otherwise unremarkable.

4.3.2. Symptoms in DM2

The main symptoms in DM2 are: fatigue, dry mouth and excessive thirst, polydipsia, and polyuria.

John has suffered these symptoms for about three weeks. He may have also experienced some weight loss, but this is much less prominent in John than it might be in someone with DM1. Similar to DM1, blurred vision may occur in DM2. Both men and women may suffer from genital fungal infections as John does.

The clinical course of DM2 is usually gradual and the risk of keto-acidosis is small. In exceptional cases, and particularly in people with decreased awareness of thirst, there may be a hyperosmolar hyperglycemic syndrome (HHS) caused by high serum glucose levels. HHS includes severe hyperglycemia and significant dehydration in the (almost complete) absence of ketone production. The first symptoms are confusion and drowsiness with dehydration which may further progress to a comatose state. In HHS, we see an increased risk of thromboembolic complications, such as heart attacks or strokes.

At the time of diagnosis, most DM2 patients already have one or more chronic complications such as cardiovascular disease, delayed wound healing (especially on lower legs and feet), fungal infections, and cognitive disorders.

Possible complications of DM2 are numerous, may manifest in almost any tissue, and may lead to a wide variety of functional disorders. Among the most well-known complications in addition to the aforementioned are retinopathy, neuropathy, depression, sexual dysfunction and rigidity of connective tissue structures with joint stiffness and musculoskeletal complaints.

DM2 is strongly associated with obesity and generally occurs in middle to older age. However, as obesity begins to plague younger populations, DM2 is increasingly diagnosed in adolescents and young children.

> The symptoms of DM2 can be grouped into the same categories as those of DM1. This simplifies the comparison between the two later in this chapter.

Table 4.3.

Category	Laboratory findings
Metabolic changes	• (Very) High blood sugar • Thirsty, excessive drinking, polyuria, and glycosuria • Usually overweight with increased abdominal girth
Changes in consciousness and perception	• Fatigue • Blurred vision • Lethargy • Coma (HHS; rare)
General changes	• Gradually emerging • More common in mid life through old age
Chronic complications	• Effect of vascular injury such as cardiovascular disease, nephropathy, retinopathy, neuropathy, cerebropathie • Frequent infections/immune problems • Depressive disorders • Stiffness of the motor system

In more acute cases, the loss of glucose and water is pronounced. The more chronic complications such as frequent infections due to impaired immune function and tissue damage to end organs due to micro- and macrovascular pathology may likewise contribute to the overall impression that the body is "falling apart." In general DM2 may be characterized as an impending loss of cohesion in the organism. The rigidity of the musculoskeletal system is indicative of a hardening tendency. Consciousness and perception are less focused on interaction with the environment and trigger feelings of increasing isolation similar to symptoms in depressive disorders.

Resume

The symptoms of DM2 show reduced cohesion in the organism and its functions. Anatomical and functional areas disintegrate and become disconnected from the functioning of the body as a whole; tissues become hardened. Consciousness and perception are less involved with the outside world and the inner world has a tendency to become isolated.

4.3.3. John's Blood Tests

John's serum glucose was measured at 27.8 mmol/L (normal values non-fasting from 2.7 to 11 mmol/L), the total cholesterol was too high at 6.7 mmol/L (1.5 to 6.5 mmol/L), HDL-cholesterol was on the low side at 0.78 mmol/L (0.9 to 1.7 mmol/L), LDL-cholesterol level is increased: 5.9 mmol/L (typically 2.0 to 4.5 mmol/L), the triglyceride likewise at 3.6 mmol/L (0.8-2.0 mmol/L).

4.3.4. Laboratory Tests in DM2

As in DM1, the diagnosis DM2 is confirmed by laboratory tests. The best parameter for diagnosis is the fasting glucose level in the blood.

In addition to an increase in serum glucose level, lipid metabolism disorders are often present: increased triglycerides, increased LDL-cholesterol, and decreased HDL-cholesterol. Dehydration may cause renal impairment. Renal dysfunction can also be caused by microvascular damage.

Oftentimes, abnormal laboratory values fit the clinical findings in metabolic syndrome. Metabolic syndrome is a collection of abnormal metabolic values including central obesity (increased waist circumference), hypertriglyceridemia, low HDL cholesterol, hypertension, and impaired fasting glucose. The diagnosis is established when at least three of these characteristics are present. Patients who already have some of the factors that match metabolic syndrome but normal serum glucose levels have an increased risk of developing DM2.

Table 4.4.

Category	Laboratory findings
Organ: endocrine pancreas	• Normal to high C-peptide
Metabolic changes	• High serum glucose levels • High triglycerides • Low HDL cholesterol • High LDL cholesterol • Glycosuria
Osmotic changes	• Reduced sodium • Increased creatinine and urea
Kidney damage	• Albuminuria

Resume

Laboratory examination shows an abundance of nutrients in the form of glucose and fats present in the blood in combination with normal to elevated insulin levels. Osmotic changes may be seen. Other organ systems are often affected.

4.3.5. Histological Changes in the Pancreas in DM2

Patients with DM2 present with various pancreas abnormalities: there may be hyperplasia of the pancreatic islets, which is also seen in patients with obesity and insulin resistance and seems to be related to the adjusting to a larger glucose load; the islets usually have a reduced number of β-cells with impaired function that secrete less insulin; there are more macrophages present than normal.

In addition, more fibrosis and amyloid plaques[16] may be seen in the connective tissue of the islets. These plaques resemble amyloid plaques found in the brain of patients with Alzheimer's disease. The mechanism by which amyloid plaques in the islets come about is not known, but there may be an association with the loss of β-cells (Westermark et al 2011).

Inflammation may also play an important role in the reduction and reduced function of β-cells. How this inflammatory reaction starts is still unclear but several factors play a role, such as chronic exposure to elevated serum glucose levels, an increased exposure to saturated fatty acids, and/or the extracellular deposition of amyloid; moreover, an increased amount of pro-inflammatory cytokines accompanies both obesity and chronic dental infection which are often present in DM2.

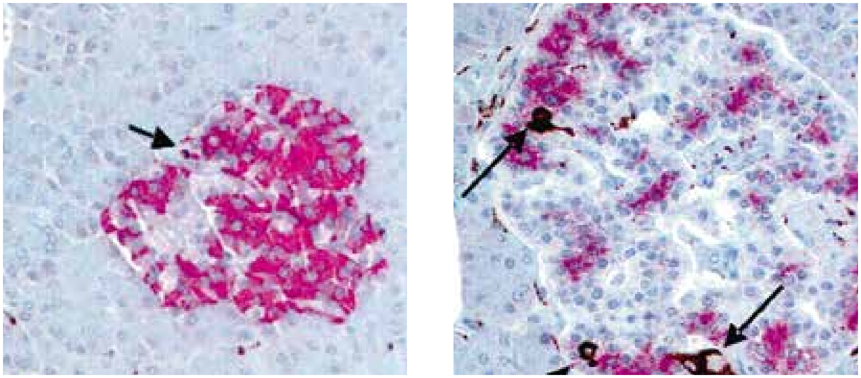


Figure 4.11. On the left a healthy person's pancreatic islet. On the right the pancreatic islet of a patient with DM2. Insulin is tinted pink and macrophages are brown colored (see the black arrows). Source: Ehses et al, Diabetes 2007

When compared to the physiological healing process (section 4.2.5.), the DM2 disease process could be characterized as stagnation in the third, proliferative phase of this process as confirmed by the fibrosis that is present and the amyloid deposition.

16 amyloid plaques are insoluble aggregates of polypeptides

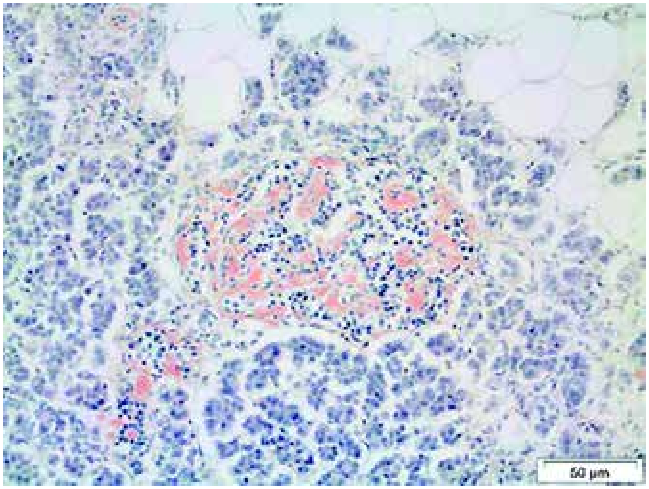


Figure 4.12. Pancreatic Islet of a Patient with DM2; the amyloid deposit is stained pink. Source: Westermark et al 2011

Resume
Pancreas histology reveals a chronic, low-grade inflammation in DM2 with a decreased number of β-cells, fibrosis, and amyloid deposition. These reflect a tendency toward consolidation and a loss of cohesion in the pancreas.

4.3.6. Pathophysiology of DM2

DM2 pathophysiological changes are increased peripheral insulin resistance and impaired pancreas β-cell function. Insulin resistance is particularly high in the liver, muscle, and in adipose tissue. Resistance in this context means that the cells are less responsive to insulin.

Diminished sensitivity of liver cells to insulin will make it harder for the liver to switch from glucose output to glucose uptake. Muscle cells that are resistant will only take up glucose when higher

insulin levels are present; fat cells will secrete more fatty acids, resulting in elevated triglyceride levels in the blood.
It is assumed that insulin resistance occurs first and the progressive loss of pancreatic β-cells happens later.

Resume
Pathophysiology of DM2 shows reduced sensitivity to insulin activity in several tissues (insulin resistance), which implies a decline of anabolic processes and growth in, and energy supply to those tissues. The insulin system's periphery (the various tissues) is less connected to its center, the pancreas. Pancreatic β-cells can adapt to a high degree, but in DM2 become overloaded and begin to break down and decompose due to inflammatory reaction.

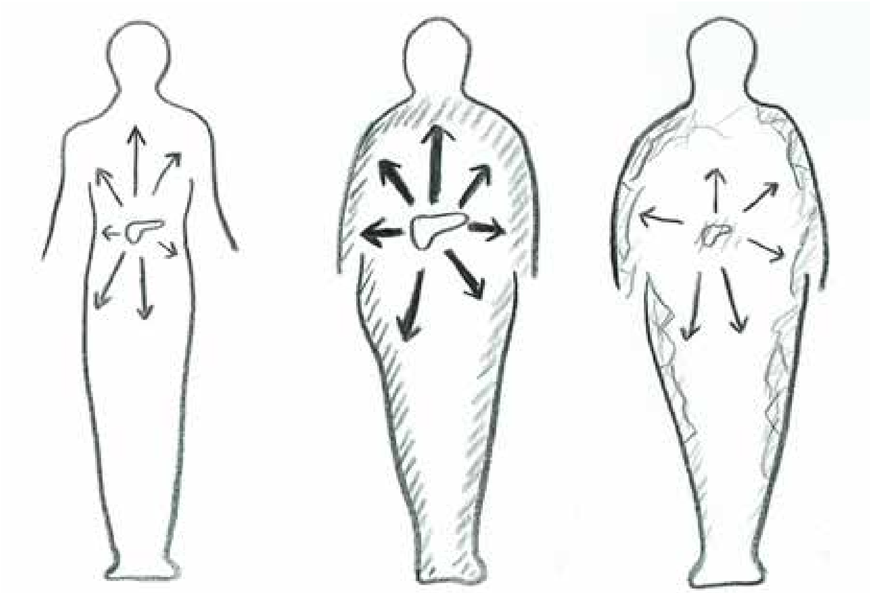


Figure 4.13. Metabolic Changes in DM2: the picture on the left represents sufficient insulin production by the pancreas; the middle picture represents insulin resistance in peripheral tissues and hypertrophy of the pancreatic islets; on the right an inadequate production of insulin with loss of glucose to the urine and reduced cohesion in the periphery is shown with disintegration and consolidation.

Resume of DM2

The symptoms of DM2 represent reduced organic cohesion; various parts disintegrate and lose their connection with the organism as a whole; tissue consolidation occurs as a result. Consciousness and perception are less focused on interaction with the outside world and the person's inner world tends to become isolated. Laboratory examination shows an abundance of nutrients in the blood in the form of both glucose and fats in combination with normal to elevated insulin levels. There may be osmotic changes.

Pancreatic histology in DM2 shows a chronic inflammatory process and a slow decrease in the number of β-cells.

There is reduced sensitivity to insulin activity in various tissues in DM2. Anabolic processes and growth in, and energy supply to those tissues are restricted (insulin resistance). The periphery and center (pancreas) of the insulin system are less connected. Pancreatic β-cells can adapt to a large extent but become overloaded, break down, and decompose in a chronic inflammatory process.

