Georgi Stankov

The General Theory of Biological Regulation

The Universal Law in Bio-Science and Medicine

Volume III

NEW EUROPEAN ACADEMY PRESS
(NEA PRESS)

Stankov, Georgi

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ISBN 3-00-004077-3

New European Academy Press
München, Sofia

Printed in Germany

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INTRODUCTION

The mystery of biological regulation has not been unravelled yet. The prevailing opinion is that it is impossible to establish a general theory of biological regulation comparable to the equivalent theories in physics. I have proved that this estimation is essentially wrong. In the past, the two edifices of physics - *classical mechanics* and *quantum mechanics* - were also regarded as separate theories for the physical micro- and macroworld, and it is still believed in physics today that the two disciplines cannot be integrated. In this context, *thermodynamics* is generally ignored and the *theory of relativity* - which is considered a further, albeit partial, development of classical mechanics - is integrated into quantum mechanics (QED). I have discovered the **Universal Law of Nature** (the **Law**), from which all known physical laws and their applications can be derived and epistemologically explained. In this way I have integrated physics on the basis of mathematical formalism and thus eliminated the aforementioned physical disciplines as separate areas of knowledge.

The Law was originally discovered in connection with the biological regulation of the cell and the organism, and was initially called the "**Bioenergetic Principle**". This discovery led in turn to the development of the **General Theory of Biological Regulation,** referred to as the **General Theory**. The present volume is an introduction to its basic principles. The General Theory includes the totality of our knowledge of medicine, pharmacology, and bio-sciences and is virtually infinite - there is no cognitive, factual, or intellectual limit to this theory. As the General Theory is based on **physical and mathematical axiomatics,** as outlined in the German volume I on mathematics and physics (1997), and in the English volume II on physics and cosmology (1999), it can only be properly understood and evaluated after this axiomatics has been fully comprehended. The scientific theory of the Universal Law leads to the following fundamental conclusions in science:

1. There is no experiment or phenomenon - be it physical (inorganic) or biological (organic) - that infringes upon the Universal Law.

2. All mathematical presentations of physical phenomena are applications of the Law.

3. Many non-mathematical interpretations of mathematical or other results obtained from scientific experiments infringe upon the Law and should be eliminated from science as erroneous concepts. This is particularly true for the basic concepts of medicine and the bio-sciences.

In this volume, the basic mechanisms of cell regulation will be analysed in the light of the Law. Their elaboration establishes the methodological basis with which any specific biological phenomenon can be appropriately assessed and explained. Detailed solutions to fundamental biological phenomena and diseases will be presented. To illustrate the ubiquitous applicability of the General Theory in medicine, the pathogenesis of cancer, AIDS, and some other common chronic diseases is explained and some new effective therapies are introduced.

The new theory brings together several well known partial bioenergetic approaches and amalgamates them into a unified theory. These are:

a) The chemiosmotic theory of P. Mitchell
b) The soliton concept of A.S. Davydov
c) The concept of biological excitations of H. Fröhlich
d) Supramolecular chemistry
e) The biochemistry of cell metabolism

These approaches will be critically reassessed. I shall explain why none of them has been able to forward a coherent explanation of biological regulation. The General Theory departs from the new physical and mathematical axiomatics and considers the state-of-the-art in biology, biochemistry, genetics, medicine, and pharmacology up to the present day; it is based on the retrospective and prospective evaluation of more than 10 000 pivotal publications. It introduces two fundamentally new concepts which are basic to an understanding of cell metabolism and its regulation:

1. **The soliton triplet**

2. **The functional Unit of Energy transLocation**, called **FUEL**.

1. **Soliton triplets** represent specific *amino acid sequences* that are regularly found in proteins. They are of central importance to the kinetic (energetic) behaviour of proteins. In addition, they determine the spatial structure of transmembrane proteins and cytosolic enzymes. The existence of such amino acid sequences and their role in cell regulation have so far evaded the attention of scientists. The functional meaning of the soliton triplets, their modulation by means of genetic mutations, and their role in the pathogenesis of various diseases will be elucidated in the context of the Law. Thus, for the first time since the discovery of the genetic code in the 50s, a consistent energetic explanation of the DNA code which determines the amino acid sequences in proteins will be presented with respect to their function and kinetic behaviour in the cell. This includes the reading and understanding of the amino acid sequence code of proteins; the latter is a mirror image of the DNA code.

2. The new term "FUEL" is the U-set (the set of all sets that contain themselves as an element) of all transmembrane proteins, independent of their actual function (e.g. receptors, channels, ATP-ase, etc.), and of all enzymes in the cytosol. The biomolecular basis of these two energetic systems or levels of the cell will be presented in detail.

The General Theory explains in a straightforward and consistent way the pharmacological effects of all drugs and the physiological effects of all *hormones*, *humoral factors*, and *neurotransmitters* by introducing the concept of the "**dipole model**". This model allows the prediction of the therapeutic and adverse effects of any chemical moiety based on its *chemical* and *supramolecular* structure. It includes the theory of quantum mechanics as presented in the light of the Law. Due to the complexity of the theory involved, this model can only be outlined here in general, non-mathematical terms.

The dipole model proves that any chemical compound which is applied to the organism for therapeutic purposes has either **cell-stimulating** or **cell-inhibiting** effects. The two terms are introduced with respect to cell metabolism, which is a particular energy exchange in space-time. Therefore, the two concepts are axiomatically derived from the primary term, that is, from the Law. Cell-stimulating compounds such as some drugs and most vital substances augment the turn-over of the cell and the organism, while cell-inhibiting drugs decrease same. It can be proven that almost all biological compounds that participate in the natural regu-

lation of the organism are cell-stimulating. This means that cell-stimulation is the only functional mechanism of biological regulation. The very existence and longevity of cells and organisms depend exclusively on the appropriate biochemical stimulation.

Cell-inhibiting drugs on the other hand are deleterious to the organism because they impede physiological cell metabolism. Such drugs cause cell lysis and numerous toxic effects at the organic level (adverse events). When they are chronically applied to humans, they **significantly increase morbidity and mortality**. Many excellent double-blind, placebo-controlled, clinical trials published in the last few years overwhelmingly confirm this basic conclusion, which follows consistently from the Law when it is applied to the level of organic matter. These recent clinical data prove beyond any doubt that modern medicine has contributed to the systemic annihilation of millions of patients by treating them chronically with cell-inhibiting drugs, such as *calcium antagonists*, β-*blocking agents*, *antiarrhythmics*, *cytostatics*, etc. (see chapter 2.9). The total number of these "iatrogenic murders" committed during the last 50 years of applied pharmacology may exceed by far the number of victims in the numerous wars, including the two World Wars, which have been so characteristic for this most brutal and bellicose century in the history of mankind.

The dipole model is undoubtedly one of the most outstanding applications of the Law in bio-science and medicine. While it reveals the dreadful truth about modern pharmacology, at the same time it permits the rapid development of cheap and effective cell-stimulating agents for the treatment of a variety of diseases for which there is no therapy at present. The application of this model will save the pharmaceutical industry billions of dollars, which are currently wasted in futile research. At present, the search for effective drugs is based on the empirical "trial and error" method because there is still no consistent theory of biological regulation and pharmacological effects. As a rule, the companies have to synthesize and check more than 9000 chemical compounds before they register a single drug. For this reason the level of expenditure in pharmaceutical research has been growing exponentially in the last 10-15 years. The primary cause for this increase in R & D lies in the elevated statistical standards of clinical research as demanded by national and international registration authorities. In this respect, we should emphasize the pioneering work of the Federal Drug Administration (FDA) in the USA. The latest recommendations of this institution have prompted

the conducting of some excellent, large, controlled trials, which have yielded negative results for some of the most commonly used drugs. When compared to placebo, these drugs significantly increase mortality and morbidity in all the indications tested. The most relevant "negative results" will be presented in the last chapter of the present volume.

The General Theory establishes an integrated framework of *cellular* and *supracellular* regulation, based on the three fundamental axioms of the new physical axiomatics: 1) the axiom of the conservation of action potentials (CAP) 2) the axiom of reducibility (AR) and 3) the axiom on the reciprocal behaviour of the LRCs of two contiguous levels in a system. These axioms are basic to the formulation of all known physical laws. They can also be applied to explain the micro- and macroeconomic behaviour of society (general theory of economics), which is a subset of organic matter.

The immediate virtue of the General Theory is that it explains in a consistent way the dynamic pathogenesis of various diseases, such as cancer, AIDS, other viral diseases, and chronic diseases with immunopathogenesis, such as rheumatoid arthritis (RA), multiple sclerosis (MS), Alzheimer disease (AD), atherosclerosis (AS), etc., while incorporating the latest scientific data in each of these fields. The present vague and conflicting hypotheses on the pathogenesis of human diseases, as presented in any comprehensive textbook on this issue (e.g. in Harrison's Principles of Internal Medicine), will be substituted by a new, coherent **medical theory of pathogenesis** based on the Law. This theory is credibly confirmed by all relevant data in the field concerned.

Finally, the novel bioenergetic approach affords a profound insight into the molecular mechanisms of *neuronal connectionism.* This will promote the development of *artificial intelligence* (AI) and the construction of new types of computers based on *supramolecular* (*nanomolecular*) *chips*, also known as *molecular wires*. These chips will imitate the properties of the FUELs. The same technology will be used for the development of new sources of energy based on the *principle of photosynthesis*, that is, on the transformation of photon energy into electric energy by the simultaneous production of oxygen. This new energy source is opposite to combustion, which is the prevailing form of energy exchange employed today. Combustion leads to oxygen consumption and its subsequent depletion in the atmosphere. If this kind of energy production continues at the same pace, this will ultimately lead to the annihilation of mankind (see vol. I). The new energy sources based on photosynthesis

will regenerate the oxygen which has been consumed by combustion since the beginning of the industrial revolution. The development of such new technologies will determine the scientific research of mankind in the coming millennium. In all these fields, I have achieved major theoretical breakthroughs which are beyond the scope of this present elaboration. The present overview reveals the interrelated character of the **Unified Theory of Science** based on the Law.

During my clinical research activities, I discovered empirically that the two polyenes **Amphotericin B (Amp)** and **Nystatin (Nys)** are highly effective in various clinical conditions. This fact led to the discovery of the Law and the development of the General Theory. In the process, it was established that these drugs dramatically reduced mortality in severe trauma patients, lowered high plasma cholesterol levels in humans, cured various forms of chronic allergy, exacerbation of neurodermatitis, recurrent aphthous stomatitis, and acne, promoted the healing of wounds and burns, improved the clinical condition of patients with chronic immunological diseases, such as cold agglutinin disease (CAD) and rheumatoid arthritis, and had a positive impact on various other diseases such as diabetes mellitus (e.g. through a reduction of high-dose insulin, stabilization of glucose levels and improvement of clinical symptoms). In addition, the *life expectancy* and *quality of life* of marastic cancer patients could be improved and the adverse effects of chemotherapy and radiation markedly reduced, or even offset. Nys and Amp also caused the encapsulation of tumours, as was histologically observed in several patients.

These preliminary clinical results were observed both by myself and independently by other physicians and were found to be in accordance with a large body of published data. None of the authors writing on Nys and Amp have provided any satisfactory explanation for the vast array of *in vitro* and *in vivo* effects exhibited by these drugs. For instance, there is clear in vitro evidence that both Amp and Nys are effective in the suppression of HIV - a fact that fully complies with the predictions of the General Theory. Therefore, these drugs can be given as an early chronic treatment of HIV-positive patients to postpone the occurrence of the AIDS-related complex.

