BOLK'S COMPANIONS

FOR THE STUDY OF MEDICINE

BIOCHEMISTRY

from a phenomenological point of view

Christa van Tellingen, M.D.

LOUIS BOLK INSTITUUT

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For further information:
Louis Bolk Instituut
Hoofdstraat 24
NL-3972 LA Driebergen
Tel.(++31)(0)343-523860
Fax.(++31)(0)343-515611
Web: www.louisbolk.nl
E mail: c.van.tellingen@louisbolk.nl

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About the author

Christa van Tellingen, M.D. (born in Holland in1949) has been a family physician in California since 1982. From the beginning of her medical studies she has recognized the importance of a new approach to science for understanding the human being in health and disease. In her practice she has found the goethean phenomenological method of observation to be of great value in understanding and treating patients. She has taught medical students and physicians in the United States, Canada, and Europe.

In 1998 she was one of the originators of "Renewal of Medical Education", a project to produce a complement to the current biomedical scientific approach of the human being.

About the Project

The project "Renewal of Medical Education" aims to produce modules which demonstrate how the facts of current biomedical science can be understood differently by using Goethe's phenomenological method. This results in new concepts in biomedical science. These new concepts recapture an understanding of biochemical, physiological and morphological factors in living organisms and their development in time and space. This enables one to see, for instance, the relations of consciousness, psychology and behavior to the shape of the body.

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

1. Metabolism

Introduction

Metabolic flow is based on anabolic and catabolic reactions. Metabolism begins with the ingestion of food that is foreign to the organism (containing a varying amount of smaller and larger compounds), which is broken down in the digestive tract to smaller molecules by hydrolysis.
An anabolic phase occurs when the smaller molecules are taken up into the organism's bloodstream and become part of the organism. Catabolic reactions constantly break down the organism again for its functional needs.
We will demonstrate the connections of processes in organs and organisms as well as the interconnectedness of organisms within the whole of living nature.

1.1. Anabolic and catabolic processes and energy transfer

The flow of substances in metabolism in principle has two opposite directions.

1. Anabolic:
In the anabolic stream of metabolism, larger compounds are formed from smaller ones. Chemical *reductions* play a predominant role in these reactions. An example is the formation of complex carbohydrates from lactate or carbon dioxide.

2. Catabolic:
Catabolism is the opposite type of process, the breakdown of more complex compound into smaller ones. Chemical *oxidation and*

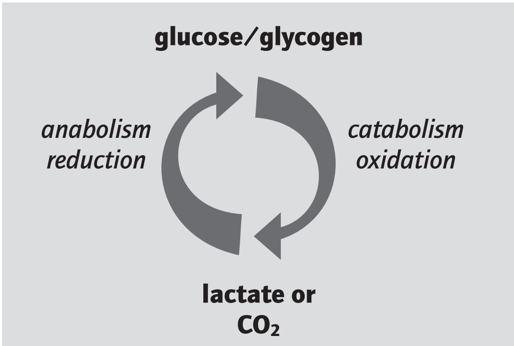
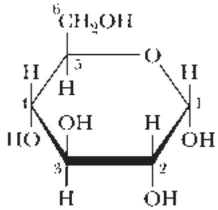
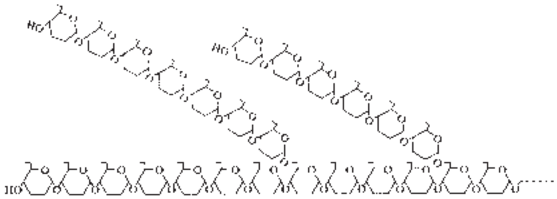


Fig 1.1 Anabolic and catabolic processes in carbohydrate metabolism

dehydrogenation play an important role in these reactions. An example is conversion of glucose or glycogen to carbon dioxide.





α-D-Glucose **Glycogen (from Campbell, 1999)**

The effect of *anabolic reactions* is the formation of larger molecules, which will contribute to the organism's seemingly constant structures. Anabolic reactions usually *require energy* to carry out the process. The energy is needed for the reaction process as well as to hold together the structure of the more complex compound that is formed. The *energy captured* in the structure of compounds is stored, potential energy. This energy is expressed, for instance, in the linkages between molecules. Examples are:

- all covalent bonds including the glycosidic linkages in complex carbohydrates and the peptide bonds of the primary structure of proteins;
- the different bonds that hold together the three dimensional structure of proteins like peptide bonds, hydrogen bonds, disulfide bonds;
- the hydrophobic interactions and van der Waals bonds in lipid structures.