4.4. From Characterization of DM1 and DM2 to Their Treatment

4.4.1. Introduction

This section discusses and compares the similarities and differences between DM1 and DM2. It provides insight into the role of insulin, how the system's functioning becomes disrupted and disease develops, and it describes the characteristics of the resulting disorders. This will give a better understanding of both types of diabetes mellitus and may aid the physician in giving appropriate advice and choosing suitable therapeutic modalities for the patient.

We will not discuss regular pharmacologic treatment of diabetes such as oral antidiabetics and insulin. For this, the reader is referred to existing treatment guidelines.

Our aim is to apply the characteristics of DM1 and DM2 that we obtained using the *4-step* approach and show them to be two polar opposite disease processes: central dysregulation due to auto-immune induced destruction in DM1 versus the dysregulated peripheral resistance leading to overload of the pancreas in DM2.
It is important to remember that in a clinical setting we rarely see patients who have pure type 1 or type 2 diabetes. An example is the lean patient with DM2 who also shows some DM1 characteristics. Diabetes manifests differently in different patients both centrally and peripherally. With regard to acute and chronic complications of the disease, patients also have their own stories.

4.4.2. Consciousness and Pathophysiological Process

Pathophysiological changes are typically already established in both DM1 and DM2 before the patient experiences symptoms, and as such, the patient remains unconscious of the disease prior to diagnosis. In DM1, the hidden disease process is the autoimmune destruction of β-cells. In DM2 it is the development of insulin resistance in the liver, muscle, and fat cells. The pancreas can compensate for much of this deficiency, but eventually reaches a limit, after which the serum glucose level will increase. At that point, the patient becomes aware of symptoms of fatigue, excessive thirst, polydipsia, and polyuria.

It is typical for the underlying disease process of the endocrine pancreas to remain unconscious for a relatively long time period given that pancreatic functions are part of the body's metabolic processes of which we are not normally aware. Yet, the availability of glucose is a prerequisite for our conscious awareness and muscle function. Glucose supports humans in being aware and active.

Anabolism and Catabolism

Anabolic processes, creating metabolic pathways for energy storage, growth, and recovery, and catabolic processes, causing the break-down of energy supplies and of tissue, are tightly regulated in the organism. They have an important role in shaping the body. These two processes are attuned to the needs of the moment. If

our bodies would be subjected to anabolism and growth only, we would be round in shape and continue to expand. The combination with catabolic metabolism and breakdown allows the body to develop its specific shape.

During the growth and development of children, anabolic processes prevail; nonetheless, there is simultaneous breakdown and these two opposite processes require coordination. The result of this balance ultimately determines the degree of the child's growth as the physical body takes its adult form.

In wound healing, there is also a breakdown phase—the second "inflammation phase," and a growth phase, the third "proliferation phase." Breakdown creates the opportunity for something new to develop. In wound healing, the "clean up" of the wound in the inflammation phase creates room for new tissue in the proliferation phase. You can read more about this in the Companion The Healing Process (Van der Bie et al 2008). In the embryonic period, organs often have a temporary structure that later disappears with the help of breakdown processes so that it finally can give way to the permanent organ shape.

The excessive storage of fat contributes to round body shapes that prevail in obesity. Too much breakdown leads to becoming underweight with pointy shapes. This reformulates the dynamic patterns of DM1 and DM2.

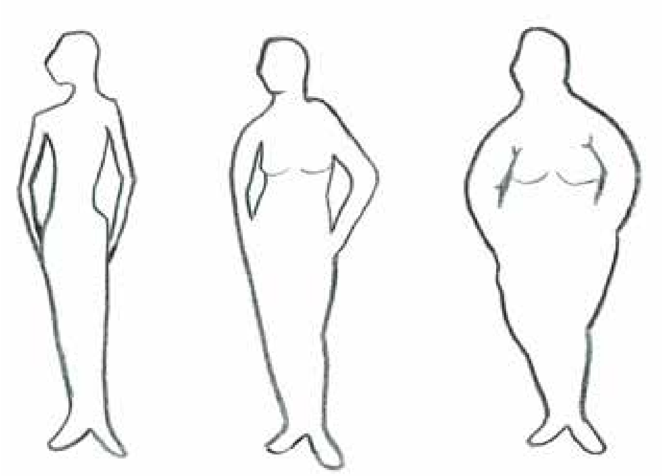


Figure 4.14. Pointy Versus Round Shapes

What is your impression when you look at these two different body shapes? Pointy forms are perceived as active, awake, and aware. Round shapes are experienced as more quiet, dreamy, gentle, and nurturing. These experiences are similar to the effect of anabolism and catabolism in the body. Anabolism makes you sleepy as you may remember from a postprandial dip or can recognize in the sleep need of growing children. Catabolism makes you initially alert as you may know from the adrenaline rush in hypoglycemia or from the breakdown of glycogen in fright or during intense exercise. This may aid you in recognizing the underlying disease process of DM1 and DM2, the third *step of the* 4-step *approach.*

4.4.3 Anabolism and Catabolism in DM1 and DM2

To restate, we can say that DM1 is dominated by **catabolic** tendencies in several areas from the start as the immune system attacks pancreatic β-cells and breaks them down. The absolute insulin deficiency that results creates a catabolic state of the body in which the cells that are dependent on insulin for their glucose uptake use up their glucose stock. The patient consequentially loses weight. Eventually, a metabolic acidosis occurs as break-down gains the upper hand.

Initially in DM2 an overall **anabolic** state prevails with weight gain, an increase in adipose tissue, and high insulin levels. This accompanies the anabolic lifestyle in the western world: too much, too often, and too easily available. We do not engage in enough intensive exercise or have fasting periods that appeal to the body's catabolic processes. The pancreas cannot keep up with the demand for insulin and as a result, hyperplasia of the Langerhans islets can develop. This eventually causes permanent damage to the pancreas, thus creating a pathological catabolic process that occurs in tandem with the anabolic process of DM2.

The life-saving treatment for DM1 is the substitution of the anabolic hormone insulin. But even this cannot match the needs of the body as well as the pancreas production can in a healthy person. Sometimes we may titrate a bit too much insulin and sometimes a bit too little, which causes more glucose fluctuation in the blood and tissues than in a healthy state. The insulin pumps that are popular today may help reduce these fluctuations. The fact that glucose and insulin levels are not properly matched makes patients with DM1 prone to the same complications we see in DM2, especially as they age, gain weight, and insulin resistance begins to occur in peripheral tissue.

4.4.4. Active Movement and DM

Muscle tissue enables us to act in the outside world, changing it. To effectuate this, nutrients are converted to energy needed for muscle action. With the aid of insulin, muscle tissue takes in about 80% of the available glucose after a meal.

In addition to the insulin effect, muscle cell contraction facilitates the uptake of glucose into the cell by repositioning vesicles with GLUT4 (glucose transporter-4) near the cell membrane. This is called the *contraction pathway*. This pathway is especially important in the heart, but also occurs in skeletal muscle cells. In addition, moving the muscles makes them more sensitive to insulin. Movement provides muscle cells with a suctioning dynamic as it were, which draws in the glucose to be used as energy.

Physical activity tailored to the individual's need is therefore of prime importance in both DM1 and DM2. In patients with DM1, it seems especially important to "invite" them to experience their body and enjoy moving while exercising, and not aim at excessive catabolic training. The latter is, however, just what is needed in patients with DM2. They particularly need to be challenged to move and in such a way that the movements launch an intensive catabolic process in the organism. In DM2 patients should be motivated and encouraged to engage in vigorous aerobic exercise and cross their boundaries in training. When insulin-resistance decreases, maybe in conjunction with robust physical activity, the muscles will no longer be involved in the disintegrating process of DM2.

Since the rise of computer technology, people lead increasingly sedentary lifestyles. But perhaps more important is that what we look at (TV images, computer games) is a virtual reality and therefore our normal physiological reaction to what we watch does not fit real life. Pressing a button with your finger is an activity that does not match your physiological reaction when you perceive someone running away on the screen. So the *physical activity* (moving your finger) is not consistent with the *sensory perception* (running), while at the same time a running movement *intent* arises in the mind. This intent prepares the body to move by raising the serum glucose level, but the glucose is not used accordingly by the muscles since we only lift a finger. A pilot study investigated the effect of playing computer games in children with DM1. This led to higher serum glucose levels, which in turn increased the need for insulin in this group (Phan-Hug et al 2011). The virtual reality that was created stands next to and is virtually independent of the physical reality in such situations. The reaction in the mind prepares the body for action but the muscles do not use the available glucose for running activity. This is a typical problem of our present age, as is the rise of DM2.

From this perspective, watching excessive amounts of TV or engaging in computer/video games is contraindicated for people with DM1 and DM2 because these activities further disconnect body and mind.

4.4.5. Stress and DM

Stress causes a reduction of insulin production via (nor)adrenaline as well as increased peripheral insulin resistance via cortisol. Stress reduction is therefore important for both DM1 and DM2 patients. It is important to choose a form of stress reduction that closely fits the patient's individual needs. Janine (DM1), for example, is (over) active and is easily influenced by what her surroundings ask of her and may react impulsively and emotionally to external stimuli. Mindfulness or other body-oriented meditation exercises would help strengthen her and bring some inner calm.

For patients that worry[17] or have unsafe behavior such as careless handling of insulin administration in stressful situations, mindfulness or other body-oriented meditation exercises are also effective. These not only promote relaxation, but also lead to a better (self) perception.

John (DM2) has been struggling to express himself on an emotional level[18]. Introverted people

17 worrying symptomology fits our characterization of DM1 patients if we regard the *4-step* approach. See also the history of Janine in 4.2.1.
18 this would fit DM1 patients if we look at our characterization with the *4-step* approach. See also the history of John in 4.3.1.

may benefit from learning to express themselves more freely. They can learn this with the help of music, drawing, or painting, but also by writing, speaking, or by moving. Acquiring the habit of reflecting on the emotions of the day before going to sleep, may be helpful in processing them.

The sleep-wake rhythm and a balanced alternation between rest and activity is also of great importance for diabetic patients. When the patient has sleep problems, it is important to assess whether or not he or she has both enough exercise and periods of rest during the day and how sleep hygiene is in general.

Children with traumatic experiences have an increased risk of DM1 or DM2 later in life. Stress may influence the immune system and increase the chance of auto-immune disorders and therefore of DM1 (Nowotny et al 2010). A chronic hormonal stress reaction can cause epigenetic modifications of the DNA and result in low-grade inflammation with increased risk of developing DM2 in later life.

4.4.6. Nutrition and DM

Diet, eating habits, and the 24-hour eating and fasting pattern should be investigated and modified if necessary for diabetic patients.
In DM1 and DM2 glucose cannot be stored nor burned in the cells . Nutrients that are quickly and easily broken down to simple sugars in the intestine, called “fast” carbohydrates,[19] increase the serum glucose (too) quickly. Therefore, fast carbs are to be avoided in the diet.
For a healthy intestinal flora and a well-functioning immune system, a varied diet with plenty of fiber and low in fast carbs is important.

Nutrients with a slow passage through the digestive tract due to high fiber content or “slow” carbs seem better absorbed and have a positive effect on satiety and the metabolic/immunologic balance. Mindful chewing and a peaceful environment during eating and digesting are also important.

19 nutrients with a high glycemic index (GI)

The deliberations above can facilitate an clinical intuition and aid us in understanding the essence of the disease stimulus or impetus in diabetes mellitus, the **fourth step** of the *4-step* approach. For ***DM1*** we could characterize this process as ***the need to connect.*** Based on this description, we may select warm and attractive foods for Janine (DM1). Food can become more attractive for Janine in different ways: eating foods she really has an appetite for, chewing and tasting the food well, enjoying a peaceful atmosphere while she eats, and by observing how the food agrees with her, Janine can develop a better relationship with the nourishment she takes in as well as be more aware of her body and its metabolic processes.

Nutrition significantly interacts with the immune system and in diseases like DM1, the immune system attacks its own pancreatic β-cells, becoming hyper-alert. A gluten-free diet can be attempted to avoid immune stimulation in the intestine, as studies have shown an association between celiac disease and DM1. Eating gluten before the age of three months is associated with the development of antibodies to the pancreatic islets. It is still unclear whether a gluten-free diet influences the course of DM1. It is certain however, that a healthy intestinal flora, which maintains the immune system balance in the gut, is quite important in potentially preventing disease processes like diabetes.

The **fourth step** of the *4-step* approach also can pave the way to an intuitive understanding of the essence or disease stimulus for ***DM2***: we could characterize this as ***the need for challenge***. Based on this characterization we may select a diet for John (DM2) that is different from what he is eating now, one that departs from old eating patterns. In patients like John, it is important to challenge the habit of eating too much and the preference of "fast" foods, comfort food that is quickly digested, and introduce new, varied, and healthier foods. The word "challenge" also implies that dietary advice is given on a positive note. Instead of lists of what may or may not be eaten, emphasizing the experiment of changing one's diet as a discovery voyage is likely to be more effective.