At present, the two drugs are only used in the treatment of yeast. Until the discovery of their novel effects, it was believed that Nys and Amp were not resorbed from the gastrointestinal tract and hence did not

enhance any systemic effects. Therefore, they are still exclusively used for gut decontamination and the topical treatment of candidiasis. Amp is also given intravenously (i.v.) in systemic mycoses, but its use is limited due to high toxicity. Contrary to the general belief that these drugs are not resorbed from the mucosa, I found that they are well resorbed from the intestinal tract and enter the circulation via the lymphatic vessels. Due to their amphipathic properties, Amp and Nys avidly associate with adjacent cell membranes. In terms of pharmacokinetics the latter can be regarded as the "deep compartment" for drug distribution in the body, while the drug concentration in the ionic and lipophobic plasma (the first compartment) is very low. This has led to the wrong notion that polyenes are not resorbed from the gastrointestinal tract. Due to their kinetic behaviour, polyenes accumulate predominantly in the liver and in other secondary immunological organs and reach only in negligible concentrations, via blood circulation, vital organs such as kidney, heart, and lungs. In these organs, systemic polyenes exert their most pronounced adverse effects, some of which will be re-evaluated in the light of the General Theory. This explains the dichotomy in the safety profile of Nys and Amp, which are very well tolerated after oral administration but are quite toxic after i.v. application.

Within the General Theory it can be explained why Amp, Nys, and the group of polyenes are the *most potent immunostimulating drugs* currently available on the market. In general, they stimulate cell metabolism, growth, and the proliferation of all cell types, and can be used in the treatment of a variety of diseases for which there is no effective therapy. When the dipole model was applied to 4000 chemical moieties currently available on the pharmaceutical market, it was found that Nys, Amp, and the group of polyenes are the only potent cell- and immunostimulating drugs for oral application. Most of the drugs used today are *cell-inhibiting* drugs, as their names suggest (β-blocking agents, calcium antagonists, antiarrhythmics, cytostatics, antibiotics, etc.). We shall present clinical evidence in support of our conclusion that such drugs increase mortality and morbidity in humans. In this way we shall give some inkling of the most depressing aspect of modern medicine - the unwanted genocide of millions of patients through the collective effort of physicians, pharmacologists, and the pharmaceutical industry, which is generously sponsored by the state and the national healthcare system in each country.

The General Theory opens up new therapeutic strategies that will be discussed briefly. The rationale behind the chronic treatment of various

diseases with IFN-β, IFN-γ, vitamin A, and various interleukins, a new trend that has been emerging in the last few years, will be elucidated. At the same time we shall present evidence for the deleterious effects of many common drugs, such as cytostatics, NSAIDS, antibiotics, cardiaca, etc., as predicted by the General Theory. We shall show that these drugs exhibit a common inhibitory mechanism of energy exchange across cell and plasma membranes and thus infringe upon the Law.

The aforementioned aspects clearly demonstrate that the General Theory is anything but an ivory tower discipline. While it represents a major theoretical breakthrough that will undoubtedly influence all aspects of bio-research, it offers at the same time new therapeutic strategies for many diseases that are at present incurable. The discovery of the broad therapeutic potential of Amp, Nys, and other polyenes permits the immediate implementation of cheap and safe oral drugs in the treatment of cancer, AIDS, atherosclerosis, sepsis, wound healing, and various chronic diseases with immunopathogenesis. This constitutes a major medical breakthrough of enormous economic and ethical importance. This is one of the many possible applications of the General Theory that will revolutionize medicine and the pharmaceutical industry in the coming years.

PART 1

BIO-SCIENCES

1.1 MITCHELL'S CHEMIOSMOTIC THEORY TODAY: A CRITICAL REASSESSMENT

In 1861 Pasteur published the historical discovery that, per gram of glucose, more yeast is formed in the presence of air than in its absence. This is considered as the first demonstration that aerobic metabolism is more efficient than anaerobic metabolism. But Pasteur also observed that in the presence of air glucose disappeared more slowly than anaerobically, which pointed to the existence of a regulatory mechanism, later called "Pasteur effect". This effect has puzzled biochemists and evoked a voluminous and highly confusing literature right up to the present day. But the Pasteur effect also gave birth to a new biological science, called *bioenergetics.*

Bioenergetics is not a coherent science based on axiomatic principles, such as the General Theory, but a collection of heterogeneous bioenergetic views with little or no physical foundation. Theoretically, it stems from *Gibb's interpretation of the 2nd thermodynamic law of entropy*, as applied to chemical reactions at equilibrium. The interpretation of the entropy law was rejected in the new physical axiomatics as a one-sided presentation of energy exchange at the thermodynamic level, while its numerous mathematical formulations were found to be derivations of the Law (see vol. I & II). For this reason this conventional law is eliminated from physics once and for all. This fact explains why all previous biochemical and bioenergetic approaches to cell regulation were doomed to failure. Among them, the chemiosmotic theory of *Peter Mitchell*, published for the first time in 1961, 100 years after the classical paper of Pasteur, assumes a predominant place.

Mitchell proposed a chemiosmotic mechanism for **oxydative phos-**

phorylation (OP) in mitochondria: an asymmetric respiratory chain catalyzes electron transport that is associated with a vectorial translocation of protons across the mitochondrial membrane giving rise to an *electrochemical proton gradient*, called the "*proton-motive force*", which generates ATP[1]. The uncertainty as to how OP operated was so great before Mitchell's proposal that it prompted some cynical jokes of the kind: "Anybody who is not thoroughly confused just does not understand the problem." This observation is as valid today as it was 40 years ago.

The chemiosmotic hypothesis met fierce resistance when it was first postulated, but subsequent research confirmed its validity and enriched the theory with more detailed insights into the complex processes of OP in mitochondria. Below, the present state of the chemiosmotic theory will be critically reassessed as summarized in two comprehensive books: "The Vital Force: A Study of Bioenergetics" by F.M. Harold (1986) and "Bioenergetics 2" by D.G. Nicholls and S.J. Ferguson (1992). We assume that the reader is well acquainted with this theory. We shall therefore restrict our discussion to its basic statements and inherent contradictions, which have hindered the consistent explanation of biological regulation.

The chemiosmotic theory proposed by Mitchell deals with the energy exchange during OP or *photosynthesis* in a single *mitochondrial*, *bacterial cytoplasmic*, or *thylakoid* membrane. The OP is the final cycle of animal cell metabolism where all known metabolic pathways join. According to the axiom of the conservation of action potentials (CAP), it is sufficient to describe this cycle in order to determine the total energy balance in the cell (see chapter 1.2). The theory postulates that the energy obtained from these processes is used to establish a *proton-motive force* across the mitochondrial membrane. The terminology of the chemiosmotic theory is rather confusing and metaphysical, probably because it was established by non-physicists. For this reason we shall express the quantities used in the chemiosmotic equations in the new space-time symbolism (see vol. I & II). In the following, we shall refer to the

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[1] Biochem. Society, 1976, 4: 399-430; Science, 1979, 206: 1148-1159. Nota bene: The total reference list of this book consists of more than 3000 pivotal publications. We shall quote the most relevant in the footnotes. Further basic references are listed at the end of the book.

oxydative phosphorylation (OP) in mitochondria.

According to the general stoichiometric **equation of respiration,** the *four electrons* that are supplied from the respiratory chain in the mitochondrion are the final product of the metabolic redox cascade in the cell:

$$O_2 + 4\ e^- + 4\ H^+ = 2\ H_2O \qquad (1)$$

They are involved in pumping protons out of the mitochondrial matrix and in establishing an electrochemical potential of about 200 mV across the mitochondrial membrane. Driven by this electrochemical gradient, the protons on the cytosolic side which is positively charged enter the matrix through the F_1F_0-ATP-synthase and generate ATP. Mitchell proposes the following equation of the **proton-motive force**:

$$dP\ [V = m^2s^{-2}] = dU - k\Delta pH = SP(A)[2d\text{-}space\text{-}time] \qquad (2),$$

where *dP* is called "*proton-motive force*", but is in fact an electric proton gradient *LRC* = *U* = [2*d-space-time*]; *dU* = *LRC* = [2*d-space-time*] is the electrochemical potential between the P-phase of the cytosol (P for positively charged) and the N-phase of the matrix (N for negatively charged); ΔpH = *LRC* = [2*d-space-time*] is the difference in pH between the P-phase and the N-phase (according to the new axiomatics, pH is a coefficient of energy exchange, a dimensionless number that belongs to the continuum); *k* is another dimensionless constant (energy relationship = SP(A)). Equation (2) is derived from Gibb's standard free energy change of equilibrium ($dG^o = dH^o - TdS^o = E$) by employing the Nernst's equation, where dH^o is the enthalpy change, *dS* is the entropy change of the system, and *T* is the temperature. It is an application of the universal equation.

Equation (2) is obtained through the axiom of CAP; alternatively, it can be interpreted by the axiom on the reciprocal behaviour of the LRCs of contiguous levels (principle of last equivalence). In Mitchell's chemiosmotic theory, the proton-motive force *dP* is considered proportional to the redox span *dE* of the respiratory chain, but opposite in direction. This assumption is another application of the universal equation:

$$ndP = 2\ dE = E_A f \qquad (3)$$

It is assumed that 2 electrons passing through a redox span *dE* within the respiratory chain pump *n* protons across the membrane against the proton-motive force *dP* to obtain an equilibrium between the two parameters. The chemiosmotic theory regards the mitochondrion as a closed equilibrium system, to which the classical equilibrium thermodynamics based on Gibb's interpretation of entropy in chemical reactions is applied. The theory postulates an equilibrium between the proton-motive force and the redox potential of the respiratory chain. This is the common static view of nature in science - it is an application of CAP. However, organic life in general and mitochondria in particular are open systems that exchange energy and substrates with their surroundings. This becomes evident when one considers the fact that OP is interrelated to the metabolic web in the cytosol, while at the same time all substrates of cell metabolism, such as fats, proteins, and carbohydrates that enter the cell come from food consumption (see Fig. 1).

I have proved that classical thermodynamics only considers the thermal equilibrium at the material level that is established by photon radiation as a vertical energy exchange (Stefan-Boltzmann law and Wien's displacement law as applications of the Law), and at the same time completely ignores the occurrence of thermodynamic gradients at the photon level. The one-sided perception of thermodynamic energy exchange as embodied in the law of entropy was rejected by deriving *Stankov's law* of photon thermodynamics (see vol. II).

The key statement of the chemiosmotic theory is that ATP-synthase should not sense changes in respiratory chain activity directly, but through alterations in the steady state of *dP*. This approach considers the dislocation of the proton-driving pump from the ATP-synthase, called "*delocalized coupling*". The chemiosmotic theory states that an artificially generated electric gradient *dP* should be able to induce the synthesis of ATP in any energy-transducing membrane with a functional ATP-synthase. The delocalized coupling between a proton-driving pump and an ATP-synthase was confirmed in various *reconstitution experiments*[2]. Further experimental evidence in support of the main postulate of the chemiosmotic theory is the triggering of ATP synthesis after a sudden imposition of an artificial *dP* with a minimal delay that is more rapid than the following initiation of respiration.