Catabolic reactions break down substances in the organism, and the resulting *energy is freed* for other aims. The freed up energy may be used to move muscles (bio-mechanical energy), to facilitate conduction in the nervous tissue (bio-electrical energy), to enable synthesis of biochemical substances, and to effectuate active transport of substances.

Anabolic reactions incorporate bond energy into the larger compounds, which are in turn part of cellular or tissue structures, for instance cellular membranes, connective tissue fibers, or glycogen in the liver. Catabolic reactions effectively free up this energy. The structuring substances of organisms therefore have the additional function of being a source of potential energy in situations of need.

In trauma, or extreme situations like hunger states, the needs of the organism are met by breaking down more and different structural compounds. Eventually the substance of every organism ends up in its surrounding again, either in the form of energy, for instance as the effect of muscular action, the fluorescent light of certain fishes, etc., or as substance, as excretory products or when the living organism finally dies.

> ***QUESTION:*** *Are different types of bonds prototypical for different types of compounds? Are different types of energy stored in the different types of bonds?*

> ***QUESTION:*** *Where does the energy come from that we use for mental processes like thinking, emotions, or intentions? Is that also released from structures in the organism that are broken down?*

1.2. Biochemical cycles in metabolism

Anabolism and catabolism are opposite processes, and yet one is not simply the reverse of the other. Usually several key reactions of the anabolic pathway need different enzymes and/or produce different intermediate compounds than those used in catabolism. Anabolism and catabolism can take place in the same cell, but they often take place in different cell compartments (such as lipid anabolism in the cytosol and lipid catabolism in the mitochondrion) and probably at different times. Anabolism and catabolism are not simply opposites but have a cyclic interaction, whereby the one follows the other and prepares for the other. There is no catabolism without there first being something built up that can be broken down. There is no anabolism without there being energy from catabolism to be built into larger structures.

1.2.1. A biochemical cycle in the organism as a whole

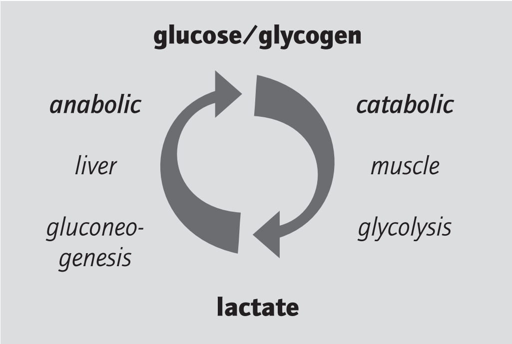


Fig.1.2 An example of anabolic and catabolic processes as a cycle in the organism as a whole: the Cori Cycle

The metabolism in anaerobic exercise provides an example of a metabolic cycle between organs. The so-called Cori cycle comprises glycolysis in the exercising muscle and gluconeogenesis in the liver.

In strenuous exercise, glucose in the skeletal muscle is broken down anaerobically to lactate (glycolysis) for extra directly available energy. The blood transports lactate to the liver. In the liver, glucose can be built back up from lactate (gluconeogenesis). This can be stored as glycogen or transported back to the muscle by the blood to be used as an energy source for muscle contraction again.

Anabolic and catabolic metabolism can alternate cyclically between organs in the human organism.

1.2.2. A biochemical cycle in nature

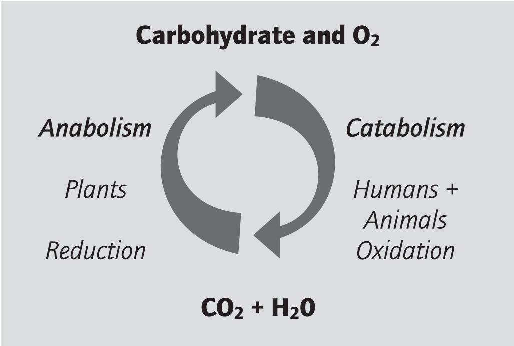


Fig.1.3 An example of coupled anabolic and catabolic processes in nature

A carbohydrate metabolic cycle occurs *between organisms in nature.*

Green plants reduce carbon dioxide and water to carbohydrates and oxygen in the process called photosynthesis. They build up their organism with the carbohydrates formed in photosynthesis and release oxygen. This is a reductive, anabolic process in the plant using external sunlight as the energy source.