The timing and rhythm of meals and of fasting also has an effect on digestion. Nocturnal fasting is important for improving insulin sensitivity of peripheral tissues and in the mornings the organism needs less insulin than in the evening. Being more aware of the rhythm of eating and fasting can also be quite a challenge.

4.4.7. Individual Approach and Treatment of DM

We may characterize individual diabetic patients by locating their symptomology on the broad spectrum between insulin deficiency (DM1) and insulin resistance (DM2)—between center and periphery. To do so, we observe how impressions coming from the environment are handled (hyper alertness, stress) and how he or she can express him or herself in the world, the extent to which the patient must be *invited* to connect (to his or her body) or rather be *challenged* to connect (section 4.4.6.). The resulting characterization enables us to realize a truly individual treatment plan.

The life style changes we discussed above address themes such as exercise, stress reduction, and dietary changes.
These themes also offer possibilities for input from different forms of integrative medicine if desired.

4.4.8. Summary

Insulin is a key hormone to the integration of the human mind and its ability to express itself in the world, including, but not limited to, muscular action. We may observe disintegration between these two components in DM due to an absolute (DM1) or a relative (DM2) insulin deficiency. In addition to regulating the serum glucose level, therapeutic intervention can focus on the reintegration of body and mind. The *4-step* approach can aid in discovering and developing individualized treatment and therapeutic resources to this aim.

5. A Phenomenological Approach to the Endocrine System

by Guus van der Bie MD
and Ricardo Ghelman MD PhD

5.1. Introduction

In previous chapters, we attempted to methodically link patient complaints to the biological phenomena of the endocrine system, as well as conscious awareness and other psychological phenomena. We made an attempt to clarify the relationship and interaction between biological occurrences and the mind. To this end, patients were described suffering from thyroid disease —hyper- or hypothyroidism—and diabetes mellitus type 1 or 2 (DM1 or DM2). This gave us a more comprehensive understanding of the interplay between the endocrine system and psychic phenomena and experience.

The physician's observation of his/her inner experience was also discussed. When you systematically develop personal awareness of these experiences, they may mature to a form of skilled intuition (Groopman 2007). They will aid in understanding how to build the bridge between the quantitative and qualitative aspects of the sick patient, as well as of the illness (Stolper 2011). This approach gives us more insight into the qualitative aspects of endocrine organs, their functions, and their psychology. It also provides insight into the symptoms and inner experience of the patient. Seemingly unconnected phenomena in physiology may appear to be part of one and the same coherent system of which the patient's inner psychic experience is part.

In this context it is important to first explain what is meant by inner psychologic phenomena and experience. We understand psychologic phenomena broadly to be aspects of conscious awareness such as waking, dreaming, and sleeping, as well as of inner experience such as thoughts, feelings, and impulses, and of actions, deeds, and behavior.

5.1.1. Chapter Aim

We will discuss the whole of the endocrine system as one functional unit in this chapter. We will show the role of the endocrine system in human (and animal) physiology and in human psychologic experience including conscious awareness and behavior. The description of the shape, function, and topography of endocrine organs as well as of their hormonal secretions leads to a consistent picture of the endocrine system as a functional unit. Evolutionary data of the human (and animal) organism further elucidate and broaden our understanding of connections between endocrinology, awareness, and (animal) behavior.

5.1.2. Polarization

Human and animal organisms evolve embryonically due to growth and cellular differentiation in various tissues and organs (Langman1995). The differences between these tissues can be so great that there seems to be no more relationship or similarity between them. Take, for example, the renal corpuscle (glomerulus and the lens in the eye, which are such drastically different tissues, yet they are both integral parts of the same organism.

Diverging differentiation is always an expression of functional differences. From the perspective of growth through cell proliferation (proliferative growth), intestinal mucosa and nervous tissue exhibit clear differences. The cells of the intestinal mucosa have a lifelong high proliferation rate, and spontaneously or after damage, regenerate within days. In contrast, nerve cells lose almost all proliferative capacity during the first ten years of life, such that damage to the central nervous system after this time may cause lasting effects. In this example, differentiation leads to two polar opposite cellular properties in the adult organism: tissue with continued growth potential (gut) and tissue without significant potential for regeneration (nerve tissue). Obviously, this is a relative qualification that only addresses proliferation potential.

We speak of *polarization* when tissues or organs exhibit great differentiation in both form and function, but at the same time have a very close relationship. An instructive example of this is the development of the gonads and sex cells in relation to fertilization. What develops in male bodies to sperm cells, with the loss of cytoplasm, the condensation of DNA, the increased motility, decreased size, and the extreme morphological specialization, does not occur in the female egg cell. Egg cell development leads to an increase of cytoplasm, making the cell the largest in the human body in which DNA structure and chromosome form are lost; morphologically the egg cell is hardly specialized. Nonetheless, conception is the expression of the very close relationship between these otherwise vastly different tissues and cells. Section 5.4.2. describes the thinking in polarities in more detail.

We will study the endocrine system based on the following questions:

- Are there signs of a wholly or partially polarized differentiation within the endocrine system?
- What kind of close functional relationship exists between polarized organs and tissues?

Perspectives for investigation (in this case of polarization) must be seen as a "tool" that can elucidate certain relationships. Chapter 5 deals with the endocrine system as seen from "the perspective of polarization."

5.2. Evolution and Methodology

When studying evolution, it is important to keep in mind that the endocrine system develops in the context of the whole organism (Withers 1992). Different evolutionary levels, such as fish, amphibians, reptiles, or mammals each have their specific level and form of endocrine development. In the same way that differentiation, specialization, and the development of specific organs are an aspect of evolution (phylogeny), they also occur in individual embryonic development (ontogeny): in embryonic development, the organism coordinates its own development through self-regulation (Van der Bie et al 2008).
In addition to studying the evolution of the origin of species (phylogeny) we will also follow the process of differentiation and polarization in humans. *Polarization* is the differentiation process that leads to polar opposite development. As we mentioned before, an example of this is the development of the female egg cell and male sperm cell. These are opposite in terms of shape,

motility, size, and numbers, and yet they have an evident connection to one another. Polarization also occurs in the endocrine system in humans and animals (see Companion "Wholeness in Science", Van der Bie 2012, Chapter 10, 11, 12). This expands our understanding of the human endocrine system as a whole.

The connection between physical development and development of conscious awareness and behavior in evolution is clearly evident: form and function are one. The term "function" is used in its broadest sense, including organ function as well as exercise, activity, and behavior, and expresses itself in the development of species—phylogenetic development—as well as in individual, ontogenetic development (Gould 1977).

The four steps that are discussed in this chapter are a specialized usage of the steps described in Chapter 6. They will demonstrate the applicability of the approach and its usefulness in comparative morphology, physiology, and behavioral science. Phylogenetic and ontogenetic perspectives will be landmarks in the search for a comprehensive understanding of the endocrine system within the context of the organism as a whole. Rather than using a microscope—zooming in on increasingly smaller details—we will elect to use a "macroscope," which enlarges the picture in order to view the system in its context, and with it the *meaning* of endocrine function in the human body.

Interlude

This systematic *4-step* ***approach first describes the facts and symptoms brought to light through*** *analytical research.* ***The second step describes the*** *pattern of dynamic and functional connections* ***between endocrine organs in their final location in the body. The third step outlines the*** *developing process of* ***endocrine*** *cooperation.* ***The fourth step will identify the endocrine system in*** *the context of the human organism as a whole.* ***These four steps eventually clarify the coherent relationship of all parts of the endocrine system, biochemically, morphologically, and functionally (see section 6.1.1.)****.*

5.3. Development of the Endocrine System

The developing organism eventually “gathers” those cells, tissues, and organs that produce hormones and forms them into a cohesive “endocrine system.” Hormones are compounds that act *a distance away* from the place where they were produced by an endocrine gland and that are transported from their place of origin via the blood circulation to the place where they exert their action. The same substances active in the synapses of our nervous system are called neurotransmitters.

An interesting example of a metamorphosis in endocrine function during evolution (phylogeny) can be observed in adrenaline production. As long as it was only active in the synapses of sympathetic autonomic ganglia, adrenaline was considered a neurotransmitter. During reptile development two of these ganglia migrated from the thorax to the abdomen in the vicinity of the kidneys. They connected to the blood circulation, and from that point on adrenaline has been classified as a hormone. This transformation resulted in prolonged and more efficient reactions of organisms to acute stress and a greater range of action in the organism, including places where there is little to no nervous tissue.

In contrast to exocrine glands that excrete hormones for action outside of the organism like those in mucous membranes and skin, endocrine glands release their products inside the organism directly into the blood stream. Even the endocrine glands of the nervous system (pineal and pituitary gland), which lie within the blood-brain-barrier, secrete their hormones directly into the blood and therefore these hormones pass the blood-brain-barrier.

During animal evolution, the endocrine and nervous systems develop as separate units with distinctive organs, but *their development proceeds in parallel*. Both systems, the endocrine and the nervous system, facilitate the typical animal phenomena of consciousness and behavior.
Initially a **neurosecretory** system develops in invertebrates as both a peripheral exocrine gland and a primitive nervous system. Both systems become more internalized during the course of evolution.
This development can be understood as a double process.

First, an internalization takes place in which previously excretory processes in lower animals become incretory in higher developed animals during evolution, such as the development of exocrine to endocrine glands. Secondly, a polarization occurs (section 5.2.). The nervous system and endocrine organs grow ever more apart, become more differentiated, yet remain strongly connected functionally.

Insight into the relationship between the endocrine organs, nervous system, immune system, and human conscious awareness led to the understanding of the psycho-neuro-immune-endocrine axis in the organism (O'Connor et al 2000).

Evolutionary Interlude: the Cranio-Caudal Axis

Over the course of evolution, another polarity develops within the endocrine system. In a sense, one could say that the organism as a whole becomes the place where the polarization of the endocrine system becomes apparent. As the organism developed, specific endocrine organs develop ***cranially*** ***as*** *unpaired organs*, ***such as pineal, pituitary, and thyroid glands; on the*** ***caudal*** ***end, as we will see in the following paragraphs***, *paired organs* ***such as gonads, adrenal glands, and the pancreas grew and developed.***

This is in contrast to the structure of the central nervous system, where the reverse is true: the brain hemispheres are *paired* ***in their structure and the more distal spinal cord is*** *unpaired.*

Above-mentioned evolutionary steps of the endocrine and nervous system developing and growing ever more apart, yet functionally staying connected, successively can be identified in the vertebrates in the development from the evolutionary older jawless fish (cyclostomes or Agnatha), to cartilaginous fish (Chondrichthys), bony fish (Osteichthys), amphibians, reptiles, birds, and mammals. For examples see sections 5.4.4., 5.5.5., 5.6.4., and 5.7. below.

In all vertebrates, we find multiple endocrine organs: pineal gland, pituitary gland including neurosecretory cells in the hypothalamus, thyroid, islets of Langerhans, heart and endothelium, adrenal glands, and gonads. We will study their connections in the following chapters.

5.4. Pineal Gland and Gonads

5.4.1. Pineal Gland

The epiphysis is an unpaired organ located in the middle of the brain under the skull near the epithalamus (diencephalon). The pineal gland in humans is approximately 8 mm in size, has the shape of a cone and is therefore named for its shape: pineal body. The pineal gland produces melatonin that is synthesized by light-sensitive cells, called pinealocytes. Melatonin crosses the blood-brain-barrier. The rhythmic nocturnal release of melatonin enables the pineal gland to regulate the body's circadian rhythm.

Aaron Lerner and collaborators isolated melatonin from the pineal gland of cattle (Lerner 1958). Five years later, the circadian rhythm of melatonin in relation to exposure to light was described (Quay 1963). In the 1960s, the relationship between the sympathetic nervous system and serotonin N-acetyltransferase (NAT) was discovered (Wurtman et al 1964, Klein et al 1970, Chowdhury et al 2008).

The relationship of the epiphysis with light can be elucidated by evolutionary study. In fish and amphibians, external light on the skin of the head stimulates a rhythmic synthesis of melatonin from serotonin via NAT, mainly in the pituitary gland. In amphibians, we find a complex structure on the roof of the diencephalon that is part of the optical system via the pineal nerve, which also occurs in the human embryo (Møller1978). The pineal nerve has a connection to a kind of "third eye," a parietal organ with light sensitive cells capable of light perception located right beneath the epidermis of amphibians. In reptiles, the area in the brain where the nerve fibers from the eye via the optic nerve end, forms a pineal organ. In birds sympathetic nerve fibers develop to a transitional form between direct light perception as in amphibians and a connection to the epiphysis as in reptiles (for comparison see figure 5.1.).