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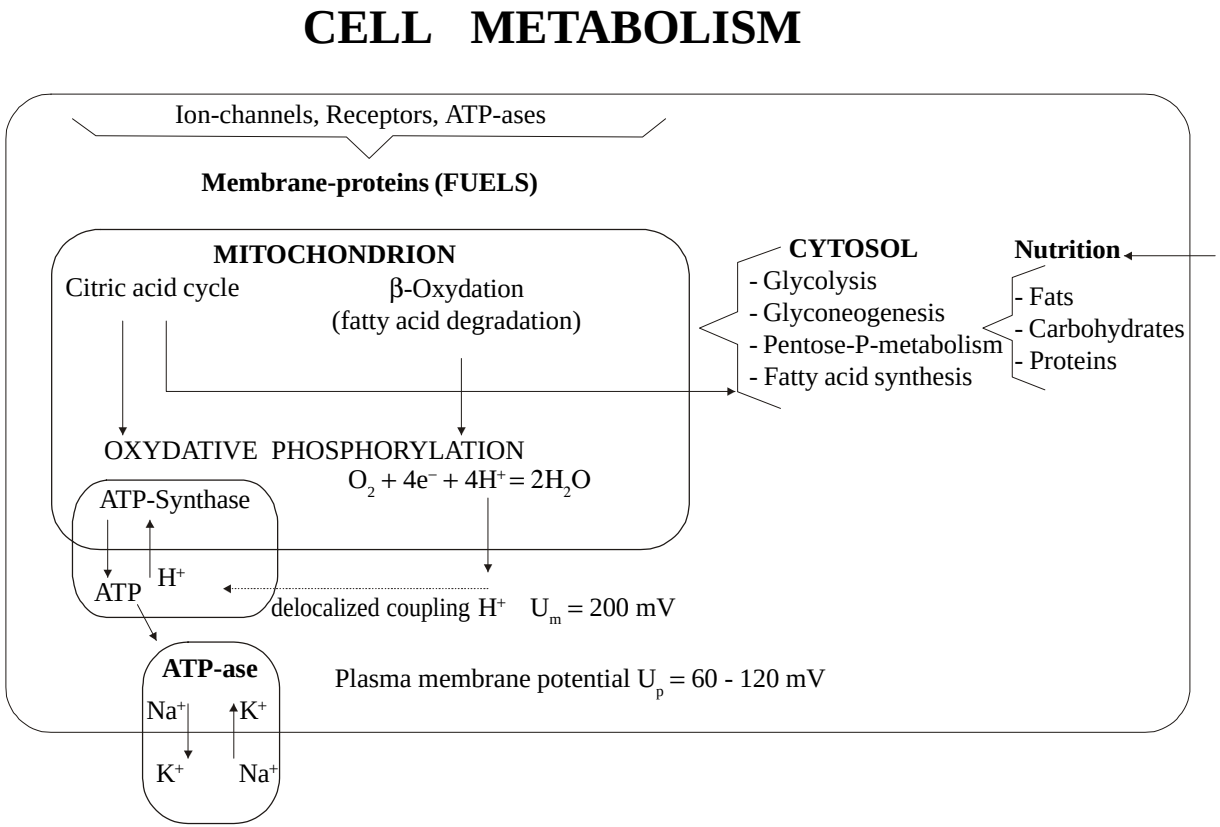
[2] Federation Proc., 1980, 39: 210-215.

Figure 1: Metabolic pathways of energy exchange from nutrition (chemical energy = metabolic LRC) into electric energy of membrane potentials (electric LRC) in the cell according to the axiom of reciprocal LRCs of contiguous levels in a system.



This experimental evidence confirms the existence of a delocalized coupling between the proton-motive gradient on the one hand and the production of ATP on the other. At the same time it rejects the deterministic stoichiometric approach employed in biochemistry today. It backs the fundamental conclusion of the new physical axiomatics, which states that all systems are open and therefore subjected to the influence of any other energy exchange in space-time (relativistic change in energy). We prove the unity of space-time by showing that all fundamental physical constants can be derived from each other and constitute an *input-output* model of the power of the continuum (see vol. I & II). Mitchell's concept of "delocalized coupling" is an intuitive notion of the openness of space-time with respect to the system "mitochondrion". His principal flaw was to restrict his concept to this particular organelle. Mitchell's revolutionary idea of a delocalized coupling in the cell is not fully realized in biology, although the chemiosmotic theory forms the bioenergetic basis of modern biochemistry.

The quantification of *dP* is important for the chemiosmotic theory because a single demonstration of a net ATP synthesis in the absence of sufficient *dP* would have demolished the entire edifice of this theory. In addition, the observation that there are apparent inadequacies in the magnitude of *dP* has cast doubts on the concept of delocalized chemiosmosis. Controversies have arisen around two issues: the mechanism by which the proton-driving pumps operate and the mechanism that connects the proton circuit across the membrane with the coupling of OP to ATP-synthase.

The mechanism of the proton-driving pump cannot be adequately explained by the chemiosmotic theory, although several working models have been suggested (see below). The quantitative aspects of the *proton circuit*, which exhibits a non-linear kinetics, also pose great problems for the chemiosmotic theory. In vitro, all mitochondria show a significant state of slow respiration (all ADP converted to ATP). This is attributed to an "*endogenous proton leak*" that shows a non-linear dependence between the magnitude of *dP* and respiration. At high *dP*, a disproportionally large increase in the proton conductance of the membrane is seen, called "non-ohmic leak", that limits the maximal potential across the membrane. This proton leak occurs at different sites from those of the ATP-synthase and contributes significantly to the resting respiratory rate of intact cells. The delocalized coupling of OP to ATP synthesis is thus less deterministic than modern protagonists of chemiosmosis would like to see it. This

fact merely indicates that mitochondria are open systems and exhibit a non-linear recurrent kinetics of energy interaction with their surroundings.

The exact determination of *dP* from measurements of the electrochemical gradient across mitochondrial membranes is another challenge that creates some insoluble problems for the chemiosmotic theory. The electrochemical gradient of about 200 mV establishes a powerful electric field of $\mathbf{E} = [1d\text{-}space\text{-}time]\ f = 10^8\ [\mathrm{Vm}^{-1} = \mathrm{ms}^{-2}]$. Consequently, it is not surprising that some natural membrane constituents respond to the electric field by altering their spectral properties. This *electrochromism* is due to the effect of the imposed electromagnetic field of the membrane potential on the quantum energy levels of the delocalized π-electron systems carried by such molecules (see below). The most widely used intrinsic probes of the electrochemical potential are *carotenoids*, which are a heterogeneous class of polyenes with long chains of **conjugated double-bonds** that act as *light-harvesting* molecules. These substances are known to protect the organism against oxydative damage caused by free radicals by accommodating free electrons in their **delocalized π-electron anion**. The π-electron systems of carotenoids give a characteristic visible spectrum when they associate with biological membranes. The shifts in their absorption spectra in response to changes in the membrane potential only amount to a few nanometres ($\Delta\lambda$); the signals are detected by dual wave spectography. The response is extremely rapid (nanoseconds). However, measurements with carotenoids regularly yield much higher *dP* values than those obtained with other methods, e.g. with the ion distribution method. These results are paradigmatic for a situation in which the method of measurement interferes with the object of measurement and thus influences the outcome (open system).

A major preoccupation of the chemiosmotic theory is to find the exact stoichiometric ratio between the number of electrons produced by the respiratory chain and the number of protons expelled on the P-side, which then flow through the F_1/F_0-ATP synthase to generate ATP molecules in a delocalized manner. The estimates vary between 2 and 5 electrons per ATP, depending on the initial conditions. This non-linear behaviour is also demonstrated by the variable *proton-electron stoichiometry* of the proton-driving pump. If conditions are arranged such that the ATPase is at equilibrium, the determination of the magnitude of *dG* for the ATPase reaction and *dP* allows the calculation of the H^+-stoichio-

metry. From an equilibrium point of view, one would expect that the H^+/e^- ratio would stay constant at a variety of *dP* values. In the chemiosmotic theory, this ratio is expected to behave linearly. However, the experimental evidence shows that there are deviations from the expected stoichiometry. The assumed $2H^+/2e^-$ stoichiometry of the respiratory chain complex seems to change, depending on the magnitude of *dP*. Another aspect of the delocalized coupling of OP to ATP synthesis is that various external factors influence chemiosmosis in a way that hardly fits in with the current concepts of this theory.

These facts merely confirm that the reciprocal behaviour of the LRCs of contiguous levels in an open system depends on the overall energetic conditions of that system (prestabilized harmony or constructive interference of U-sets). From this discussion, it becomes evident that the chief cognitive problem of the chemiosmotic theory is the deterministic outlook that dominates present-day biological research. This approach is embodied in the belief that "a full cause always leads to a full effect" and goes back to the *initial-value problem* in physics - a concept which was repudiated as a mathematical fallacy in the new axiomatics (see vol. II).

"*Uncouplers*", also known as *proton translocators* or *protonophores*, are molecules of non-mitochondrial origin that play a major role in the chemiosmotic theory. These substances possess extensive π-electron systems, which can delocalize the charge of the anion along the supramolecular structure and thus retain lipid solubility. By shuttling across the lipid bilayer, they can facilitate the transport of protons and increase the proton conductance of biological membranes. The same holds true for Amp, Nys, and the polyenes, which are potent **ionophores** widely used in the *patch-clamp technique*.

Protonophores uncouple OP by inducing an artificial permeability in the lipid bilayer. As a consequence, a state of *rapid respiration* can be induced in the mitochondrion. In the chemiosmotic theory, this is defined as a "short circuit". It is believed that protons which are expelled by the proton-motive force on the P-side normally flow back through the ATP-synthase to generate ATP. This is usually defined as a "proton circuit". Uncouplers are said to "short-circuit" the proton current and allow the generation of *dP* to be uncoupled from ATP synthesis.

Obviously, there are external chemical factors that can interfere with the postulated proton circuit across the mitochondrial membrane and even completely disconnect it. This clearly indicates that the relationship between the redox span and the proton-motive gradient which, in turn, en-

hances ATP synthesis in a delocalized manner is not unique, as is originally postulated in the chemiosmotic theory, because it can be modulated by various external factors of non-mitochondrial origin. The delocalized coupling is thus an open process - it is not exclusively restricted to cell respiration and ATP synthesis. This observation is very important for our understanding of the General Theory of cell regulation as outlined in chapter 1.2.

The ability of extended π-electron systems to delocalize charge (recall that charge is a synonym for *cross-sectional area*) and enhance lipid solubility is exploited in the synthesis of cations and anions which can be transported across the lipid bilayer although they carry a charge. Lipophilic cations and anions are of historical value to the chemiosmotic theory. Experiments demonstrating their energy-dependent accumulation in mitochondria and in *inverted sub-mitochondrial particles* (SMPs) have eliminated the possible existence of specific cation pumps driven by the so-called "squiggle". This name was initially given to a hypothetical chemical moiety that was favoured as an energy carrier in OP before the chemiosmotic theory gained broad support in biology.

The mechanism of uncoupling is, indeed, quite common in organic matter and plays a vital role in the thermoregulation of organisms. Brown adipose tissue of cold-adapted rodents and new-born mammals is the place of *non-shivering thermogenesis*, by which these animals can increase their respiration and generate heat without having to shiver. Brown adipocytes of cold adapted rodents are packed with mitochondria. The extensive inner membranes of these organelles indicate a high capacity for resorption. Adrenergic stimulation of brown adipocytes leads to the hydrolysis of triglycerides.