The oxygen and the plant carbohydrates produced in photosynthesis are used up by higher organisms in oxidative processes that break down the carbohydrates in the digestive process. The metabolic cycle that exists between plants on the one hand, and humans and animals on the other, involves different organisms in nature.

The overall role of animal and human metabolism in nature is catabolic. Plant metabolism plays a *prototypically* anabolic role in nature and provides the energy required by the overall catabolic metabolism of higher organisms.

1.2.3. The citric acid cycle

The aerobic part of metabolism begins in the mitochondrion. In the eight steps of the citric acid cycle, which takes place in the mitochondrion, the metabolites of carbohydrates, proteins and lipids are finally oxidized to carbon dioxide and water. This catabolic process results in the formation of large amounts of biochemical energy in the form of adenosine triphosphate (ATP). To complete this process, some energy-carrying compounds that are formed in the citric acid cycle have to go through oxidative phosphorylation in the inner mitochondrial membrane to convert the energy to ATP with the help of the reduction of O_2 to H_2O. These are for instance NADH (the reduced form of nicotinamide adenine dinucleotide) and $FADH_2$ (the reduced form of flavin adenine dinucleotide). The citric acid cycle is also the starting point for gluconeogenesis. And it provides intermediates for the synthesis of proteins and lipids and for the heme group of hemoglobin. In the citric acid cycle anabolic and catabolic pathways connect. Cycles interconnect with other cycles with the citric acid cycle at the center.

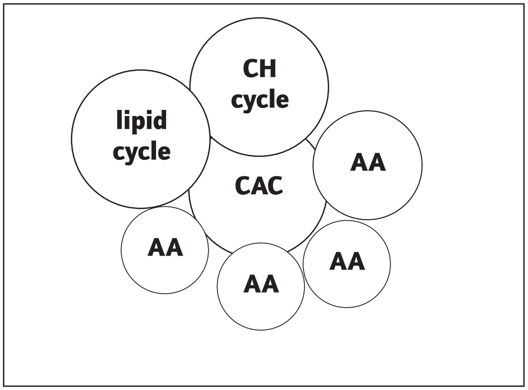
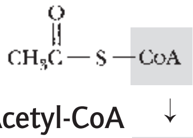


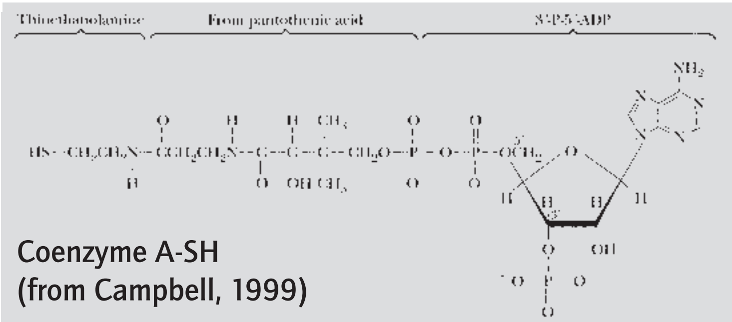
Fig. 1.4 The central place of the citric acid cycle (CH= carbohydrate; AA= amino acid cycle; CAC= citric acid cycle)

Acetyl-CoA and the citric acid cycle

Acetyl-CoA is the molecule that starts the citric acid cycle by binding to its "end" product oxaloacetate. All metabolites of carbohydrates and lipids enter this cycle as acetyl-CoA, and it is the link to ultimate oxidative breakdown for many amino acids.



Acetyl-CoA



Coenzyme A-SH (from Campbell, 1999)

Acetyl-CoA is possibly *the* key molecule in metabolism (see also sections 2.1.3 and chapter 5). In addition to being the starting molecule for the citric acid cycle it is also the starting point of fatty acid and cholesterol synthesis.

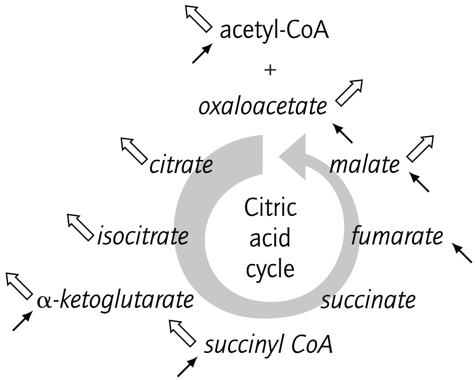
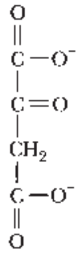


Fig. 1.5 The citric acid cycle and its anabolic (⇦) and catabolic (→) connections. + indicates the condensation of AcCoA with oxaloacetate.