Phylogenetic development in reptiles shows therefore that there is a direct link between the epiphysis and external light that is captured by the "third eye." In birds, an intermediate form develops, and among mammals, the pineal gland becomes completely cut off from external light:

a functional relationship with the visual system is the only remnant. In mammals, the connection with the outside world is further lost due to the forming of the skull in which the epiphysis is completely enveloped. The control of melatonin synthesis, however, remains connected to the diurnal rhythm. Light enters the brain through the eyes and directly affects the suprachiasmatic nucleus in the thalamus. From there the impulse spreads superiorly (to the epithalamus) and caudally (to the hypothalamus) through sympathetic fibers. This creates a "crossing over of the light" at the location of the diencephalon in the center of the brain (figure 5.1.).

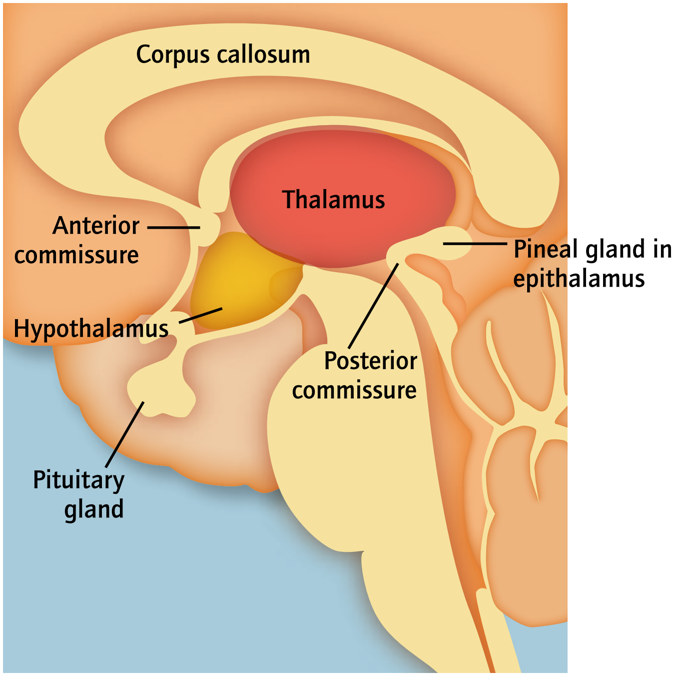


Figure 5.1. Morphological Diencephalic 'Light Cross' of Hypothalamus-Epithalamus-Optic Tract

The pineal gland is a *chronobiologic organ*, an "internal clock" that is synchronized with the sun. In all mammals, melatonin is produced when it is dark and the retina does not register light; stated differently, the production of melatonin is inhibited by exposure of the retina to light. Melatonin is also produced during meditative activity. The most important development of rhythmic melatonin production in humans takes place in the time from birth to the second year of life and then wanes until the age of six or seven years. The establishment of a sleep-wake rhythm in childhood is associated with the production of melatonin.

Biochemical and Clinical Aspects

Melatonin can also stimulate the release of interleukin 1 and 2, which cause fever and activation of the immune system. Thus they address warmth processes and the immune response (through the formation of Th1 cluster CD4-1 cells). These processes correspond to the immunological response pattern typical in childhood and are mostly active at night. Sick children's temperature will typically be higher at night and immunological response stronger, which contributes to the "healing effect" of nightly sleep.

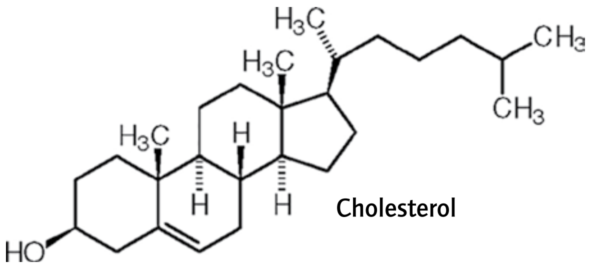
Explicit aspects of pineal gland function in humans include immune stimulating and anti-aging effects. Humans have a longer growing and maturation period between birth and adulthood than primates. This relative growth delay up to about the age of twenty, as well as the delay in aging are specific for humans, whereby a very high age can be achieved. This is in contrast to the animal organism, which is determined more by sex hormone activity from the gonads for its growth and maturation.

> Its direct connection to the circulation gives the epiphysis the character of a metabolic organ, analogous to the anabolic abdominal organs, even if the pineal gland is situated in the middle of the brain.

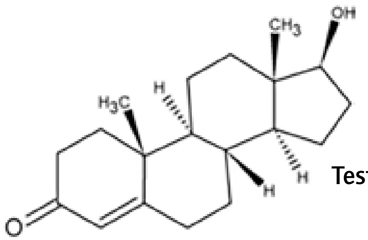
Case reports of epiphysis pathology mention precocious puberty with a lack of melatonin or late onset of puberty with an overproduction of melatonin, depending on the localization of the tumor. This accentuates a relationship of the epiphysis with the gonads.

5.4.2. Gonads

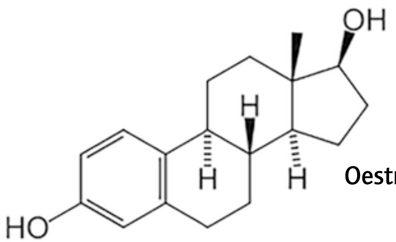
The male and female gonads, testes and ovaries, are paired organs that are part of the genitourinary tract. The gonads have a clear connection with fatty tissue. Their hormone activity creates the typical distribution of peripheral adipose tissue in the male and female body. Adipose tissue determines the characteristic features of the female or male body shape. The relationship of sex hormones to fat is illustrated further by the metabolism and biochemistry of these hormones: the sex hormones are all "steroid" hormones, and as such, are metabolites of cholesterol, a lipid.
The difference between male and female is not only expressed in physical characteristics. In politics, fashion, sports, literature, technology, art, and science it is evident that being male or female, along with the specific physicality, is accompanied by a distinct difference in conscious awareness, behavior, and perception. In that sense gender differences in humans entail much more than just being physically different.



Cholesterol



Testosterone



Oestradiol

Figure 5.2. Interrelated Forms of Cholesterol and Sex Hormones

The human gonads originate embryologically in the head and neck area of the intermediate mesoderm. They arise in the same region of the mesoderm from which the kidneys also derive. In further gonad and kidney development, parts of the developing kidney become included in the genitals, however, the included kidney parts differ in males from those in females (see *Embryological intermezzo* below). One speaks of the genitourinary system to indicate their relationship. From the head and neck area, the gonads and kidneys migrate bilaterally to a retroperitoneal location in a caudal direction. Embryologically and phylogenetically this migration or “kidney descent” takes place along the central nervous system at the back of the organism. This migration is the largest known in the human embryo, and successively the pronephros and the mesonephros—both early iterations of the mature kidney—and finally the metanephros appear. These developmental stages are consistent with the successive development of the kidneys in fish (pronephros only), reptiles (mesonephros) and mammals (metanephros). Development of the individual (ontogeny) appears to be a repetition of the development of species (phylogeny).

Embryological Intermezzo

The female sex organs originate from the Müllerian Duct and are a product of pronephros development. When a Y chromosome is present, the development of these structures is inhibited and the Wolffian Duct develops into the male vas deferens and epididymis ductuli. These originate from the mesonephros.

Human primary gonads were originally connected to the Müllerian and Wolffian ducts embryonically but developed into separate glands. They develop from mesoderm in the seventh and eighth week at the end of the embryonic phase, after the primary genital cells that originate from endoderm have migrated to the primitive gonads.

In the same period (seventh and eighth week) an important development takes place in the procencephalon[20] with the expansion of the paired right and left large hemispheres of the brain. This brain enlargement coincides with the development of the gonads. This points to the relationship between nervous system and endocrine organs.

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20 front part of the brain

Phenotypically, the embryo is asexual until week 7 to 8. After week eight sexual differentiation sets in. In the absence of a Y-chromosome the medulla of the primitive gonad degenerates and the cortex *develops to become the ovarian cortex. In the presence of the Y chromosome, the* medulla *develops into the testicle with spermatogonia. The ovaries develop from the peripheral portion of the primitive gonad, the testes out of the central portion (Browder, 1985, Ghelman 1995).*
In the development of the external genitalia, the female phenotype remains closest to the undifferentiated embryonic and fetal morphology. In the presence of testosterone the penis and scrotum of the male develop and the descent of the testes sets in.

The final separation of male and female takes place at the beginning of puberty when secondary sexual characteristics develop. Testosterone or estradiol are drivers of this process, directing most notably the fat distribution in the body. These hormones are decisive for the male or female typical morphology.

5.4.3. The Connection Between Pineal Gland and Gonads: A First Endocrine Polarity

Melatonin inhibits the onset of sex hormone synthesis and delays the onset of puberty. This enables us to understand that the average onset of puberty (pubarche and menarche) varies in populations and depends on the place on earth where one is born. At the poles, with less exposure to sunlight, adolescence tends to begin later, at age 15 or 16. This enables people in those areas to grow taller in height. In the equatorial zone where exposure to sunlight is greater and the epiphysis and thus melatonin production are inhibited, puberty tends to start earlier, sometimes even at ages 9 to 11. This also means that ossification of the long bones is accelerated since sex hormones ossify the growth plates and there is less growth in height.

As populations move to other regions of the planet with a different light exposure, pubarche and menarche will change after two or three generations. The pineal response to local light stimuli may lead to a change in the genetic pattern within families. The inheritable genetic change caused by a change in light exposure therefore induces a new, epigenetically determined pattern of inheritance.

The polarity between the pineal gland and the gonads also becomes visible in their form as well as in their relation to light exposure and their distribution in the body. The pineal gland is a morphologically unpaired organ, localized at the very cranial side of the body, the gonads are paired organs located at the very *caudal* end of the body (see also section 5.3. grey block: Cranio-Caudal Axis). The changing day light in the seasons affects both organs and plays an important role in the reproductive sexual stimulus and associated behavior, and its inhibition by the pineal gland.

5.4.4. Morphology, Physiology, Conscious Awareness, and Behavior

The above described relationship between the form and function of pineal gland and gonads, as well their interaction, clarifies the importance of the connection between human morphology, physiology, conscious awareness, and behavior. These phenomena do not have a causal relationship but can be understood as different aspects of the evolving organism developing in tandem, which allows them to remain connected. They are an example of polarization as described in section 5.1.

Melatonin is strongly related to sleeping and waking behavior. Sleeping and waking are some of the most elementary properties of consciousness and the psyche in the broadest sense of the word. In lower animals, too, light exposure regulates their behavior, albeit at the very basic level of sleeping and waking.

Morphological evolution keeps pace with the evolution of consciousness, psyche, and behavior (see section 5.4.2.) as these grow ever further apart and yet remain connected.

The Effect of Light

The circadian rhythm bound to sunlight which becomes apparent in sleeping and waking is the means through which the epiphysis influences the connection between body and mind. This explains why exogenous melatonin has recently become a popular sleep aid.

The gonads principally determine mating behavior and reproduction in animals and are in turn strongly affected by the amount of light exposure. The meaning of the word estrogen is “origin of the rut.” In spring time, with increasing day light, numerous physical and behavioral phenomena reveal the effects of animal sex hormone activity. Body shapes change and the colors and shapes of mammal fur and bird feathers transform, often in unrecognizable new ways. The singing of birds and their migration across the earth and the leaping of whales are just a few examples of the amazing changes in animal behavior under the influence of increasing light exposure.

5.4.5. Summary

The pineal gland and the gonads together play an important role in animal life cycles, which is evident in our crucial rhythm of sleeping and waking.

Perception and active (mating) behavior are present during waking life. Yet, metabolic (hormonal and cellular) processes related to reproduction take their course in deeply unconscious spheres of the organism’s physiology. One can hardly conceive of a greater span between waking and sleeping processes than that between (conscious) mating behavior and the deeply unconscious process of reproduction at a cellular level.

This characterizes the psychosomatic aspect of the pineal gland and gonads in endocrinology. We first discussed *phenomena* of their anatomy, embryology, and physiology. Then we described *the range of the dynamic patterns* in animal and human pineal gland and gonad function via their role in the interaction between the body on the one hand and the mind and behavioral patterns on the other. The third step describes how phylogenetic and ontogenetic *development of the dynamic pattern* takes place. This in conclusion reveals a clear association between the pineal gland and the gonads.

Figure 5.3. Pineal Gland and Gonads

5.5. Pituitary Gland versus Adrenal Gland and Kidneys

5.5.1. Pituitary Gland

The pituitary gland develops embryologically from two germ layers: the endoderm and ectoderm.

The anterior pituitary gland develops from the primitive embryonic foregut (endoderm) at the *cranial* end of the pharynx region. Phylogenetically, jawless fish (Agnatha) already develop a cranial protrusion of the nasopharynx, and fish with a lower jaw (Gnathostomata) develop a primitive anterior pituitary from a protrusion of the nasopharyngeal area called Rathke's pouch.