The problem with shivering thermogenesis is to explain how the fatty acids liberated by lipolysis can be oxidized in mitochondria when the pace-limiting factor in the proton circuit is the re-entry of protons into the mitochondrial matrix. The problem is aggravated by the relatively low amount of ATP-synthase and the absence of any significant extramitochondrial ATP hydrolysis activity in these cells. In the context of the chemiosmotic theory, there are two alternatives: either the respiratory chain of brown adipocytes is modified so that it does not pump protons, or the membrane is modified to allow re-entry of protons in the absence of ATP synthesis.

As is the case with uncouplers, the second alternative holds true. The mitochondrial inner membrane contains a 32 kDA *uncoupling protein*,

which binds a purine nucleotide to its cytoplasmic face and is inactive until the free fatty acid concentration in the cytoplasm starts to rise. The protein then binds a fatty acid. Subsequently, it alters its conformation and becomes *proton conductive*. The uncoupling protein thus acts as a self-regulating endogenous uncoupling mechanism of the proton circuit that is automatically activated in response to lipolysis; this process is triggered by the supracellular noradrenergic sympathetic activation (see chapter 2.2). Observe that adrenergic activation always enhances a depolarisation of the cell (see below). The expression of the uncoupling protein in adipocytes occurs in response to the adaptive status of the animal to external temperatures. Cold-adaptation or over-feeding can lead to a re-expression of the protein. This example indicates that the delocalized coupling in the mitochondrion can be relativistically changed by the (thermal) energy exchange with the surroundings - this organelle is an open system subjected to the energy exchange in space-time.

The aforementioned examples contain a collection of recurrent motifs; they form the line of argumentation which we shall follow throughout this survey. We shall briefly summarize them here:

a) There are various external factors of chemical and thermodynamic origin that interfere with the delocalized coupling between OP and the proton-driving pump on the one hand and ATP-synthase on the other. This coupling is not restricted to processes in the mitochondrion, but involves all energy interactions of the cell with its surroundings. The chemiosmotic approach is in this respect rather deterministic and narrow-minded: it assumes a full cause for a full effect and has great difficulty in interpreting experimental evidence which shows that external factors also influence the proton circuit. The chemiosmotic theory considers the proton-motive gradient of the mitochondrion as a local event in a system which is considered disentangled from the rest of the cell. The methodological deficiency of such a local determinism is a recurrent theme in our critique of the conventional scientific view (see also vol. I & II). From this we conclude that the delocalized coupling between respiration and ATP synthesis in the mitochondrion is paradigmatic for the openness of all systems - organic and inorganic. Each system exchanges energy with all other systems of space-time and changes relativistically according to the energetic conditions of the surroundings.

b) There are various external factors that can influence the ATP-synthase. In the first place, we have chemical moieties such as *protonophores*, but also intrinsic uncoupling proteins of biochemical origin. These factors are subjected to the energy exchange with the thermodynamic level of matter and photon space-time.

c) The 32 kDA uncoupling protein of non-shivering thermogenesis is an integral protein that binds a purine nucleotide and is activated when free fatty acids interact with it in the lipid bilayer. Evidently, the *lipid composition* of biological membranes is essential for the activation of integral proteins. Interactions between proteins and lipids may induce conformational changes to the former and enhance ion conductance across the membrane. Therefore, the action of integral proteins is co-determined by the composition of the lipid membrane and is effected through energy interactions (horizontal energy exchange between adjacent systems).

d) External activation, e.g. adrenergic innervation, enhances endogenous uncoupling mechanisms and can modulate OP and the synthesis of ATP in mitochondria. This clearly indicates that the coupling of mitochondrial respiration to ATP synthesis is not a local event but an intrinsic part of the whole cell metabolism. The chemiosmotic theory on the other hand is a local theory - it cannot explain the intricate interplay between the various intracellular processes: "However, the distribution of control between the electron-transfer chains, ATP synthase, proton symports for nutrients, and other cellular processes is unknown.", write D.G. Nicholls and S.J. Ferguson in their book "Bionergetics 2" with a tone of resignation.

In the chemiosmotic theory, the proton-motive force is regarded as the only transmitter between respiration and ATP synthesis. On the other hand the proton-motive force is regarded as a constituent of the electrochemical gradient across the mitochondrial membrane, as is the pH-gradient. Thus the role of the proton-motive force is unduly emphasized in the chemiosmotic theory: it piously observes the general stoichiometric equation of OP as part of the metabolic web and does not consider other ions as possible carriers of energy transport. Respiration does, indeed, represent a redox process, in which 4 electrons are ultimately transferred into 4 protons to produce water. But this stoichiomet-

ric approach merely reflects the chemical aspect of OP: chemistry is a metaphysical discipline based on the energy exchange at the quantum level as assessed by Schrödinger wave equation, which is then applied in a formal way to the chemical level of matter by introducing the abstract concepts of *covalent bonding* and *molecular orbit*. Both terms are intuitive perceptions of the closed character of space-time, as traditionally expressed by the law of conservation of energy. This discipline has no own theoretical foundation and is therefore incapable of shedding light on the epistemological background of biological regulation. Hence the current deadlock in the bio-sciences - their approach is essentially biochemical.

The final product of cell metabolism is the establishment of a proton-motive gradient across the mitochondrial membrane (see Fig. 1). Once an electric gradient is spanned across this membrane through the extrusion of protons out of the matrix, this electric LRC no longer follows the static equilibrium as assumed for chemical reactions, but obeys the Universal Law of dynamic energy exchange between electromagnetic systems and levels, which are U-subsets of space-time and contain themselves as an element (axiom of reciprocal LRCs).

In the mitochondrion, the electrochemical gradient is predominantly a proton gradient. However, other ions such as Na^+ and K^+ also contribute to this gradient, as they are part of the cytosol. This fact poses a major theoretical dilemma for the chemiosmotic theory. Alkaliphilic bacteria that grow under aerobic conditions, in environments with a pH as high as 12, exhibit a cytoplasmic pH between 8 and 9. This means that the pH-gradient can be as much as 3 pH units, acidic inside, which is equivalent to a potential of 180 mV. This gradient is opposite in direction to the proton-motive force *dP*, as given in equation (2). Unless the bacteria were to maintain an exceptionally high *dU* in the order of 400 mV to compensate for the reversed pH-gradient, it is difficult to explain how they could synthesize ATP if they are only driven by the proton-motive force. In the most thoroughly investigated species, *Bacillus firmus* and *Bacillus alcalophius*, *dU* is in the order of 180 mV, positive outside, as is the case in mitochondria. Thus the total proton-motive gradient *dP* appears to be in the range of 5-80 mV as calculated in equation (2).

The magnitude of *dP* depends on the kind of species and becomes smaller the higher the external pH becomes. This magnitude of the proton-motive gradient is considered too low to drive ATP synthesis. The possibility that a Na^+-flow (sodium-motive gradient) may also contri-

bute to the synthesis of ATP is not discussed in the chemiosmotic theory. The alternative explanation that the total electrochemical potential is the actual driving energy gradient of ATP synthesis is not seriously considered either. In the light of the Law, this is the key fallacy of the chemiosmotic theory.

The enzyme ATP-synthase is reversible in its function. In fact, this holds for all ion-motive ATPases. The F_1/F_0-synthase produces ATP only in the presence of a proton gradient when the F_1 unit is orientated towards the N-side. Any electrochemical gradient which has this orientation with respect to F_1 can drive the ATP-synthase to produce net ATP. This relationship was proven in various reconstitution experiments. When the F_1 unit is orientated towards the P-side of the membrane, the F_1/F_0-synthase operates as ATPase - it consumes ATP and expels ions against their gradient (ion-pump). ATP that is produced in mitochondria is hydrolysed in the plasma membrane to generate an electrochemical gradient (plasma potential), which is comparable to that produced by the proton-driving pump of the respiratory chain. This is another recurrent motif that has so far evaded the attention of biologists; it is central to our further considerations.

Both the synthesis and hydrolysis of ATP in the mitochondrial membrane can be inhibited by chemical substances, such as *oligomycin* and *dicyclohexylcarbodimide* (DCCD). It can be shown that DCCD interacts with an *aspartate* residue (**Asp**) in the c-subunit of the F_0 unit of the ATP-synthase in *E. coli* and inhibits its activity. F_0 represents the transmembrane part of the integral ATP-synthase and consists of three subunits, a, b, and c. Aspartate is a negatively charged amino acid residue. In other species, a *glutamate* residue (**Glu**) is found at this position. Glutamate and aspartate are the only two negatively charged amino acids that belong to the "functional amino acid alphabet" consisting of 20 amino acids. Both Asp and Glu play a central role in the concept of the "soliton triplet" (see chapter 1.4). DCCD has two tertiary amino groups which are positively charged. The presence of more than one amino group in a chemical moiety leads to the inhibition of the activity of integral proteins such as ATP-synthase, as positively charged groups avidly bind to the active sites of transmembrane proteins. This is another recurrent motif in the present book and one which is basic to the novel dipole model (see chapter 2.1).

The actual mechanism of ATP synthesis cannot be explained by the chemiosmotic theory, although there is considerable information on the

chemistry of the covalent bond formation between ADP and the phosphate group (P). A working hypothesis based on some experimental evidence has been forwarded. As current knowledge of the structure of ATP-synthase is limited, we shall only present the pieces of evidence that underly the current chemiosmotic view on this issue. These experimental data also challenge the key statements of Mitchell's chemiosmotic theory.

ATP hydrolysis is more easily studied than ATP synthesis, as the former only requires soluble F_1. For this reason most chemiosmotic experiments study ATP hydrolysis and then draw conclusions on the possible mechanism of ATP synthesis under physiological conditions. Using labelled oxygen, the hydrolysis of ATP is analysed in SMPs. The extra incorporation of labelled oxygen into the phosphate group can be observed even in the absence of a proton-motive gradient. This shows that a proton-motive gradient is not a prerequisite for the synthesis of ATP from ADP and P. Further support in this respect is provided by the observation that the hydrolysis of ATP to ADP and P, as catalysed by the soluble F_1, is to some extent reversible even without any input of energy from *dP*. The equilibrium constant (K′) of this reaction is equal to the ratio of the forward and reverse rate constants. Since K′ for ATP hydrolysis in free solution is found to be approximately 10^5 mol, this indicates that the reverse reaction k_{-1} should be undetectably low. This means that at equilibrium the substrates are available in the free form as ADP and P. In the mitochondrion, or more precisely in F_1, this reaction is shifted towards ATP. Evidently, F_1 alters the equilibrium constant of ATP hydrolysis by augmenting the rate of the reverse reaction in a significant manner.

Superficially, it appears that ATP is synthesized without any energy input and this seems at first glance to contradict the law(s) of thermodynamics. In reality, the F_1 does not catalyse free ATP, but binds ATP to its complex. The F_1-ATP complex in the mitochondrion needs the input of approximately 40 kJ energy to remove ATP from the complex and present it in a free form. From a chemiosmotic point of view, this energy is provided by the proton-motive gradient *dP*, but in fact this energy can be provided by any electrochemical potential *dU*, independently of its ionic composition.