In bacteria and plants, acetyl-CoA can be converted to oxaloacetate and other intermediates of the citric acid cycle via the glyoxylate pathway and as such can become the starting point for the synthesis of both amino acids and carbohydrates. The glyoxylate pathway is not available in mammals, which precludes them from converting fats to carbohydrates. This is the reason that mammals can not exist on a diet that contains only fats. Many bacteria use just acetic acid via a conversion to acetyl-CoA for the synthesis of their organism’s compounds.



Oxaloacetate must be kept at specifically sufficient levels in the mitochondrion to allow acetyl-CoA to enter the citric acid cycle. Oxaloacetate is *also* the starting point of gluconeogenesis.

Oxaloacetate

1.2.4. Biochemical cycles in time

The emphasis on either anabolic or catabolic processes in biochemical cycles is different at different times of the day (circadian rhythm) and at different times in the life cycle of an organism.

Photosynthesis in plants

Photosynthesis mainly occurs in the leaves of green plants. It actually represents two processes, the light reactions and the dark reaction.

1. The light reactions:
The light reactions occur under the influence of light which is absorbed by chlorophyll (chlorophyll is a biochemical compound in plants similar to hemoglobin in the blood of higher organisms). The light reactions involve the oxidation of water to produce oxygen.

$$H_2O \rightarrow 2H^+ + \frac{1}{2} O_2$$

The energy freed in this *catabolic* process is captured in the plant, via the conversion of $NADP^+$ to NADPH, by the photophosphorylation of adenosine diphosphate (ADP) to ATP, a conversion that is coupled to the oxidation of water. The second light reaction is:

$$ADP + P_{inorganic} \rightarrow ATP$$

ATP is an energy-carrying compound and it represents a biochemical form of directly available energy (see also section 3.3.). Under normal circumstances the light reactions of photosynthesis are daytime processes. The light reactions use solar energy to free the energy that holds together the water molecule, which in turn is converted via NADPH to ATP.

The light reactions convert sunlight to biochemical energy in the plant.
Light drives the transfer of protons from one substance to another in a thermodynamically uphill direction.

2. The dark reaction:
The second process of photosynthesis is the *dark reaction.* It involves the fixation of CO_2 for the production of sugars:

$$6\ CO_2 + 12\ H^+ \rightarrow [C_6\ H_{12}\ O_6] + 3\ O_2$$

The energy for this *anabolic* process comes from the ATP formed in the light reactions. The dark reaction results in the formation of disaccharides and polysaccharides (starch and cellulose). As the name indicates, this reaction is not *directly* dependent on sunlight, only *indirectly*.

The *overall equation* for photosynthesis is:

$$6\ CO_2 + 6\ H_2O + \text{sunlight} \rightarrow \text{carbohydrate}\ (C_6\ H_{12}O_6) + 6\ O_2$$

Chlorophyll in the plant absorbs the sunlight during the day and makes it directly available for the light reactions and indirectly, converted to chemical energy, for the dark reaction of photosynthesis. Plants are our example for using solar energy!

The plant builds up its organism in the dark reaction of photosynthesis, it grows visibly as a result of it. The light reactions do not result in visible growth but in energy production, which is invisible to the naked eye. The visible growth of the plant takes place where the light does not shine. The growth of plants towards the sun and the intricate process of the turning of the sunflower's head towards the light are based on more intensive growth on the side of the plant turned away from the sun, i.e. where the dark reaction can take place.

On the illumined side of the plant, solar energy is converted to biochemical energy as water is oxidized.

The light reactions of photosynthesis cannot take place at night unless an artificial light source is provided. Plant metabolism is linked to the cycle of day and night. The inner time clock of plants is normally set by the rhythm of the sun's light. Plant rhythms can be easily influenced by changing their exposure to light as is done in artificially lit greenhouses.

> ***QUESTION:*** *When does the plant grow more, during the day or at night?*

Metabolism of higher organisms in time

In human beings and higher animals anabolic processes predominate after eating. Anabolism also predominates during periods of growth. At the beginning of life, when growth is more pronounced, metabolism has a stronger anabolic quality than later in life. Humans can produce catabolic states by fasting. During illness catabolism predominates.