The neurohypophysis (posterior pituitary gland) develops from an ectodermal caudal extension of the third ventricle (diencephalon) in the region of the hypothalamus. The neuro-pituitary gland is made up of a collection of axonal projections from the hypothalamus that extend past the anterior pituitary. These projections derive in particular from neurons of the supra-optic and paraventricular nuclei in the hypothalamus. These axons secrete peptide hormones.
In this particular area, the optic tract[21] crosses with the aforementioned nerve pathways associated with the pineal gland that are related to light perception (see section 5.4.1.). The posterior pituitary gland does not itself produce hormones; rather its function is to secrete the hormones already stored there: oxytocin and antidiuretic hormone (ADH). Oxytocin stimulates smooth muscle cells of the breast and uterus. This promotes the release of milk from the breasts as well as uterus contractions during labor. Another important role of oxytocin was described more recently promoting the emotional bonding between mother and child as well as between adults (Heinrichs et al 2009). ADH promotes the reabsorption of sodium (Na +) in the kidneys, and with it, increases arterial blood pressure.

The posterior pituitary gland promotes catabolic activity, in particular via its effect of increasing muscle tone and blood pressure. The anterior pituitary has an overall anabolic effect in the organism, especially via the so-called tropic hormones, which promote growth in the gonads and adrenal glands.

Endocrine Interlude

The hypothalamus secretes the following hormones: prolactin-releasing hormone, prolactin-inhibiting hormone (dopamine), growth hormone releasing and inhibiting hormone, gonadotropin releasing hormone, thyrotropin releasing hormone, and corticotrophin releasing hormone. The anterior pituitary synthesizes a number of anabolic hormones under the influence of these hypothalamic hormones from acidophilic cells secreting growth hormone (GH) and from mammatrope cells that stimulate the production of breast milk through prolactin (PRL).
The anterior pituitary also contains basophilic cells. These have a trophic[22]

21 nerve fibers originating in the eyes
22 growth stimulating

effect on the thyroid (TSH), ovaries (LH and FSH), and the adrenal cortex with thyrotrophic, gonadotrophic, and adrenocorticotrophic activity.

5.5.2. Renal and Adrenal Hormones

The adrenal glands are paired organs. The adrenal cortex comprises mesodermal tissue and the medulla ectodermal tissue, containing chromaffin cells. The joining of these two tissue types began in reptilian development during the descent of the mesonephros (section 5.4.2). In earlier stages of phylogenetic development, in teleost fish, the production of steroid hormones (a function of the later adrenal cortex) and of catecholamines (a function of the future adrenal medulla) takes place in separate, isolated cell groups of adrenal tissue in the fat around the kidneys. These cells migrate later in evolution to form the adrenal medulla and cortex.

In humans and mammals, the adrenal medulla secretes catecholamines (epinephrine and norepinephrine) into the blood, which is a function of the autonomic nervous system that migrated to the metabolic region of the organ over the course of evolution (section 5.3.). Coincidently, neurotransmitters developed into hormones. Catecholamine action on the nervous system has myriad effects. They stimulate conscious awareness, invigorate catabolic metabolism, and generate acute physical stress reactions in response to an event in the outside world that elicits fear, anxiety, or anger.

The adrenal cortex produces several anabolic hormones such as the corticosteroids and sex hormones. These are metabolites of cholesterol, a substance that in itself is non-specific in relation to gender development.

Anabolism and Catabolism

All organisms need to have a balance between anabolic and catabolic activity. Anabolism initiates organ growth. Organs form and mature with the aid of catabolic activity. Once formed, the organs are utilized and therefore broken down. The anabolic (recovery) phase is bound to the sleep cycle whereas the catabolic (breakdown) phase mainly occurs during waking life, particularly with stress.

The balance between these two activities is vital for health. It is the balance between unconscious growth processes and conscious activity.

Anatomical Interlude

The adrenal cortex surrounds the adrenal medulla and consists of three layers that produce different corticosteroids.

The outer layer produces mineralocorticoids and aldosterone, which trigger sodium retention.

The middle layer produces glucocorticoids that raise the serum glucose level, have an anti-inflammatory effect, and affect fat distribution in the body.
The inner layer produces sex hormones that have similar effects in both sexes; after menopause and andropause they remain at a basic level.
We may compare the three layers of the adrenal cortex to the trifold embryonic germinal disk and the development of the three germ layers: mineralocorticoids have a connection with ectoderm, glucocorticoids with mesoderm, and sex hormones with endoderm.

Since the adrenals substantially support stress reactions in the acute phase mainly by means of adrenaline and in chronic stress by means of cortisol, we may characterize adrenal glands as "stress glands." Adrenal function plays an important role in stress reactions; it is a necessary condition to achieve an intensifying of awareness and the development of reflex "animal-like" behavior, triggering fight, flight, freeze, and fright reactions. It facilitates the ability to be mentally alert and tense. In Addison's disease[23], as well as in chronic fatigue syndrome and burnout, hypotonia, hypotension, dreariness, asthenia, adynamia, and a lack of willpower may occur.

A more comprehensive understanding of the adrenal glands will be important to better understand

23 acute adrenal insufficiency

the growing pandemic that is metabolic syndrome[24] among adults. Metabolic syndrome is becoming an increasing threat to younger populations and appears to be associated with our modern lifestyle: excessive (carbohydrate) consumption, lack of physical activity, stress overload, and increasing commoditization and consolidating within our Western culture, which contribute to a loss of coherence (Antonovsky 1979).

5.5.3. Renal Juxtaglomerular Apparatus

The renal juxtaglomerular apparatus comprises the juxtaglomerular cells of the macula densa and lacis kidney cells. These structures appeared consecutively in evolution in reptiles, birds, and mammals. The juxtaglomerular apparatus detects blood pressure and oxygen content in the blood. Hypotension effectuates renin release (Edelman et al 1961), which restores arterial blood pressure and also psychological tensile strength. This is a catabolic process. The renin from the kidney corresponds to the first stage of a nephro-hepato-pulmo-hypothalamus-pituitary-nephro-control circuit that begins and ends in the kidneys[25]. This control circuit orchestrates the processes of an increase in tension and tone in humans and animals, which, among other things, manifests as increased blood pressure. In hypoxia or anemia when there is a shortage of oxygen, the kidney produces erythropoietin which stimulates the bone marrow to synthesize erythrocytes, an anabolic trophic effect. Erythrocytes are also important for consciousness, and thus behavior, as is evidenced by the impairment awareness and inactivity present in anemia. The strengthening effect of hemoglobin on performance levels, both physically and psychologically, has led to EPO abuse in sports.

24 Symptoms of metabolic syndrome are increased cholesterol, triglycerides, and blood pressure, central adiposity, and increase of blood sugar, uric acid, and insulin resistance. In women polycystic ovaries (PCO) may be found more frequently. All of these changes can be related to hyperactivity of the neurological component of the endocrine system, which coincides with reduced vitality and lack of exercise and body perception.

25 Renin induces the hepatic conversion of angiotensinogen into angiotensin I that is converted into angiotensin II in the lungs that in turn acts out in the hypothalamus releasing ADH and in the adrenal increasing aldosterone, having an effect on kidney function.

5.5.4. Connections Between Pituitary and Adrenal Glands

The connection between the *cranial* neuro-endocrine system of hypothalamus and pituitary and the *caudal* abdominal endocrine system of kidneys and adrenal glands can be seen as an interacting system. We may observe this interaction from their morphological history up to and including their functional connection in humans.

The pituitary and adrenal glands have each developed from two germ layers. They have one part that is of neuronal/*cranial* origin (the posterior pituitary and the adrenal medulla) and they have a section that stems from the *caudally* located entodermal- or mesodermal-abdominal region (anterior pituitary and adrenal cortex respectively) (see also section 5.3. grey block Cranio-Caudal Axis). The neuronal-related activity of these glands is mainly catabolic, their entodermal-abdominal activity is mostly anabolic.

5.5.5. Morphology, Physiology, Conscious Awareness, and Behavior

The polarity between the hypothalamus/pituitary gland and the adrenal/kidney system (figure 5.4.) shows yet another aspect of the relationship between the physiology and consciousness than was at stake in the polarity of epiphysis and gonads.

The phenomenon of mixed endodermal/mesodermal and ectodermal tissue in these organs points to an interaction between metabolic activity in these glands on the one hand and neuronal activity supporting awareness on the other. Both organs play a role in anabolic and catabolic processes. Anabolic stimulation is based on a variety of growth hormones for different tissue types, which is a completely unconscious process that mainly occurs during the sleep phase. Controvertibly, stress and elementary behavioral responses triggering fight, flight, freeze, and fright reactions induce a catabolic process of consummation and degradation of body substance. Conscious awareness enlightens the mind and at the same time breaks down growth and recovery processes. Chronic stress mostly decreases appetite, reduces the ability to digest food, and produces weight loss and sleep disorders. Some people, however, will eat more as a reaction and therefore gain weight.

The polarity of hypothalamus pituitary gland and adrenal/kidney system calls up the hypothesis that the endocrine system "serves two masters," being both growth and conscious awareness. These "two masters" are deeply connected and control the same processes: enabling the organism to develop conscious and self-conscious action, using the well-prepared unconscious instrument: the body.

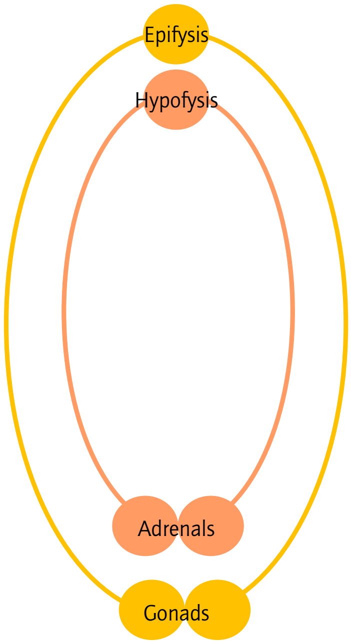


Figure 5.4. Pituitary and Renal/Adrenal Hormones

5.6. Thyroid and Parathyroid Glands and the Pancreas

Chapters 3 and 4 discussed the thyroid gland and pancreas. An abbreviated description will therefore suffice of some important aspects that were not previously mentioned.

5.6.1. Thyroid and Parathyroid Glands

During evolution, the thyroid metamorphosed from an iodine-producing exocrine organ in tunicates and lancet fish (Tunicata and Cephalochordata) known as the endostyle, to an endocrine organ, now known as the thyroid. In higher vertebrates the thyroid develops to become one compact organ, while in jawless fish (Agnata) and bony fish (Teleostoi) it constituted more scattered tissue islands.

Between the fifth and seventh week of embryonic development, the origin of the thyroid gland descends from the endodermal tongue base to the neck (larynx area) via the thyroglossal duct, thereby uniting the originally distinct lobes into a single body, similar to how the pancreas develops from a ventral and a caudal lobe. The parathyroid glands settle inside the thyroid, two on each side.

From early on in embryonic development through early childhood, thyroid hormone is of great importance for the psychosomatic development of animals and humans. Examples are the metamorphosis from tadpole to frog, from fish to amphibian, as well as the disastrous effects of an undetected congenital hypothyroidism in humans. Important metamorphoses in growing and maturation are entirely dependent upon the production of thyroid hormone. In experiments in which the thyroid gland is removed in tadpoles, the metamorphosis to frogs does not take place.

The physiology of calcium metabolism has its evolutionary beginnings in bony fish in the region of the kidneys with the production of stanniocalcine. In amphibians the parathyroid glands are organized into small organs within thyroid tissue that produce parathyroid hormone (PTH), a hormone that brings about decalcification of bone, causing increased calcium concentrations in the blood. Calcitonin, the counter-acting hormone[26], induces the mineralization of bone with the aid of calcium phosphate and calcium carbonate. The action of calcitonin shapes the skeleton. In humans this process is of specific importance because of their upright gait and bipedalism that requires a unique body construction.

Another important contribution of thyroid hormone is the myelination of the nervous system, in

26 calcitonin is a product of the parafollicular cells in the thyroid (Braverman 2002, Larsen 1993)

particular in the brain during human fetal development, which causes the axons to be surrounded with a layer of lipid and protein (myelin) in the seventh month. This process ends between the fifth and seventh year of life and enables the next phase of development: conceptualization. This change in the child's mind between the fifth and seventh year of life—the transition from fantasy to rationality—corresponds to the development of consciousness from a non-myelinated to a myelinated brain.

Newborns suffering from congenital hypothyroidism are threatened by a major slowdown in the myelination of the nervous system and therefore in their psychomotor development. This state is referred to as cretinism of which mental retardation is an apparent component. In adults, the thyroid gland stimulates the catabolic metabolism of proteins, carbohydrates, and lipids by promoting phosphorylation.

The striking contrast between the symptoms of hyperthyroidism and hypothyroidism focuses on catabolism and alertness on the one hand (hyperthyroidism) and anabolism and drowsiness (hypothyroidism) on the other (Chapter 3). Thyroid disease has effects on both consciousness and metabolism.

The most frequent thyroid disorder is Hashimoto's disease, an auto-immune thyroiditis. In this disease process, the immune system no longer recognizes its own tissue and initiates a chronic and destructive process in the thyroid gland.