There is substantial evidence that *dU* triggers conformational changes in F_1, which lead to the release of bound ATP. Confirmation of this hypothesis came from measurements of the dissociation constant for F_1-ATP complex at equilibrium, for which values of about 10^{-12} M were

obtained. This means that under equilibrium conditions the complex is almost completely found in the bound form. When *dU* is generated across SMPs carrying the F_1-ATP complex, the binding affinity of ATP to F_1 dramatically decreases. Experiments with bacterial vesicles suggest that during ATP synthesis the competitive binding of ATP to the catalytic site has a dissociation constant of 10^{-5}, which accounts for an increase in the dissociation constant that is induced by *dU* in the order of 10^7 M.

The core of the chemiosmotic theory is the postulate that there is an equilibrium between the redox span and the proton-motive force that is generated by the former. This is an intuitive application of the axiom of CAP for this particular metabolic interaction. On the other hand, there is a clear correlation between the magnitude of the proton-motive gradient and the rate of ATP synthesis. The immediate question that arises is how the dissociation constant of the F_1-ATP complex responds to changes of *dP* and *dU*. Indirect evidence suggests that that there is a non-linear relationship between the two parameters, which confirms the cyclic character of energy exchange between these systems.

The central role of ATP/ADP in cell metabolism is stressed by all bioenergetic concepts, although they differ in their interpretation. At present, ATP is regarded as the "universal energy carrier" in the cell. Considering the fact that space-time is energy (primary axiom) and that all components of the cell are energetic systems, the absurdity of this central belief in biology should be cogent to everybody. The ATP concept will be critically reassessed in chapter 1.5. In anticipation of the discussion there, we ought to mention that much of the confusion in present-day bioenergetics can be traced back to the fallacious interpretation of the actual function of ATP and ADP, respectively, of their ATP/ADP ratio in cell metabolism (ATP/ADP ratio is an absolute constant of vertical energy exchange; see vol. I & II).

The mechanism of electron transfer in the respiratory chain is central to the chemiosmotic theory. How do electrons pass from one redox centre to another? Firstly, the redox centres are not physically in contact in most circumstances, but are separated by distances in the order of several nanometers. On the other hand, there is growing evidence that electrons can travel over considerable distances along supramolecular structures (see chapters 1.3 and 1.4). Considering the fact that space-time is continuous, this observation is a simple iteration of this property of space-time (primary axiom). Secondly, the electron carriers do not operate in a simple linear sequence - electrons may divide between carriers in paral-

lel (complex III), or may be temporarily stored on components to enable a multi-electron reduction to occur (e.g. in cytochrome oxidase).

In the new axiomatics, we explicitly state that energy exchange is at once vertical and horizontal and therefore has no preferential direction. For this reason we reject the principle of causality which is central to the current biological view of nature as an erroneous scientific concept. Thirdly, only part of the components of the respiratory chain is sufficient to generate a proton gradient. Evidently, the system is efficient without the presence of the whole complex of more than 20 discrete electron carriers that are found in the mitochondrial membrane. From this it can be concluded that electron transfer and proton expulsion seem to be highly random processes. The only mystery that still has to be unravelled in this respect is how these random processes have come to be so neatly expressed in such accurate biochemical equations as those found in numerous textbooks without the authors being plagued by the slightest doubt as to their appropriateness.

Indeed, very little is known about the physical mechanisms of electron transfer in the respiratory chain at the quantum level (see chapters 1.3 & 1.4). This is also true for any other biochemical structure. Some facts at the supramolecular level are, however, well established. They will play a central role in our further discussion. The most detailed information on electron transfer is available for mitochondrial *cytochrome* c (cyt c). The haem (tetrapyrolle ring with an extended π-electron system) sits in a largely hydrophobic crevice with only one edge of the porphyrin ring exposed to solvent. Experimental evidence indicates a single route of electron transfer that involves *lysine* residues (Lys), especially in the positions 13, 86, and 87; the latter are found in the vicinity of the exposed haem edge in all cyt c molecules investigated so far. Substitution of these amino acid residues leads to an inhibition of electron transfer. In the following, we shall often encounter examples where mutations of the amino acid residue Lys in proteins are associated with a loss in functionality. Evidently, Lys has an important functional role in proteins. This is another recurrent motif that will be extensively discussed when the structural basis of the soliton triplet is introduced below.

The exact mechanism of proton translocation from the matrix N-side where respiration takes place to the cytoplasmic P-side of the mitochondrial membrane against the electrochemical gradient is not elucidated by the chemiosmotic theory. Biology is quite vague on this issue. The final step in the electron-transport chain in mitochondria is considered to be

the transfer of 4 electrons from the cyt c to oxygen to form water, as is summarized in the stoichiometric equation of OP (1). In addition to the electron transfer, cyt c oxydase acts as a proton pump, but the mechanism which collates electron transfer to proton pumping cannot be explained by the chemiosmotic theory.

Two basic models of proton-driving pumps have been proposed. The "*loop*" *mechanism* suggests a one-for-one exchange of electron for proton to the P-side. However, this type of stoichiometry has not been confirmed. The *conformational pump model* presupposes a mobile redox carrier, which undergoes conformational changes and is accessible from either side of the membrane. In the absence of convincing evidence in support of any of these models, both alternatives are currently favoured. This kind of "political correctness" is a common phenomenon in modern science and a key source of intellectual confusion. The conformational model is also applied to other ion-pumps.

Very little is known about the function of F_1F_0-ATP-ase. Both the proton-driving pumps and the ATP-ase of the respiratory chain cease their activity when they are solubilized. Their function is reconstituted when they associate with lipid bilayers or physiological membranes. This phenomenon is common to all integral proteins, including all receptors and ion-channels, and is another recurrent motif in nature.

While ATP-ase, stripped of its membrane, loses its synthase activity, it nonetheless behaves in an "uncoupled" manner with no respiratory control from the redox part (NADH) and induces high proton permeability in lipid membranes, i.e. it acts as an *ionophore*. This is another common theme in nature that has not been comprehended so far.

Another recurrent motif in OP is the ubiquitous presence of **π-electron systems** in the carriers. The respiratory chain of the mitochondrion consists of more than 20 discrete electron-carriers grouped into 4 polypeptide complexes. Three of these complexes (I, III, and IV) act as redox-driven proton pumps. The present structural and functional understanding of these systems is far from clear. The respiratory chain transfers electrons through a redox potential span of 1.1 V from the $NAD^+/NADH^+$ couple to the $O_2/2H_2O$ couple. The reactive part of NAD^+, the major electron acceptor, is its nicotinamide ring, which is a highly reactive π-electron system. During oxydation of a substrate the nicotinamide ring of NAD^+ accepts a hydrogen ion and two electrons. The other electron carrier, $FAD^+/FADH$, has an isoalloxazine ring with 4 nitrogen groups, which is another highly reactive π-electron system and exchanges 2 elec-

trons and two hydrogen ions (protons). The number of exchanged electrons and protons is given in the stoichiometric equations of the redox reactions in biochemistry, but these figures give us no clue as to where the electrons and protons actually come from.

Further components of the respiratory chain are: 1) flavoproteins (flavons) which contain tightly bound FAD or FMN as prosthetic groups and undergo a $2H^+/2e^-$ reduction; 2) cytochromes carrying porphyrins (tetrapyrroles) that undergo a one-electron reduction (complex III); 3) iron-sulphur (non-haem iron) proteins that are reduced in a one-electron step (complex IV). Ubiquinones, also called coenzyme Q, UQ, or simply Q, which carry a side chain of ten 5-carbon isoprene units (polyene) and cytochrome C, which is found on the P-side of the membrane, are unique in their ability to operate independently as proton-driving pumps, while the other components of the respiratory chain are related to each other. Thus all components of the respiratory chain are **integral proteins with prosthetic groups that carry π-electron systems.**

The presence of π-electron systems in the respiratory chain merely reflects the ubiquitous occurrence of biochemical molecules with *delocalized π-electron systems* in organic matter; their **conjugated double-bonds** form either *aromatic rings* or *long conjugated chains*. There are several major groups of π-electron carriers in organic matter. These are: 1) multicyclic compounds such as tetrapyrolles (porphyrins) which are found in chlorophyll, photochlorophyll, phytochrome, haem, etc.; 2) flavins, ubiquinones, and isoprenoids, which are ubiquitous compounds and play a central role in the respiratory chain; 3) polyenes with long conjugated chains such as retinal (vitamin A), β-carotenoids, and other related substances.

In addition, three amino acids with aromatic side chains, **phenylalanine** (**Phe**), **tyrosine** (**Tyr**), and **tryptophan** (**Trp**) contain phenyl or indol rings with delocalized π-electrons, which may join to form extended π-electron systems in the *transmembrane α-helices* of integral proteins. DNA and RNA can also be regarded as large supramolecular structures - their strings are stacked with extended π-electron systems that form a complex energetic pattern. Their constituents, the nucleotides such as ATP/ADP and GTP/GDP, play a central role in cell metabolism as universal π-electron carriers in various functional proteins (see chapters 1.5 & 1.6). The ubiquitous presence of π-electron systems in organic matter is thus a major recurrent motif that will be extensively discussed in the present volume. This aspect has so far evaded the attention of biologists.

The mechanisms of OP suggest that electron transfer is always associated with a translocation of charges across lipid membranes and - in the case of the respiratory chain - of hydrogen ions (protons). The *coupled translocation* of ions and electrons across biological membranes which always carry integral proteins is a ubiquitous phenomenon in organic matter. In physics the movement of charges (cross-sectional areas of systems) across the cell membrane is defined as "current" E_A = SP(A)[2*d-space*] *f*; it is a synonym for the universal **electromagnetic action potential** of energy exchange between the cell and the surroundings (space-time). Recall that the action potential is the only event in space-time. This also holds in all biological membranes, including those that belong to intracellular compartments. The modulation of this energy exchange abides by the Law and represents the single fundamental principle of biological regulation (see chapter 1.5). The consistent explanation of this particular mechanism of regulation departs from the cognitive monism of the new axiomatics and leads to the development of the General Theory as outlined in this volume.

The main achievement of the chemiosmotic theory is the postulated delocalized coupling between respiratory chain and ATP-synthase through the proton-motive gradient. This intuitively correct application of the axiom on the reciprocal behaviour of the LRCs of contiguous levels in a system was a breakthrough when it was first proposed in 1961. Initially, the concept of delocalized coupling met with fierce resistance. However, subsequent experiments confirmed that the chemiosmotic theory was in a position to explain in a consistent way the various phenomena associated with OP in the mitochondrion, whereas the numerous previous hypotheses had failed to do so.

Nevertheless, there is still a body of conflicting evidence which the chemiosmotic theory, dominated by the prevailing deterministic thinking in bio-science, cannot explain. This inherent shortcoming of the chemiosmotic theory has hindered its development into a general theory of biological regulation, although the beginning was very promising. The bioenergetic concept of this theory is based on Gibb's definition of the first and second law of thermodynamics for chemical systems at equilibrium. Mitochondria and cells are, however, open systems that exchange energy and substrates with their surroundings in an unrestrained manner. In the first place, we should consider the energy exchange with the thermodynamic photon level which comprises about 60% of cell metabolism. This portion of the metabolic energy is not available to the organ-

ism. Another portion of the thermodynamic energy exchange is used to maintain a constant temperature in the organism. This constant temperature co-determines the structure and function of all biochemical elements in the cell. These further energetic aspects are not considered in the chemiosmotic theory, although they are of major theoretical importance.