In animals and humans the rhythm of the inner time clock moderates the metabolic flow. Light plays a role in setting the inner time clock here too. Animals and humans have a metabolic circadian rhythm (rhythm of day and night). A metabolic circadian rhythm has been demonstrated very early on in the embryos of birds, as well as in human newborns.
In the adult human organism the solar diurnal rhythm has shifted, as in the rhythm of sleeping and waking and in metabolism.

1. The ergotrope phase: Between 3 AM and 3 PM.
Hildebrandt et al (1998) demonstrated that one 2000-calorie meal taken during this time results in a weight decrease of over 500 grams in 5 days. They also measured oxygen consumption when equal, small, low protein meals were given frequently during day and night (every 2-4 hours). Oxygen use is 50% higher during the ergotrope phase (120% of average daily oxygen consumption). Catabolism predominates during this phase.

2. The trophotrope phase: Between 3 PM and 3 AM.
The same one meal taken during the trophotrope phase of the human organism results in a weight gain of more than 500 grams within a week. Oxygen consumption is 80% of the daily average. Anabolism dominates the metabolism during this phase.

In the adult human metabolism the solar diurnal rhythm has shifted to a 3 AM/3 PM rhythm.

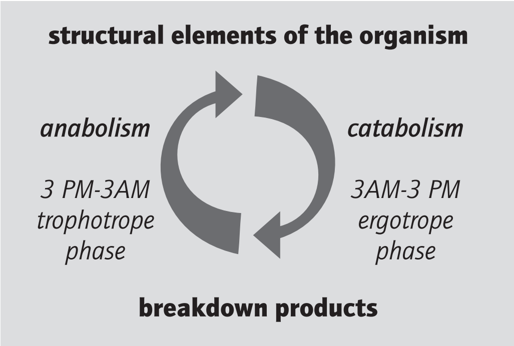


Fig.1.6. Time rhythms in metabolic processes

The human time clock has a resistance to change; it is harder to influence than the time clock of plants (Hildebrandt et al, 1998). It may take human beings 1-3 weeks to adjust physiologically after air travel across time zones. After jet lag many internal rhythms need to shift their phase. Some rhythms adjust to the day and night rhythm of the new time zone on the day of arrival, others take weeks to synchronize. In general, the inner time clock can change 1-2 hours/day after travel across time zones.

1.2.5. Ontogeny, phylogeny and time rhythms

Hildebrandt et al describe different rhythms in organisms:

A. Long wavelength rhythms:
- the circannual rhythm, a yearly rhythm
- the circalunar rhythm, a monthly rhythm
- the circaseptan rhythm, a 7-day rhythm
- the circadian rhythm, a diurnal rhythm

B. Median wavelength rhythms:
hourly and minute rhythms, which we find in organs, as for instance in the rhythms of peristalsis and of breathing.

C. Short wavelength rhythms:
rhythms of seconds or parts of seconds. These are predominant in cells and tissues (as seen for instance in electroencephalogram (EEG) rhythms of the brain).

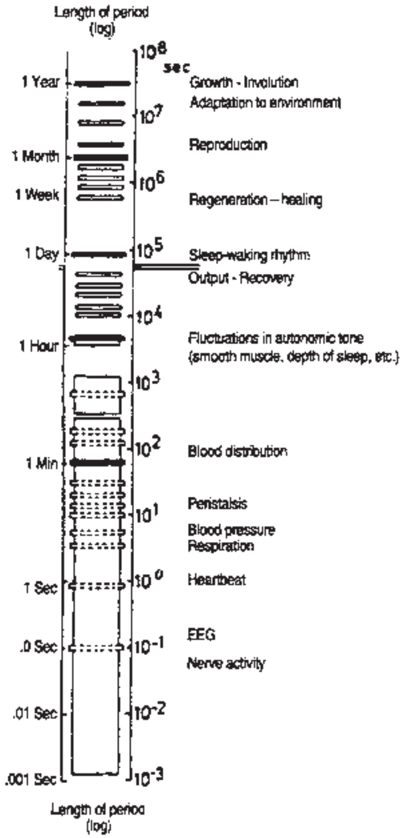


Fig. 1.7 From: Hildebrandt, 1998

In general long wavelength rhythms are more *exogenous rhythms*, which means they are dependent on outside influences, for instance on solar and lunar rhythms. In plants long wavelength rhythms (i.e. circannual and circalunar) are predominant. Plants do not have strongly developed inner rhythms, which makes it easier to change their inner time clock from without, as happens for instance in greenhouses with artificial light.