5.6.2. Pancreas

The pancreas may be considered as originating in the Gastro-Entero-Pancreatic system (GEP)[27] (Cetin 1983). So far the pancreas is the only part of GEP that is differentiated to the point that it has come free from the intestinal wall and become a separate endocrine organ secreting into the blood. The endocrine pancreas is largely informed by the entero-endocrine cells in the gut. The exocrine portion of the pancreas produces digestive juices.

27 The Gastro Entero Pancreatic System (GEP) includes jejunal gastrin and secretin, pancreatic insulin from the Langerhans' cells, enteric histamine, somatostatin, glucagon, pancreatic polypeptide, and serotonin.

The brain yields no more than 10% of serotonin present in the body, while the GEP produces the other 90%. Serotonins are the neurotransmitters of the enteric nervous system. As such, depression should be understood as resulting from low cerebral serotonin metabolism, as well as a disturbance in the entero-hepatic metabolism.

The symptoms of diabetes mellitus described in Chapter 4 can lead to a partial or total loss of consciousness and even coma via both hyperglycemia and hypoglycemia.

5.6.3. The Connection of Thyroid and Pancreas

Both the thyroid gland and the pancreas have a strong association with animal and human metabolism. Both regulate the connections between body and mind and between anabolism and catabolism, similar to other endocrine organs. Both organs have a direct relationship with the digestive system. This is already evident in embryonic development, since both organs differentiate from the primitive gut. Both organs develop from the foregut, the thyroid more *cranially* and the pancreas more *caudally*.

5.6.4. Morphology, Physiology, Consciousness, and Behavior

The morphology and (patho)physiology of the thyroid and pancreas were discussed in previous chapters (3 and 4). These chapters also described the relationship of these organs to conscious experience in health and disease. The experience of the outside world in relation to the inner world is clearly affected by both the thyroid and the pancreas. However, conscious awareness deserves some further consideration as it relates to the thyroid gland and pancreas.

Disease of these two organs is almost always accompanied by changes in conscious awareness. However, there is a big difference between thyroid gland disease, and the two forms of diabetes. Hypothyroidism yields a palpable decline in awareness, which may even lead to mental retardation in cretinism. Hyperthyroidism leads to nervous tension, sleep disturbance, a feeling of stress, and even can provoke psychotic phenomena, which are all characteristics of an excessively active mind.

In pancreatic disease, particularly the two forms of diabetes, a striking phenomenon of consciousness occurs: coma. Coma is a state of consciousness that is most often seen in diseases of the pancreas if caused by endocrine factors. Disease of the pineal gland, gonads, pituitary gland, kidneys, adrenals, and thyroid gland are all accompanied by changes in consciousness. Coma, however, is uncommon. This indicates that in pancreatic disorders, particularly in diabetes, a unique phenomenon occurs. This experience can also be regarded as the absence of core personality, in other words the "I." Diabetic coma appears as one of the main causes of metabolic coma.

It is possible to have normal contact with patients suffering from diseases of the other five endocrine organs, even though conscious awareness may be affected.
A comatose patient is not able to have normal contact with his surroundings. Diabetic patients are acutely aware of the possibility of coma should they enter either a hypo- or hyperglycemic state. As such, they will often take adequate measures to rectify their glucose imbalance as soon as the first symptoms of hypo- or hyperglycemia appear. If they are too late in righting the imbalance, and coma sets in, they essentially lose their autonomy, are completely dependent on assistance by a third party. You can hardly imagine a more poignant image of not "being there" or absence of the "I."

The phenomenon of coma creates a special dynamic between the thyroid gland and pancreas with increased polarization: the thyroid has the possibility to initiate an excessively active conscious experience (hyperthyroidism); diabetic coma represents the total absence of consciousness.

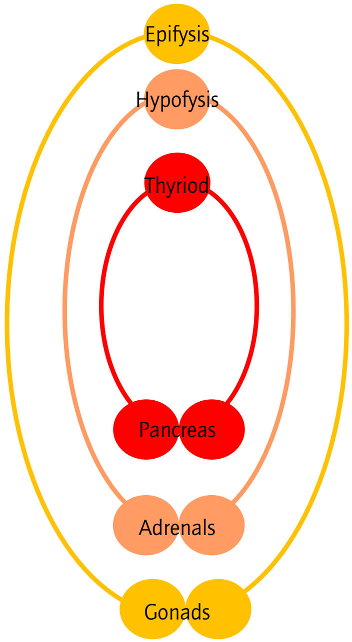


Figure 5.5. Thyroid and Pancreas

5.7. Heart and Endothelial System

The heart and related circulation are essential for organizing and bringing together endocrine effects in the organism. Because hormones are substances that effectuate the function of the endocrine gland at some distance from their origins, the blood circulation acts as a transport medium and mediator central to the success of the endocrine system. Until relatively recently, we did not know that the heart and endothelial system actually have their own independent hormonal functions.

In the 1950s “granules” were described in atrial cells of the guinea-pig heart. It took till the 1980s before the role of these granules was clarified and the natriuretic effect of heart extract in rats was observed. Subsequently, natriuretic peptide (atriopeptin) was isolated in rats and humans (Kisch 1956, Bold et al 1981, Kangawa et al 1984).

Three types of natriuretic peptide were found: type A found in the atria, type B in the ventricles, and type C in the large vessels. Natriuretic peptide has three physiological effects:

1. Increase in urine output (diuresis) and excretion of sodium (natriuresis)
2. Inhibition of RAAS[28] and endothelin[29]
3. Decrease in blood pressure via muscle relaxation in the arterioles

The heart has a modulating, integrating effect on the blood pressure, in particular, decreasing it through the inhibition of RAAS, a process that involves the kidneys, liver, lungs, hypothalamus, and adrenal glands.

In the Introduction to this chapter, polarization was discussed as a specific developmental phenomenon. Polarization creates differentiation in organogenesis; in endocrinology this can be seen specifically in organs that are located *cranially* such as pineal, pituitary, and thyroid glands, and their respective related organs that can be found at the *caudal* end of the organism, the gonads, adrenals, and pancreas, as was explained in previous paragraphs (5.3. box Cranio-Caudal Axis). Heart and circulation create a balance between the polarized cranial and caudal endocrine organs. The heart itself can be understood as the equilibrating fulcrum of the endocrine system in the same way it is also the center of the circulatory and muscular systems. With the term muscular system we refer to all muscular tissue in the body including smooth, striated, and mixed heart muscle cells. Histologically, the heart muscle stands between the two poles of autonomically innervated involuntary smooth muscle tissue and the segmentally innervated voluntary striated muscles.

28 RAAS stands for renin-, angiotensin-, aldosterone-system, which increases blood pressure; see also section 5.5.3. earlier in this chapter

29 endothelin is a hormone that causes vasoconstriction

The inner endothelial lining of the vessel wall poses major problems for scientists to date. One thing is clear: the endothelium itself plays an active and decisive role in the genesis, function, and preservation of the vascular system. The development, growth, and formation of the embryonic heart are largely determined by the consequences of blood flowing through the vessels causing shear stress on the endothelium. Shear stress induces the endothelium to produce certain substances that have a direct influence on cardiogenesis by generating genetic modification of surrounding cells (Moorman et al 2000). The estimated total amount of endothelium has the same weight as our liver. This prompts some to refer to it as the "endothelial organ," which belongs to the largest organ group in the human organism.

The endothelium regulates the degree of inflammation of the vascular wall by producing various substances and cytokines. It produces a number of factors that have pro- or anti-proliferative effects that influence the growth of smooth muscle cells in the vessel wall. It regulates the permeability of vessel walls, blood coagulation via factors that have thrombogenic or thrombolytic effect, and vasodilatation and constriction (Hall 2010).

Heart and endothelium form the essential and central element in the endocrine system. The endocrine system is actually integrated morphologically and physiologically because of the cardiovascular system. The heart as "central organ" and the endothelium as the "peripheral organ" of this one cardio-endocrine system permeate the organism from "inside out" and bring hormones to the periphery of the body. Heart action and endothelium thus spread through and enfold the endocrine system at the same time.

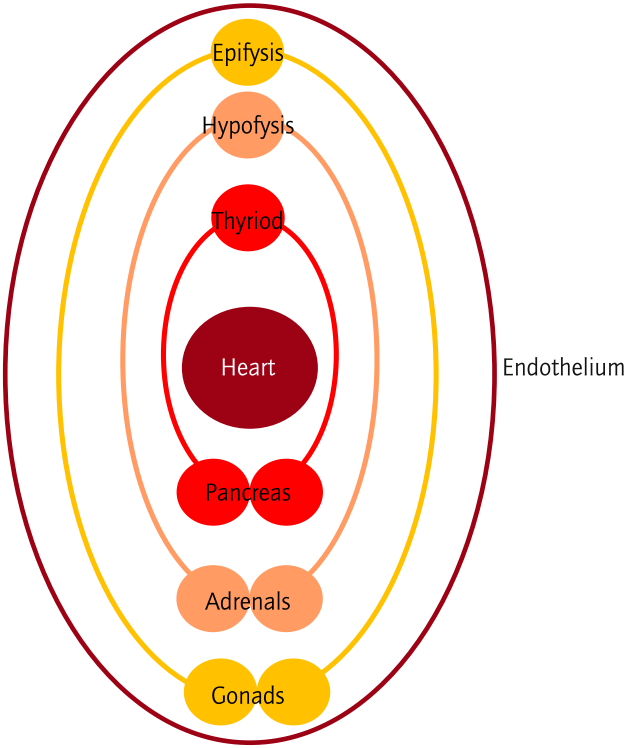


Figure 5.6. Heart, Endothelium in the Endocrine System

5.8. Summary

The perspective of "polarizing differentiation" (section 5.1.) results in a clear picture of the endocrine system as a functional unit. The endocrine system, together with the nervous system, is of vital importance for the healthy and normal development of two seemingly opposing processes: differentiating growth on the one hand, and awareness and behavior on the other.

The ontological evolutionary perspective of endocrine organs confirms the connection of these seemingly opposing processes. There is a close relationship between their evolutionary level, the polarizing differentiation of tissues and organs, the extent and the forms of consciousness, and behavior in animals.

This consequently creates a picture of the specific placement of animals and humans within the natural order: the evolutionary order of the evolving animal and human organisms in connection with evolving forms of conscious awareness and behavior.

6. ***Description of the*** *4-step* **Approach**
by Loes van den Heuvel, MD

We will explain the methodological approach used in this Companion both theoretically and in short examples in this chapter. The practical value of this approach as shown in previous chapters will be highlighted. We will conclude with a critical review of the approach and recommendations for further research.

We described an exercise in Chapter 1 that provided the reader with an example of the close connection between somatic and psychological experience. We recommended that the reader practice this exercise again after studying this Companion and test whether his/her experience has changed.

Exercise: Observe the correlation between respiration and consciousness in yourself

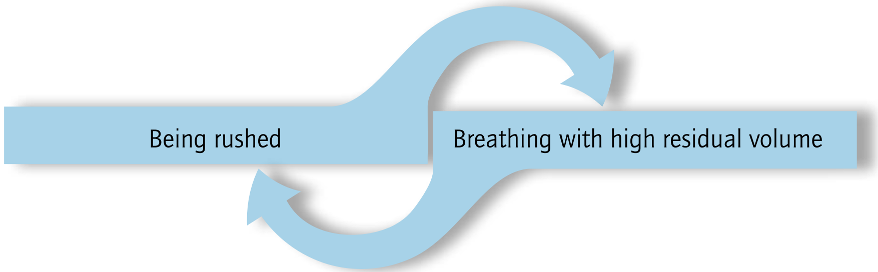
Sit up straight with both feet on the ground. Observe your breathing. It may be helpful to close your eyes. Take about 30 seconds to do this.

Then observe a different breathing pattern. Breathe in deeply and exhale the extra air only partially. As you continue to breathe and retain this extra volume, your pulmonary residual volume is increased. What do you observe now? Has the movement pattern changed anywhere in your body? Do you notice a particular mood or emotion that accompanies this breath? Has your awareness changed? Take about a minute to examine any physical or emotional changes.

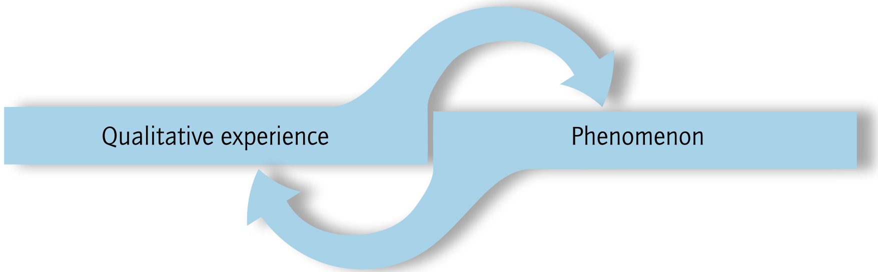
Change your breathing pattern once again.