A principal obstacle to a more adequate description of the energy exchange at the mitochondrial and cellular levels should be seen in the fact that mathematics has failed to develop any theory of disequilibrium systems with non-linear (cyclic) behaviour. For instance, in economics - the classical domain of disequilibrium systems with non-linear behaviour - the main stream of mathematical analysis is still linear and all phenomena are described at equilibrium, under the condition of *ceteris paribus* (other things being equal). The chemiosmotic theory is, of course, light years away from the use of such sophisticated mathematical tools as employed in economics today. The chemiosmotic approach to respiration and its delocalized coupling to ATP synthesis is purely descriptive determinism, just like any other approach in current biological and medical research.

The General Theory furnishes the mathematical basis of the bio-sciences (see energy balance in chapter 1.2), but it also takes into consideration the historical development of these natural sciences and the educational deficiencies of biologists and physicians in the field of mathematics and physics. Therefore, it introduces a small number of descriptive concepts such as the “FUEL” and the “soliton triplet”. These terms are derived from the primary term and are of precise mathematical character; in addition, they also comply with the traditional descriptive approach in the bio-sciences. The advantage of these two new concepts is that they can be axiomatized, while all current concepts in bio-science are non-integrable due to inherent logical and semantic inconsistencies (see vol. I & II).

For instance, the chemiosmotic theory meticulously sticks to the traditional biochemical terminology, e.g. to the stoichiometry of OP, and thus unduly emphasizes the somewhat metaphysical term “proton-motive force” which is a synonym for an electric gradient. In this way, it pays tribute to the general equation of respiration (1) that embodies the static view of nature. The protagonists of this bioenergetic theory have not realized the role of the electrochemical gradient which is established across any biological membrane as a source of universal interconvertible

energy for biological regulation - for instance as the driving force behind ATP synthesis.

Our knowledge of the function of proton-driving pumps, ATP-synthase, and other integral proteins is still fragmentary and highly hypothetical. As a "local" approach, the chemiosmotic theory has restricted itself to mitochondrial, thylakoid, and bacterial membranes. It has made no effort to widen its scope of interest and include the regulation of eukaryotes and organisms. In the few cases where such efforts were undertaken, this was done at the expense of abandoning the major concept of chemiosmosis - the existence of an LRC at each level of space-time which affects in a global manner the behaviour of the underlying elements (U-sets). This is the actual "delocalized coupling", around which the chemiosmotic theory should have evolved.

Essentially for these reasons, the chemiosmotic theory has remained a marginal field of academic research. It does not explain the mechanisms of metabolic regulation in eukaryotic cells, and, in particular, the mechanisms that couple external signals to intracellular responses. For this reason the chemiosmotic theory plays virtually no role in applied sciences such as pharmacy, pharmacology, and medicine. Even in modern biology, which is excessively dominated by the putative successes of genetics, it is hardly accorded the recognition it deserves. This is deplorable given the fact that the chemiosmotic theory is the only semi-successful attempt to explain biological events consistently from an energetic point of view.

1.2 ENERGY BALANCE OF HUMAN METABOLISM CAN BE CALCULATED WITH THE UNIVERSAL EQUATION

Current efforts to explain cell regulation revolve around the chemical interpretation of the metabolic web. Biochemistry and medicine emphasize the chemically stored energy in the cell and dedicate themselves to the elucidation of biochemical structures. This has led to an exaggeration of the role of ATP as the "universal energy carrier" in the cell, although other ubiquitous "energy-rich" molecules such as GTP are also known. Even in the chemiosmotic theory which takes into consideration the mitochondrial potential created by the proton pumps of the respiratory chain the emphasis is put on the proteinic structures of the respira-

tory chain and the production of ATP within F_1/F_0. These are selected systems of the chemical level of the cell. The electric energy of the mitochondrial potential is regarded only in the context of a delocalized coupler between the two processes - the redox span and ATP production. Its role in cell regulation has not been perceived yet.

Although it has been known for more than half a century that every physiological membrane exhibits an electrochemical potential, and that most cells such as contractile muscle cells or excitatory neurones operate through the occurrence of **action potentials**, this form of electric energy stored in the cell has not been taken into consideration in the biosciences until the discovery of the Law. In terms of electricity, cells can roughly be regarded as *spherical capacitors* that are negatively charged inside and positively charged outside. The resting potential gives the magnitude of the stored electric energy in the cell membrane as a spherical plate capacitor. The geometric form of the capacitor is of no importance - it is a mathematical approximation of the real structural complexity of the cells K_s = SP(A)[2*d-space*] (see definition by abstraction below). The cell, being a specific system of the organic level of space-time, has its own specific gradient or LRC. This is axiomatically postulated for all systems of space-time - space-time is an energetic continuum.

The role of the electric membrane potential, called **electric LRC** (long range correlation), in the regulation of the cell can be explained for the first time in the light of the Law by applying the axiom on the reciprocal behaviour of the LRCs of two contiguous levels - the LRC of the electric level, as observed in biological membranes such as mitochondrial and cellular membranes, and the LRC of the biochemical level of the cell. The latter level can be defined as “stored biochemical energy”. Further synonyms for the biochemical level are “cell metabolism”, “metabolic web”, “redox potential of the respiratory chain”, “total ATP production in the cell”, etc. These are arbitrary discriminations in the mind. In real terms, we cannot separate these subsets of space-time from each other, as they are U-sets and contain themselves as an element. This fundamental aspect of human cognition has been extensively discussed in the new axiomatics (see vol. I & II).

In terms of the Law, the cell can be regarded as an open energetic system that consists of two levels - the *electric level* with the membrane gradient(s), defined as **electric LRC** (LRC_E), and the *biochemical level* of cell metabolism, defined as **chemical LRC** (LRC_C). This is an application of the axiom of reducibility. Both levels interact, i.e. they exchange

energy and their LRCs behave reciprocally: when the LRC_E decreases, the LRC_C increases and vice versa.

Our introduction to the chemiosmotic theory substantiated this fact. The various metabolic pathways join in the OP in the mitochondrion. The final product of this degradation of substrates in a redox cascade (LRC_C decreases) is the production and separation of protons and electrons across the membrane as summarized in the general stoichiometric equation of cell respiration (1). These electric charges are dislocated on the two sides of any biological membrane and establish an electric gradient (LRC_E increases). Biological membranes function as spherical plate capacitors that discharge during *depolarisation* and recharge during *repolarisation*. The discharge and recharge of the electric LRC of the cell is called "**action potential**". It is a fundamental term in the new axiomatics that is consistently derived from the primary term. We express it in the new space-time symbolism as $E_A = E/f = \mathrm{SP(A)}[2d\text{-}space]\, f$.

Each action potential consists of two phases - a (rapid) *depolarisation* and a *repolarisation* - that can be experimentally measured. Sometimes a *plateau* can be observed between the two phases, as is the case of muscle cells. This is basic physiology. The depolarisation is achieved by opening the cell membrane for ions (protons, sodium, potassium, calcium, and chlor ions), which flow across the membrane along their gradient. The membrane itself is a *lipid bilayer* that is impermeable to ions. Its permeability is effected by transmembrane proteins, called *ion-channels*. An explanation of their function at the quantum level is given for the first time in the General Theory.

The repolarisation of the cell is effected through hydrolysis of ATP to ADP and P in ATPases; these proteins expel ions from the cytosol and the extracellular space against their gradient and thus re-establish the electric LRC of the cell. ATPases are transmembrane proteins (integral proteins). If we regard the production of ATP in an abstract way as the final product of cell metabolism (U-set), we can interpret the regular fluctuations of the intracellular ATP/ADP ratio upon activation as the manifestation of the reciprocal behaviour of the LRCs of the two contiguous levels in the cell - electric and biochemical. The decrease of LRC_E during depolarisation leads to an increase of LRC_C, as can be demonstrated by the increased production of ATP during this period.

During depolarisation, various substrates, such as *fatty acids*, *carbohydrates*, and *proteins*, enter the cell across the membrane (see Fig. 1). Their transport is coupled to ion-carriers (Na^+- and Cl^--carriers). These

integral proteins actually operate as ion-channels. The increased supply of substrates undergoes metabolic degradation in the cell and provides more energy in the form of electrons and protons during OP, that is, the electric LRC is augmented. Increased LRC_E leads to a growth in the production of ATP which, in turn, is hydrolysed by ATP-pumps (ATPases). This suggests that LRC_C is consumed in order to expel the ions which have entered the cell during the depolarisation phase from the cytosol and to re-establish the electric plasma gradient. Formally speaking, when the LRC_C of the cell goes down, its LRC_E goes up and vice versa.

This process is *open* - the substrate transport from the surroundings (nutrition) is directly coupled to the action potential of the cell - and *cyclic* at the same time: during each E_A of the cell, there is an exchange of chemical energy into electric energy and vice versa. This exchange can be assessed by the reciprocal behaviour of the corresponding LRCs. The cyclic (recurrent) character of energy exchange in the cell reflects the closed character of space-time and the reciprocity of space and time. Thus, any description of the cell can be adequately reduced to a pair of reciprocally interacting levels of this system. As they are U-sets, they aggregate the infinite metabolic processes in the cell, which are the main object of study in bio-science. This is an application of AR. For instance, the cell can be described as an energy exchange between LRC_E and LRC_C. We can, of course, apply the axiom on the reciprocal behaviour of the LRCs of contiguous levels to any other pair of levels in the cell to solve any particular problem of biological regulation in a consistent way. This exercise will be done for some basic microscopic (quantum) levels. In this way we shall prove the universal validity of the Law. As space-time is infinite, there are infinite levels of organic matter - hence the infinite character of the General Theory. In this survey, only some of the most important solutions will be discussed. They will enable the reader to apply the theory to further particular problems in the bio-sciences and medicine.

Before we proceed with the energy balance of the cell, we must first explain why the bio-sciences have failed to grasp this simple relationship between chemical cell metabolism and electromagnetic membrane potential. Until now, the grand pathways of metabolism have been regarded as closed interrelated cycles that regulate themselves through *feedback-mechanisms*. Because of this outlook only biochemical structures such as ATP, or transmitters of regulation such as first and second messengers are considered as the sole possible carriers of interconvertible

energy in the cell. This is a systemic failure on the part of the bio-sciences. Other energetic forms such as *electromagnetism* are not seriously discussed, although the idea that electromagnetic forces are central to all observed biological phenomena was predominant during the second half of the 19th century (for further information see *mesmerism, vis vitalis*, and Beron's universal theory of electricity in vol. IV). This correct outlook was further substantiated by the achievements of Maxwell, who brilliantly integrated the various laws of electricity and magnetism into four equations of electromagnetism. In this context, it is important to observe that electromagnetism and gravitation are the only two forces which can be directly experienced, and that electromagnetism is a much stronger force than gravitation. This explains why electromagnetism is basic to the regulation of organic matter, while gravitation is of practically no importance.

I have shown in volumes I and II that Maxwell's equations are differential and integral derivations of the universal equation for the level of electromagnetism. They can also be derived from the *classical wave equation*, which is another presentation of the Law within mathematics; it is the starting point for *Schrödinger wave equation* in quantum mechanics. This is a fundamental proof that space-time is of *wave character* - all systems and levels can be presented as superimposed rotations, where the terms *wave* and *rotation* are used as synonyma. While any rotational motion is a manifestation of the closed character of space-time, the superposition of waves demonstrates the open character of the systems. This novel interpretation of wave theory effects the most radical simplification of our physical *Weltanschauung*.