The shorter wavelength rhythms, such as organ rhythms, are usually *endogenous rhythms*. They are dependent on the inner time clock only. Endogenous rhythms are more developed in animals. The more highly developed the animal the more it develops a whole spectrum of rhythm frequencies, down to the very short ones.

Human beings have pronounced endogenous rhythms. Jet lag is a result of having a strong endogenous rhythm. Human beings have also developed an important additional attribute in relation to time cycles -- we are able to *emancipate* ourselves progressively from exogenous long wavelength rhythms (such as from sun and moon). These exogenous time rhythms are internalized in the human organism and may then function with a shift in phase. Besides the above-mentioned shift in the solar diurnal rhythm another example of this is the female period in relation to lunar rhythms. Human beings can be relatively free from exogenous rhythms, and more self-dependent in relation to time rhythms.

1.3. Summary and conclusion

Metabolic processes

The metabolic process of the human organism normally starts with breakdown products from the intestines that become available for anabolic or catabolic reactions. Anabolic reactions build up the substances of the organism. Anabolic reactions enable the organism to 'get substance' and take form. The organism becomes visible like a standing wave in a creek.

Larger compounds contain bond energy that holds together the compounds' structure. This energy can be made available by catabolic reactions for those functions of the organism, which require directly available energy. The metabolic flow of living organisms ends with the catabolism of its substance, which frees energy for the organism's functions (such as anabolic biochemical processes, bio-electrical, bio-mechanical and active transport needs).

The citric acid cycle, which takes place in mitochondria, is at the center of oxidative breakdown and can also be the starting point for the reductive synthesis of large compounds in the organism. Acetyl-CoA plays a major role at this center of metabolic activity.

The metabolic cycle in plants begins with the breakdown of *water*. Green plants obtain their energy from breaking down water with the help of solar energy. The oxidation of water provides the energy required in the plant to build up its organism. Plants in turn are an important part of the food cycle in nature. They supply animals and humans with nutrients, as well as being the source of oxygen for breakdown processes that are required to make foodstuff into usable energy and metabolites. Thus the energy for the functioning of higher organisms is indirectly derived from the breakdown of water by sunlight in the plant.

Characterization
The two opposite metabolic processes of anabolism and catabolism are actually part of *cycles* that involve different biochemical reactions, cell compartments, organs, and/or organisms, and time rhythms.

Biorhythms

Sunlight provides the energy in plants to break down water and also the diurnal rhythm of this process: light exposure is the dominant factor in setting the inner time clock in plants, and animals and humans as well. The human organism has an inner time clock that dominates the metabolic cycle with a cyclically changing emphasis on either anabolism or catabolism in a *shifted* diurnal rhythm (ergotrope and trophotrope phase), indicating that the solar rhythm has been internalized.

Characterization
The wavelength frequency of the metabolic cycle is related to the span of activity of the relevant process in the organism. Plants have longer wavelength rhythms, animals have more endogenous rhythms than plants, and humans can be free from exogenous rhythms.

Because we have encountered a fundamental difference here between animals and humans, specifically that humans can be relatively free from exogenous time cycles, we will research the human organism separately from now on.

> ***QUESTION:*** *What is the relation between the phase of metabolic process (anabolic or catabolic) and state of consciousness?*

Conclusion: *Metabolism plays an important role in the coherence between living organisms and their environment. Metabolic processes function in interlocking cycles and are also cyclic in time. The solar diurnal rhythm plays an important role as an exogenous influence on metabolic rhythms. The prototype of this is found in the plant. Living organisms have their own endogenous time cycles, which are more pronounced in higher animals. Humans have an additional prototypical capability: they can be relatively free from exogenous time cycles.*

Biochemistry

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? Is there a relation between biochemical processes in the single organism and processes in nature as a whole?
The scope of the answers to these questions can be enhanced by using a combination of the current scientific method and a phenomenological method developed specifically to research the coherence of processes within living organisms. The current scientific method is used to discover biological facts. The phenomenological approach helps us in finding the meaning of the facts.

What emerges is a new grasp of the interrelations between biological processes, consciousness, psychology, and behavior.

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