Breathe out deeply and as you do so, allow your abdomen to move with the rhythm of the breath: Observe it filling with your inhalation and contracting with your exhalation. Continue this for about a minute and note what changes take place in your body, conscious awareness, or in your mood.

In this exercise you can experience how a pattern of breathing can be associated with a particular mental experience. When you try to experience this (adopt an empathetic attitude, section 2.1.) you may become aware of the *impression* it gives you: breathing with a high residual volume is accompanied, for example, by a sensation of being rushed. The apparent change in how you feel can be both consequence and cause of the breathing irregularity: pulmonary embolism can result in breathing with a high residual volume and having a feeling of being rushed, but a rushed sensation can also cause us to breathe at a high residual volume.



We will call high residual volume breathing the *phenomenon* in this exercise and the feeling of being rushed the *qualitative experience* that accompanies it.



6.1. Description of the Disease Model and the *4-step* Approach

6.1.1. The Disease Model

The experienced physician may at times be able to recognize the earliest stages of disease in his/her patients in spite of the fact that not all symptoms are manifest; this is what we refer to as clinical competence. The tuned-in physician may readily perceive the pathogenic impetus, which is already present and has initiated the momentum for further disease progress. The saying "she is coming down with something" encapsulates this early disease stage nicely. Close family members frequently "see it coming."

The processes that trigger illness are often familiar to physicians.

We can show the pathogenic impetus and the following disease process schematically in the following model:

This table describes abstractly both the successive phases of becoming ill and also can be regarded as different aspects of being ill that may still be present as the patient starts to experience her/his symptoms.

The Pathogenic Stimulus or Impetus for Disease

Illness starts at a certain moment. This moment marks the beginning of a change that we can consider a new phenomenon, a new pathogenic stimulus in an organic process. You might call this the tendency to become sick or refer to it as being "susceptible" to disease.

This moment before there are specific symptoms may be likened to the moment in the introduction to this chapter [p. 112] when you decided to do the exercise again, but had not yet taken any concrete steps.

The Hidden Course of the Disease Process

Once a new pathogenic stimulus has taken hold, it can initiate a specific disease process that has its own course in time. The disease process is a set of events that are linked to various internal processes of the organism that change, yet are hardly noticeable in the very early stages of illness. The patient sometimes describes this as having a different *experience* of their body.

This corresponds to the moment in the exercise after we have changed our breathing pattern. A different mental sensation becomes apparent too: we sense the quality of "feeling rushed." These changes are only noticeable to the experienced beholder.

Disease Pattern and Localization

At a certain moment in the course of the disease, at specific localizations in the organism, the pathophysiological processes combine and become noticeable. Processes such as bleeding, hardening tendencies, inflammation, or tumor formation occur in dynamic patterns and at localizations that are specific for a particular disease.

Pattern formation begins as early as the embryonic stage as the fetus develops organs (Levin 2012, Blechschmidt 1968). Dynamic pattern formation occurs as a visible expression of a process that is organized at a systems level rather than a cellular level. It is the context within which morphogenetic or pathogenic forces may manifest themselves.

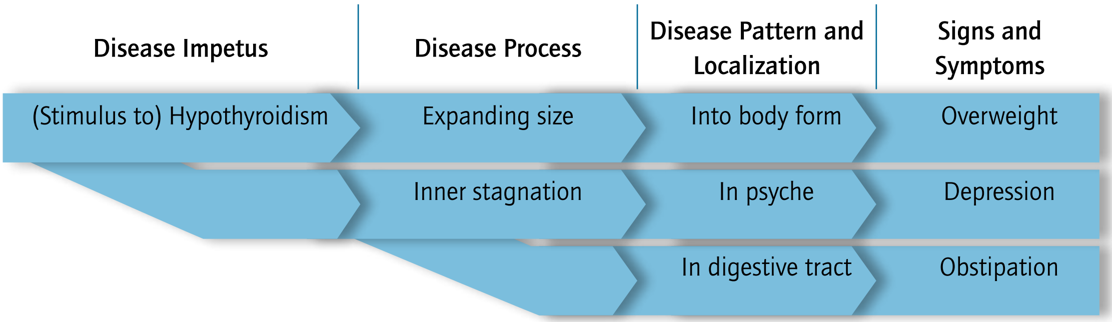
In regard to the introductory exercise it may be likened to lifting and putting forward the chest as you continue to breathe with an elevated residual volume.

The Signs and Symptoms

The change of dynamic pattern can result in the appearance of isolated signs and symptoms; there is a moment in the disease process when they become physically visible and measurable. Signs and symptoms could be, for example, a greater residual volume in the chest, a change in the serum white blood count, or vasodilation and erythema with inflammation.

The story the patient tells the physician usually includes not only specific signs and symptoms, but also how and what he/she experiences in the course of the disease process. A meticulous (hetero) anamnesis frequently brings to light the patient's experiences from a stage prior to having physical symptoms.
The pathogenic stimulus, its course in affecting the organism, the organism's altered dynamic patterns, and its physical signs and symptoms represent successive phases of becoming ill but the earlier phases may still be present at *different disease levels* as the symptoms manifest.
Above disease model can also demonstrate how therapeutic stimuli are initiated. The therapeutic incentive may instigate a reorientation of the disease process and a new dynamic pattern that ultimately decreases signs and symptoms and allows the body to evolve to a healthy, or healthier, state.

The disease model can be further actualized. Often, diseases will include symptoms in multiple organ systems. The diagram below presents this situation in Janine's patient history of hypothyroidism which was elaborated in section 3.2.



6.1.2. Individualization of Syndromes

Even though diseases do not elicit the same symptoms in all patients even when the same disease stimulus is present, the experienced physician will recognize the disease despite differences in symptomatology using *skilled intuition*. In the Companion Wholeness in Science (2012), Van der Bie uses the example of mononucleosis to remind us that this disease always appears differently in different people.

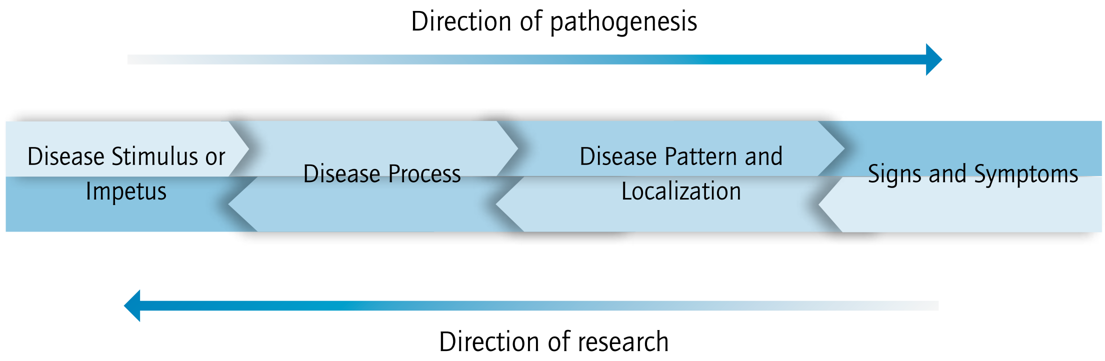
It is helpful to start from a picture of the pathogenic impetus in an individual patient to be able to initiate a healing process focused on the whole person. The picture of the disease stimulus is inevitably a *qualitative* picture. The question may be addressed as follows: how can a healing impulse take hold in this patient that lessens or even stops the pathogenic stimulus that has caused the disease? This insight has the potential to lead to individual therapeutic options for the patient. It is based on a combination of knowledge and skill and, over time, expertise and experience.

Similar to how the disease process may be expressed in both somatic and mind-related terminology, the healing impulse can be implemented on both levels. For example, people suffering from depression bring their body into movement when they go walking and, at the same time, they also mobilize their blocked emotional life and their mood may improve as a result (Stanton et al 2013).

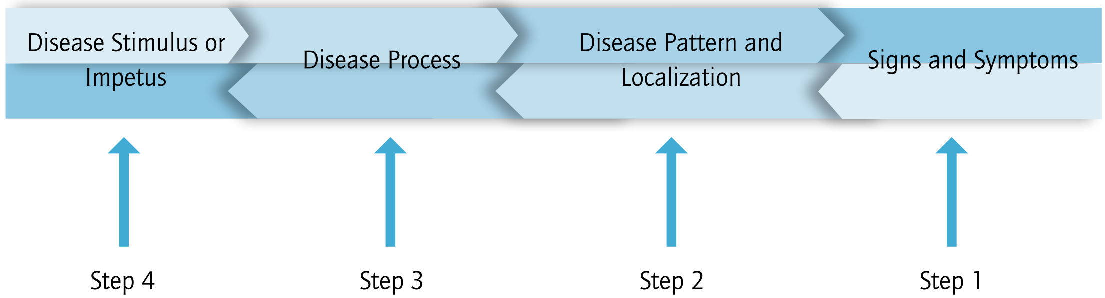
The *4-step* approach has the potential to elucidate psychosomatic processes and suggest additional therapeutic options in clinical practice. Its premise is that human organisms consist of a coherent set of interactions. When the balance of these interactions is disturbed disease may result. This idea fits into the scientific paradigm of systems biology that describes different models for complex systems that can also be used in medicine (Ahn et al 2010, Levin 2012).

6.1.3. The *4-step* Approach in Detail and Corresponding Attitudes

The above diagrams show how pathogenesis progresses from the left side of the diagram to the right. The research process in earlier chapters of this Companion began with the signs and symptoms and thus would progress from "right to left" in the diagram, which is actually how a phenomenological research method proceeds (Braude 2013, Carel 2011, Bortoft 1996). In phenomenological research the existing phenomena are the starting point and they derive their meaning from the context in which they appear.



Phenomenological research can be realized in different ways. In this and other Companions an approach in *4-steps* is applied. We have so far described the following specific steps:



- In *step 1* we observe and describe the factual signs and symptoms.
- In *step 2* we examine and distinguish the dynamic patterns and context that connects the signs and symptoms in a clear and meaningful way.
- In *step 3* we recognize and characterize the inner course of the disease *qualitatively*, the disease process.
- In *step 4* we identify the stimulus that initiated the pathogenic process in its essence and describe its specific potential in a *qualitative* picture.

In what follows, we will give a detailed theoretical description of the four steps. Each step presupposes the presence of a specific attitude or basic orientation on the part of the observer (see also section 2.1.). These attitudes are closely related to the physician's professional competence. The various attitudes require a specific (conscious) mindset and can thus only lead to specific, limited results. A quantifying attitude can only find measurable facts. The discovery of changes in serotonin metabolism in depressed patients is an example of this attitude. Yet, we have to take for granted that serotonin as a substance does not explain the symptoms of depression. Insight into this process requires a different attitude, namely one that focuses on finding the context in which serotonin metabolism plays a role in the disease process of depression.

First step - Spectator Attitude: Factual Description of Signs and Symptoms

In this step we describe the properties of a phenomenon or symptom with regard to its size, shape, consistency, et cetera. Various aspects may be compared as to their factual differences and similarities to come to a more precise description.
This phase lacks interpretations and judgment; they are held back for the sake of objectivity. It is important to stick to the facts in this step and not to proceed prematurely to the next steps in the process[30].

The researcher's inner orientation must be matter of fact, analyzing, observing, and exact. Facts are

30 For the sake of clarity, we strictly adhere to the individual steps of the methodology in this description, in spite of the fact that elsewhere in this Companion these steps were employed in a different order, or simultaneously.

recorded in clear and unambiguous terms; definitions play a role at this stage. The researcher looks as a spectator from the outside to the object and continues to observe. In the Companion Wholeness in Science (Van der Bie 2012), this orientation is called the **onlooker or spectator attitude**.

During this step it is often necessary to repeatedly perceive and study the patient or (patho) physiological phenomenon in order to continually answer newly emerging questions, thus further increasing accuracy and clarity. Fact finding on cellular, immunological, biochemical, hormonal, or psychological levels takes place in this way.

Second step - Participating Attitude: the Search for Context

After describing the facts, we regard the patterns that fit the symptoms such that they elucidate the signs and symptoms' context. We need to apply a flexible, comparative mode of thinking as we search for connections; comparison to memories of previous experience aid in this second step. This also involves clinical competence in the form of clinical pattern recognition, clinical experience and expertise (clinical skill), and prognostic estimates. The spectator orientation of the first step is inadequate for recognizing pertinent dynamic patterns.

When we thus focus on the dynamic aspects in patterns, we step into the process and take on a *responsive orientation* as researchers. The basic orientation that is required in this step is a **participating attitude**. We may now compare the factual signs and symptoms with other phenomena, such as the situation in a healthy state or an opposite phenomenon. We can consciously reinforce our participation in the pattern dynamic by making a drawing of the presumed pattern or otherwise imitating its movement dynamic inwardly or outwardly. It furthermore helps to describe the experience in terms of verbs (see Chapters 3 and 4).

Third step - Empathic Attitude: Recognizing the Disease Process

The third step requires a deeper study of the process dynamic. This is done by inwardly following along with the dynamic of the second step.