Closed biochemical cycles (systems), as described in biochemistry today, are however inappropriate to explain the open character of the cell as a system of space-time and its regulation through external factors. This is a central theme in the new axiomatics. The novel revolutionary approach of the General Theory is to consider the stored electromagnetic energy in membranes (LRC_E) as an equivalent energy form, parallel to the biochemical energy stored in the cell. Present biochemistry regards the latter as the only energy form of any importance - all explanations in bio-science, medicine, and pharmacology are of purely chemical character. This rather subjective view of organic matter has precluded the establishment of a consistent theory of biological regulation. In fact, the electromagnetic energy of cell membranes exhibits several fundamental properties, which make it the primary target of

cell regulation by external and internal factors[3]:

1. Eletromagnetic energy (photons) is easily convertible into chemical, structural energy (e.g. photosynthesis in organic matter, electrolysis in inorganic matter), electric energy in matter (Hall effect), heat (which is a prerequisite for the existence of organic matter), and photon energy (quantum Hall effect in metals, Kirlian effect in organic matter, etc.). This aspect of electromagnetism is not appreciated in biology.

2. When electromagnetic energy occurs in the form of capacitor potentials, for instance as plasma potentials in the cell, it can be easily modulated by external or internal factors. For instance, all chemical entities that reach the cell from outside interact first with the cell membrane and modulate its LRC_E. The reason for this electromagnetic interaction is that all chemical molecules have specific *dielectric* properties that determine the kind and degree of modulation (energy exchange) with the plasma membrane potential. Each chemical compound exerts a specific effect on the cell that is exclusively determined by the (supra)-molecular structure and the dielectric character of the moiety (specific electric LRC). In electricity, this property is defined as *dipole moment*. This quantity can be axiomatically derived from the primary term (see vol. I & II). This insight establishes the theoretical basis of the new **dipole model** of pharmacology; this model was developed in the context of the General Theory and confirmed for all drugs and physiological factors (see chapter 2.1).

3. The plasma potential is an electromagnetic LRC_E (a field) that encompasses the whole cell. Any modulation of it is immediately transmitted to every element in the cell in the form of electromagnetic waves propagated with the speed of light. Every element in the cell, be it chemical structure, enzyme, organelle, DNA, or RNA, is simultaneously affected in a uniform manner and responds in a similar, yet specific, way. Being U-sets of the LRC_C, the intracellular molecules interact with each other and with the LRC_E of the cell under the condition of *constructive interference* (see wave theory in vol. I & II). In this context, it is impor-

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[3] In fact, space-time is closed and for this reason it is not possible to say which level or system is more important than another. This distinction is made only for didactic purposes.

tant to reiterate that the new axiomatics proves that all systems of space-time are superimposed rotations or waves (U-sets). The action potentials are such waves at the cellular level that can be experimentally measured. For instance, ECG (heart) and EEC (central nervous system) are common diagnostic methods in medicine. They visualize the superimposed electromagnetic waves at the level of these organs; these are composed of the action potentials of the individual cells such as muscle cells (ECG) and neurones (EEC). As space-time is a unity, the electromagnetic waves of the LRC_E also interact with the quantum levels of the cell. We shall follow this pattern of energy interaction for the supramolecular structures of transmembrane proteins and the DNA code (see Davydov's soliton below)[4].

Let us now recall the key steps involved in energy transformation in the cell (see Fig. 1) before we integrate them into the energy balance calculation. Organic substances, such as fatty acids, proteins, carbohydrates, vitamins, metals, etc., are incorporated by the organism during nutrition and are degraded in the catabolic limb of cell metabolism, which is essentially a redox cascade. This process is the main topic of present-day biochemistry. Related catabolic and anabolic cycles may occur in different cellular compartments. For instance, *fatty acid synthesis* occurs in the cytoplasm, whereas *fatty acid degradation* (β-oxydation) takes place in the mitochondrion. *Glycolysis*, the main supplier of energy, takes place in the cytoplasm, but the final *oxydative degradation* of the intermediate products of glycolysis (e.g. $NADH_2$, pyruvate, and lactate) is carried out in mitochondria.

We can regard these different metabolic pathways and sites as separate systems or levels of space-time and apply the Law and its basic axioms to their energy exchange. This leads to a significant simplification in our understanding of the biochemical processes in the cell. This aspect will not be discussed in detail in the present book, although selected topics concerning metabolism will be presented on various occasions. At this point, it is our obligation to make the reader aware of the fact that our claim regarding the universal validity of the General Theory

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[4] The detailed elaboration of this energy exchange involves advanced mathematics and is beyond the scope of this survey. Scientific research in this field is just beginning to emerge and will be decisively stimulated by the discovery of the Law.

is largely based on a detailed elaboration and verification of the metabolic web with respect to the Law. The presentation of this voluminous body of evidence is beyond the scope of the present volume. Instead, we shall employ the axiom of reducibility.

The catabolic endproducts of the cytoplasmic pathways of metabolism enter the OP in the mitochondrion, where they are further degraded. The final products are 4 electrons and 4 protons, which are ultimately transferred to oxygen to produce water (1). Another product of the respiratory chain is *heat*, part of which maintains the body temperature. In fact, heat is produced at every level of energy transformation. The amount of heat exchanged with the surroundings is lost for the purposes of the organism. It accounts for the vertical energy exchange of organic matter with photon space-time, as described by the conventional laws of radiation and by Stankov's law of photon thermodynamics (see vol. II). In biology, this amount of heat is interpreted as an export of entropy, with which the order in the cell and the organism is explained in a rather metaphysical way. This view was first forwarded by Schrödinger in his concept of "negentropy" in organic matter[5]. However, I proved that "entropy" is a synonym (pleonasm) for an action potential of the thermodynamic level of matter, as given by Boltzmann's constant, and thus eliminated this confusing term from physics. Therefore, we also eradicate this superfluous term from biology.

Cell metabolism, as summarized in the general stoichiometric equation of cell respiration, includes the establishment of an electric LRC across the mitochondrial membrane that leads to ATP production. As any energy exchange occurs in both directions (see axiom of CAP), ATP is degraded in ATP-pumps and an electric LRC is established across the plasma membrane. This LRC_E modulates cell metabolism in a global manner and determines the symport of substrates in the cell (open character of the cell). Modulation of this electromagnetic potential, defined as an action potential of the cell, represents the only mechanism of cell regulation. These modulations can be described as superimposed waves and expressed with the wave equation (see Furier synthesis and analysis), which is an application of the Law (see vol. I & II).

At the descriptive level of biological disquisition, this physical background can be interpreted as follows. As space-time is an energetic continuum, each chemical moiety represents an energetic structure,

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[5] E. Schrödinger. "What's life?", German ed., Piper, Munich.

which is organized under the Law, that is, it acquires the most favourable energetic configuration in harmony with the adjacent structures. Each molecular structure in the cell exhibits a specific energetic profile, which co-determines adjacent structures (energy exchange occurs in both directions). All chemical structures in the cell change their energetic configuration synchronically and almost immediately when the electric potentials of biological membranes are modulated by external factors. Such modulations produce electromagnetic waves with the energy of $E = E_A\, f = hf$, which are propagated in the cell with the speed of light. These electromagnetic waves, also called **photons**, build the **electromagnetic long-range correlation ($\mathbf{LRC_E}$)** of the cell. This example illustrates the appropriateness of this term, which is a synonym for the physical quantity energy gradient. Recall that all physical quantities are abstract ideas created in the realm of mathematics; the only real thing is space-time/energy.

The molecular structures in the cell change under these energetic modulations or simply dislocate. We proved in the new axiomatics that *motion* is the universal manifestation of energy exchange. Any conformational change or displacement of a chemical moiety in the cell that is triggered by modulations of the LRC_E is a motion *per se* and can be assessed by the Law. Many transmembrane proteins for instance acquire metastable configurations that determine their function, e.g. ion-channels may open in the metastable state and enable the ions to pass across the membrane along their gradient. The integral proteins may return from these metastable configurations to their original form or be eliminated by endocytosis (see below).

The closed character of space-time is manifested by the parts (U-subsets) as a *conservation of energy*. This fundamental property of space-time was formulated for the first time in physics by *R. Meyer*, a German physician, as a law of conservation of energy (1st law of thermodynamics), although the conservation of energy has been common knowledge since antiquity. The notion of energy conservation is central to any philosophical or theosophical disquisition in science. At the beginning of modern times it promoted a fierce dispute between the *Cartesians*, who describe energy as a motion, and *Leibniz*, who perceives energy as a force. Both quantities are U-subsets of space-time that are defined within mathematical formalism, hence this dispute is obsolete. This holds true for most scientific disputes of a similar nature.

The limitations of the 1st law of thermodynamics are elaborated in

the new axiomatics. This law cannot be confirmed in an experimental way. It can only be deduced in a logical way from the energy exchange between the systems. An adequate experiment would necessitate the assessment of all energy interactions in space-time, which is infinite. This is impossible. I have proved in the new axiomatics that the primary term can only be assessed in *a priori* logical statements; these can be confirmed in an empirical way. This is the only theoretical objective of the natural sciences. For instance, the conservation of energy can be calculated for any system when the axiom of CAP is applied. This primary axiom postulates that one action potential is completely transformed into another action potential and vice versa, whereas each system or level can be regarded as an action potential (degree of mathematical freedom). With respect to the cell, we can regard its LRC_E and LRC_C as two action potentials that completely exchange their energy without being lost. This energy exchange follows the Law. The same approach leads to the definition of static and kinetic energy in classical mechanics.

Conventionally, this application of the Law is defined as "*energy balance*". It is generally accepted that, when an energy balance is confirmed for a system, the underlying energy model describing this system must be correct. This intuitively correct idea of the conservation of energy anticipates the ubiquitous validity of the new axiomatics based on the primary term of energy/space-time.

The closed character of space-time permits the calculation of the energy balance of any system with the universal equation, no matter how complex it is. For this purpose we must adequately define the two levels of energy interaction in the system, so that they contain all underlying levels and systems thereof. The vertical energy exchange between these two levels can be assessed by the three basic axioms of the new axiomatics. This will be done for the cell below. The calculation of this energy balance is based on established data from the literature. This calculation is a fundamental proof that empiricism is a tautology of the Law.

Energy Balance of Human Cell and Organism

We shall perform the energy balance of the human cell and the organism *at rest* because the energy exchange at any other state, e.g. during physical work, can vary to a large extent and will inevitably bias the calculation. The problem lies in obtaining reliable data for these energetic states.

In this context, it is important to observe that all we can do in science is to measure the space-, time-, or space-time relationships of the systems or levels, as space-time has only two dimensions - space and time. For this reason the conclusions from this balance calculation hold for any energetic state of the cell and the body.

The mean metabolic rate of the human organism at rest is about 1500 kCal daily, which is equivalent to 6270 kJ. About 60% of this chemical energy is transformed into heat (3762 kJ) and radiated to the surroundings. It is not available to the organism. The rest of the metabolic rate at rest is transformed into **effective metabolic energy** of the body:

$$E_{Meff} \cong 2500 \text{ kJ} = 2.5 \times 10^6 \text{ J } [\text{m}^2\text{s}^{-2}] \quad (4)$$

The exact number of cells in the human body cannot be directly measured, but it can be approximately estimated. Let us assume a standard cell with a mean radius of $r = 5\mu\text{m}$. The *volume* V_c, corrected for the flattening, of this cell is then:

$$V_C \cong 3 \times 10^{-16} \text{ m}^3 \quad (5),$$

and its weight W_C:

$$W_C \cong 3 \times 10^{-13} \text{ kg} \quad (6)$$

If we assume a mean human body weight of about 70 kg, the overall number of cells in the human body N is in the order of:

$$N = 70 \text{ kg}/3 \times 10^{-13} \text{ kg} = 2.3 \times 10^{14} \quad (7)$$

This result is quite similar to that given in the literature. Our estimation is the simplest and most accurate one because it departs from a few basic quantities such as [3*d-space*] and mass/energy relationship that can be easily measured.