In the third step our focus changes to the process that arises in us as a result of the dynamic pattern. Can we observe a qualitative change in our own awareness and emotions, or and how our actions (conscious or less conscious) are provoked? Experiencing and recognizing the pattern of falling when someone is about to fall, for example, may immediately call upon an effective action.

The third step requires that we observe the changes in our own experience.

The clinician's compassionate mind is the appropriate tool to detect and experience the *qualitative* dynamic aspects of the disease or the patient. The acquired experience in this third step may be described in terms of impression, experience, or sensing, which are manifestations of the **empathic attitude** (see Chapters 3 and 4). This experience describes the quality of the process dynamics that eventually leads to the patient's symptoms. The skilled clinician recognizes the experience of a "threat" when an acute deterioration is about to happen, as well as the feeling of reassurance with visible improvement. The disease *process* is given significance in this step.

Fourth step - Intuitive Attitude: Identifying the Pathogenic Stimulus

In the fourth step we approximate the original impetus that led to the disease—the stimulus that initiated the disease symptoms. We may experience the qualitative picture, the disease essence, or the crux of part or the whole of the endocrine system. We again need to change our orientation from experiencing process in the third step to intuiting how the disease process started. This requires an **intuitive attitude**. Instead of recognizing the disease process, such as in the third step, our focus is now on identifying the disease stimulus in its broadest *qualitative* sense.

The *4-step* approach requires a different focus in each step as well as a different inner orientation. Each basic attitude yields a different result. From a factual, quantitative description we gradually move towards a more qualitative picture.

6.2. Added Value of the *4-step* Approach and Further Development

We employ scientific investigation to arrive at factual knowledge and in doing so we are able to apply analytical methods to our patient approach. We thus discover the valuable quantifiable facts and substances that we know from evidence based medicine are of great import to medicine. If we limit ourselves to this body of research and knowledge, we lose insight into the coherent human organism as a bio-psycho-social unity, and also of the *correlation* between these bio-, psycho-, and social dimensions.

In meeting other people, we experience every human as a living entity, with biological, psychological, and ethical moral features. This experience contrasts with the analytical facts obtained in the first step. It is allegedly difficult for physicians and other healthcare professionals to apply analytical scientific knowledge in individual patients. Some of the analytical data and statistical calculation do not seem to apply to individual patients. The gap between generalizations that produce knowledge of certain populations and their application in individual patients adds to this situation (Smulders et al 2010).

In its ultimate consequence, evidence based practice undervalues or could even exclude the wealth of experiential knowledge of clinically competent healthcare professionals.

The *4-step* approach outlined in this Companion can be a valuable addition to analytical science. Previous chapters have exposed that the *4- step* approach:

- supports insight into, and understanding of humans as an organic, cohesive unity
- shows disease to be an imbalance of the entire bio-psycho-social human being and offers therapy as a potential to further human development
- employs the physician's empathic ability as an instrument, allowing compassion to further develop
- connects direct insight into the pathogenic stimulus with new therapeutic potential
- works with a qualitative approach that provides a means to treat medically insufficiently explained physical symptoms

- provides insight into qualities that promote early detection of disease
- can be valuable both in clinical practice as well as in the study of basic medical topics, including (patho)physiology.

The *4-step* approach used in this Companion needs much further research. It is only a first step in a scientific approach that places research data into a coherent context. It would be a valuable addition to the previously mentioned deficiencies of analytical science.

Since the researcher utilizes his own experience as a research instrument, it may be regarded as a form of experiential science.

Considerations for developing further research on the approach must include its reproducibility and a more precise differentiation in its application.

This will allow the *4-step* approach to make a solid contribution to personalized medicine that does justice to humans as a bio-psycho-social entity and to *wholeness in medicine*.

7. *Synopsis and Conclusions*
by Guus van der Bie MD

This Companion attempts to provide an understanding of the endocrine system and its place in the context of the human organism. A consistent understanding of this system within the abundance of endocrine facts in health and disease becomes possible with the *4-step* approach. Diabetes mellitus and thyroid pathology are good examples to elaborate this method.

The endocrine system's important impact on different organizational levels is particularly noticeable when pathology occurs. Endocrine pathology simultaneously reveals that all processes from human metabolism to the human mind are interlinked. The endocrine system facilitates and integrates the bio-psycho-social coherence in humans via the blood circulation. The endocrine system's significance in the human organism becomes clear when studying its phylogeny and ontogeny. This reveals a progressive differentiation and polarization of the human organism: a polarization between the nervous system *cranially* and the metabolic system *caudally*. Blood and circulation form a middle region and are the central organs, and at the same time also are part of the surrounding peripheral portion of the endocrine system (sections 3.7., 4.2.4., 4.2.6., 4.3.4., 4.3.7.).

> As polarization occurs, more differentiation also takes place. The human endocrine system integrates nervous system and metabolism.

The *4-step* approach can be applied in a variety of ways: in individual patients as well as in the investigation of disease or in researching the function of a particular system.

This Companion demonstrates that the *4-step* approach is an obvious scientific strategy to move towards the perspective of the organism (or any part) as a coherent unit that can be studied in its own, appropriate context.

The authors' conclusion is that the *4-step* approach is an important addition to the analytical scientific method. Indeed, with analytical methods we can only give a *(linear) account* of humans as a bio-psycho-social unit. The *4-step* approach permits the discovery of a *meaningful qualitative connection between different aspects* within this unit, allowing a deeper understanding of psychosomatics.

This Companion attempts to professionalize the *4-step* approach as a special form of phenomenology, a scientific technique that is (as yet) not being taught in graduate medical programs. The authors have applied this approach in clinical settings for years, both in the office and in multidisciplinary work conferences in which it continues to be a much valued addition. This experience has motivated the authors to explicitly describe the *4-step* approach in this Companion as a supplementary modality in conventional medicine practice.

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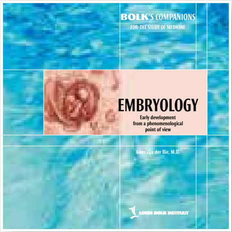

Embryology
Early Development from a Phenomenological Point of View

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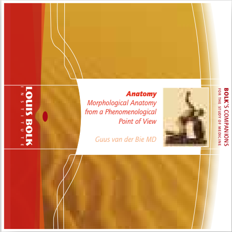
Can we give a scientific basis to our feeling that humans have unique human features? Are the human mind and the human organism 'nothing but' another variation of animal life? Can we find answers for the questions that satisfy both head and heart?
How these questions are answered depends on the scientific method we use: the current scientific method to learn about biological facts, the *4-step* approach to understand more about the meaning of these facts , or a combination.
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 MD
Publicationnumber GVO 02

Biochemistry offers insight into the continuous changes within the human organism. But can we maintain awareness of the coherence of the (changing) organism as we study the details? How can the many processes be understood as prototypical aspects of a unique organism?
The scope of the answers to these questions can be enhanced by using a combination of the current scientific method and the *4-step* approach developed specifically to research the coherence of processes within living organisms. The current scientific method is used to discover biological facts. The *4-step* approach helps us in finding the meaning of the facts.
What emerges is a new grasp of the interrelations between biological processes, consciousness, psychology, and behavior.



Anatomy
Morphological Anatomy from a Phenomenological Point-of View

Guus van der Bie MD
Publicationnumber GVO 03

Can we give a scientific basis to our feeling that the human being has unique human features? Are the human mind and the human body 'nothing but' another variation of animal life? Can we find answers for these questions that satisfy both our head and our heart?
How these questions are answered depends on the scientific method we use. In this publication two methods are used: the current scientific method to learn about anatomical facts and the *4-step* approach 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 MD
Publicationnumber GVO 04

Can physiology give more insight into the living human organism than the mere facts reveal at first? Is the level of activity the same for all organs? Are the vital qualities at work in organs unique for organisms and limited to biological activity? Can we find a scientific basis to research the coherence between organ systems?
By enhancing the current scientific method with the *4-step* approach, we can find meaning in the facts and understand them as an expression of life itself. The *4-step* approach makes the relationship between organs visible and comprehensible. It approaches scientific facts from the point of view of their coherence and can give totally new insights this way.
What emerges is a grasp of the interrelations between biological processes, consciousness, and nature.

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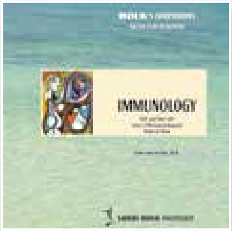


Immunology
Self and Non-self from a Phenomenological Point of View

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 the *4-step* 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

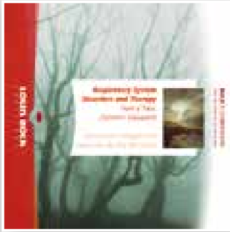
Christina van Tellingen MD
Publicationnumber GVO 06

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 the *4-step* approach. 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

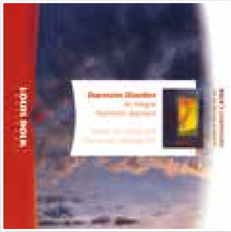
After finalizing the series BOLK'S Companions for the Study of Medicine for the moment, this module on The Healing Process introduces a new series of BOLK'S Companions that studies the Practice of Medicine. In it, we research the healing process itself. There proved to be an enormous volume of scientific literature on the subject. It is easy to lose oneself in the countless details included in the descriptions of this process.
The *4-step* approach in 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 emerge 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

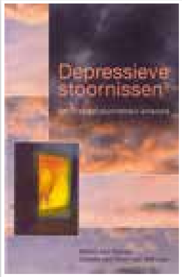
In this Companion, the experience of three of our own patients with asthma and pneumonia is used as backdrop for the study of airway disorders. Nearly all of us have had some experience with respiratory disease, given that colds, flus, sinusitis, and bronchitis are so common. Most physicians and therapists 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 opens up to a wider view with new insights and innovative avenues of individualized 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. Rhythmic processes, consequently, are 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.



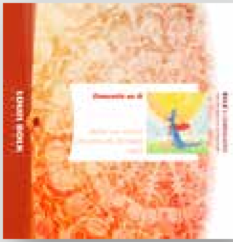
Depressieve stoornissen
Een integraal psychiatrisch antwoord

Marko van Gerven MD
Christina van Tellingen MD
Bestelnummer GVO 11

"Dit boek beschrijft op heldere wijze hoe een systematische aanpak de basis kan vormen voor een meer individuele benadering in de behandeling van depressie"

Prof.dr. Jan van der Greef, hoogleraar analytische biowetenschappen Universiteit Leiden en wetenschappelijk directeur systeembiologische research bij TNO.

Deze uitgave richt zich op psychiaters, psychotherapeuten, psychologen, orthopedagogen, paramedici werkzaam in de geestelijke gezondheidszorg en studenten in deze richtingen.



Dementia and I

(also available in Dutch)

Marko van Gerven MD
+NL versie noemen
Christina van Tellingen MD (Eds.)
Publicationnumber GVO 14

This Companion contributes to an integral approach of dementia. It does not close its eyes to the horrors of the disease, but rather provides new perspectives to meet the process of withdrawing of the mind with courage and confidence. *Wouter Endel MD, Amsterdam*

An inspiring book for the reader who searches for more than one way of looking at dementia, with an approach to dementia from a developmental perspective. The special attention to spiritual issues at the end of life is meritorious. The book combines the practice of working with the demented individual with theoretical concepts. *Tom van der Meulen, director Ideon,dementia professionals*

A special book which describes that despite brain damage, development opportunities continue to exist in dementia. *Mrs. S. de Ruiter, family member*

Wholeness in Science
A methodology for pattern recognition and clinical intuition

Guus van der Bie MD
Publicationnumber GVO 10

How do you develop clinical intuition? How do physicians gain practical knowledge about disease?
Diseases do not merely concern a partial defect, they recreate the life of the patient. The author shows that experienced physicians conceive of diseases as integrated concepts, which they can apply to the individual situation of the patient. Clinical intuition is a form
of pattern recognition that supports the ability to recognize an integrated 'whole.' This Companion presents practical exercises that allow readers to train and expand their ability of pattern recognition through Goethe's methodology. Questions and introspection aid to become aware of what you did. This makes obvious that clinical intuition, as experiential knowledge, can become a skill that is actively developed

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Endocrinology

How can we conceptualize seemingly random psychological and physical symptoms of endocrine disease in a holistic way? How can we understand signs and symptoms of disease including the anatomical and physiological changes in the involved organs in relation to the bio-psycho-social functioning of the individual?

In this Companion, the authors of Endocrinology - A methodological approach towards integrative understanding strive to elucidate the methodology of the 4-step approach, which they have long employed in their own medical practices. It is the authors' hope that sharing this approach facilitates a deeper, more integrated understanding of common endocrine disease as well as offers tools for discovering the commonalities and coherence in seemingly unrelated bio-psycho-social phenomena. The ultimate goal of this exploration is to further individualize conventional medicine in the physician's office.