According to the General Theory, the metabolic energy gained from OP is completely transformed into the electric energy of membrane potentials. The major membrane potentials are the *mitochondrial potential* and the *cell membrane potential*. The energy of these two potentials can be exactly calculated because biological membranes operate like capacitors and their potentials can be experimentally measured. Let us take a mitochondrial potential $U_m = LRC_{E,m} = 200 \text{ mV} = 0.2 \text{ V } (= \text{m}^2\text{s}^{-2})$ and

a plasma membrane potential of the cell $U_C = LRC_{E,c} = 120$ mV = = 0.12 V (= m^2s^{-2}). The latter value corresponds to the observed maximal amplitude of the action potentials of heart muscle cells: 90 mV at rest plus an overshoot of +30 mV at the end of the rapid depolarisation. The resting membrane potential in heart muscle cells is $U_{c,rest} = -90$ mV = = –0.09 V (= m^2s^{-2}). In this calculation, we shall consistently use the new space-symbolism with respect to the SI units, which we shall express in the two actual dimensions, space (m) and time (s^{-1}). We have proved that the other SI units are mathematical derivations of these two units (dimensions). This theoretical breakthrough in physics effects a great simplification in the mathematical presentation of energetic interactions (for further information, see vol. I and II).

From the aforementioned figures, we can calculate the electric energy stored in the membrane potentials as capacitor energy by using the following application of the Law $E = 1/2QU$ = SP(A)[2*d-space-time*] = = $E_A f$, where Q is the separated charge (area) at the plates. The charge (ions) that is separated on both sides of the cell membrane can be calculated by the following simple equation of electricity:

$$Q_c = \frac{A_c U_c}{4\pi kd} =$$

$$= \frac{3.14\times10^{-10}[\mathrm{m}^2]\times 0.120[\mathrm{m}^2\mathrm{s}^{-2}]}{4\times 3.14\times 9\times10^{9}[\mathrm{ms}^{-2}]\times 20\times10^{-10}[\mathrm{m}]} = 1.66\times10^{-13}[\mathrm{m}^2] \quad (8)$$

In this equation A_c is the area of the cell membrane $A_c = 4\pi r^2$ = = 3.14×10^{-10} [m^2], k is Coulomb constant $k \cong 9.0 \times 10^9$ [Nm^2C^{-2}] = = [ms^{-2}] = [m], when $f = 1$; d is the thickness of the lipid bilayer $d = 20 \times 10^{-10}$ m; U_c is the amplitude of the action potential of the cell $U_c = LRC_{E,c} = 0.120$ [m^2s^{-2}].

It is very important to observe that the separated charge (cross-sectional area) at the cell membrane is in the order of 10^{-6} greater than the elementary charge (area) of the electron e = 1.6×10^{-19} m^2 (C). This number can be regarded as a new fundamental constant that gives the constant space-relationship between the electron as the elementary electric system ($E_{A,electron}$) of the electron level and the cell as the elementary electromagnetic system ($E_{A,cell}$) of the cellular level of organic matter. It

is equivalent to the absolute electric constant of the cell $L_{E,cell}$ (see p. 615-616, German vol. I).

We can now calculate from the resting potential of the cell $U_{c,rest}$ the **electric field E_c** that is exerted across the cell membrane:

$$\mathsf{E}_c = \frac{U_{c,rest}}{d} = \frac{0{,}09[\mathrm{m^2 s^{-2}}]}{20\times10^{-10}[\mathrm{m}]} = 4.5\times10^7\,[\mathrm{Vm^{-1} = ms^{-2}}] \qquad (9)$$

From the conventional point of view, we say that the electric field of the cell potential is in the order of about 40 million volts per meter. This magnitude can only be compared with the electric potentials that occur in the stratosphere and are responsible for lightning. This powerful electric field operates in the small distance *d* of the cell membrane.

The occurrence of high energy potentials at the microscopic cellular level is anticipated by the new axiomatics. It postulates that the reciprocity of energy and space is a fundamental property of space-time: the greater the energy, the smaller the space and vice versa. This ubiquitous relationship is without exception - we can also encounter it in the cell. The $\mathrm{LRC_E}$ of the cell changes during its action potential and can temporarily become zero. Its maximal value (maximal amplitude) gives the total amount of energy exchange during an action potential (see also wave theory in vol. I & II):

$$E_c = \frac{1}{2}Q_c U_c = \frac{1}{2}\times1.66\times10^{-13}[\mathrm{m^2}]\times0.12[\mathrm{m^2 s^{-2}}] =$$

$$= 99.6\times10^{-16}[\mathrm{J = m^2 s^{-2}}] \qquad (10)$$

or

$$\mathrm{E_c} \cong 10^{-14}\ [\mathrm{J = m^2 s^{-2}}] \qquad (10a)$$

The electric LRC of the mitochondrial membrane can be calculated in the same way when the following considerations are made: the area of the mitochondrial membrane should include the cristae and is thus about $A_m = 4\times10^{-12}$ [$\mathrm{m^2}$], the separated charge is $Q_m = 0.39\times10^{-14}$ [$\mathrm{m^2}$], and the electric field is $\mathsf{E}_m = 10\times10^7$ [$\mathrm{ms^{-2}}$]. We obtain for the electric energy of the mitochondrial $\mathrm{LRC_E}$ the following value:

$$E_M = LRC_E = 0.4 \times 10^{-15} \text{ [J} = \text{m}^2\text{s}^{-2}\text{]} \tag{11}$$

The **total electric energy in the cell** $E_{c,total}$ includes the electric energy stored across each compartmental membrane :

$$E_{c,total} = E_C + nE_M + E_G + U_{ER} + etc. \tag{12}$$

where E_G is the stored electric energy across the Golgi membrane, E_{ER} is the energy stored in the membrane potential of the endoplasmatic reticulum, and n is the number of mitochondria in the cell. The actual energy stored in the intracellular compartmental membrane are not known, but for the whole cell we can assume a **total stored energy** in the range of:

$$E_{c,total} \cong 10^{-13} \text{ [J} = \text{m}^2\text{s}^{-2}\text{]} \tag{13}$$

This magnitude is in the order of 10 times higher than the energy of the plasma potential and represents a conservative estimate of the energy stored in the membranes of intracellular compartments. Future research should evaluate these magnitudes more precisely. The above estimation suffices for the purposes of our calculation.

It is not surprising that similar values can be obtained when Shannon's equation of information is used to estimate the bits of information that an average cell contains. I have proved that Shannon's equation of information is an application of the universal equation, and that the term "information" is a synonym for energy/space-time. This conclusion eliminates the concept of information from science. It confirms the tautological character of any experimental or fundamental research - one always assesses the Law in the particular experimental condition (particular energy exchange). It also explains why mathematics is the only adequate reflection of the physical world.

Let us now calculate the total electric energy available in the human body (in all body cells) *at any time*, that is, the **instantaneous electric energy of the body** $E_b = LRC_{E,body}$:

$$E_b = E_{c,total} \times N = 10^{-13} \times 2.3 \times 10^{14} \cong 23 \text{ [J} = \text{m}^2\text{s}^{-2}\text{]} \tag{14}$$

This energy is available at any instant in the body and can be transformed into biochemical energy or motion, e.g. kinetic energy of muscle cells, during cell regulation. This magnitude should not be confused with the

effective metabolic energy as given in equation (4). The magnitude of this *instantaneous electric energy* of the body seems to be rather small. This may explain why the electromagnetic energy in the body was ignored in the past, and the whole emphasis was put on the biochemical (structural) form of energy in the cell. The latter energy form renders a much higher value when regarded in a stoichiometric manner, for instance when the body is burned and the energy produced by combustion is measured.

However, the bioenergetic regulation of the human body is a dynamic process that occurs in time. Since the discovery of the Law, we know that space-time has only two constituents - space and time. This aspect is completely confounded in biological research. Cells are not regarded as systems which undergo continuous restitution by exchanging energy within cell metabolism and with the surroundings, but rather as static structural entities. This outlook is rather paradoxical when one considers the well established fact that growing cells, e.g. lymphoblasts, exhibit a turn-over rate that allows the complete renewal of the cell or parts of it within one hour or less. Even “slowly” growing cells such as mesenchymal cells have a rapid energy exchange. This aspect of organic regeneration in the organism is not appreciated in present-day bio-sciences. When we consider the speed of cellular energy exchange within a certain period of time, say, one day, we must obtain a much higher value. For this purpose we must first consider the working capacities of the different cell types in the body.

With respect to energy exchange, we can subdivide the various cell types into three major groups. The biggest group includes the muscle cells. Essentially, there are smooth muscle cells and striated muscle cells. The second group includes the neurones, which may differ considerably, depending on whether they are peripheral or central neurones, or whether they possess myelinated or demyelinated axons. The third group is rather heterogeneous and includes all epithelial and mesenchymal cells, as well as all immunocompetent cells. Heart muscle cells[6] have a resting membrane potential of about –90 mV and exhibit upon excitation a positive overshoot of about +30 mV. The absolute amplitude of their action potential is thus in the range of 120 mV, as considered in our calculation. In wave theory, it is a well known fact that the total energy of a single wave or oscillation depends only on the

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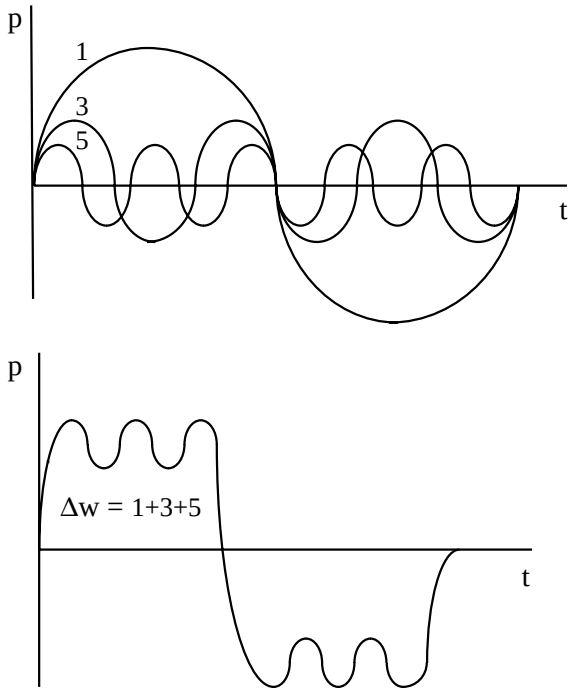
[6] Heart muscle cells are best evaluated in electrophysiology.

magnitude of the wave amplitude (see vol. I & II).

I have proved that wave theory assesses the character of the action potential in terms of a wave, and that the equations used in this discipline are derived from the universal equation and can be applied to any action potential independently of the form involved. In the same context, every physical or material structure can be regarded as the aggregated product of standing superimposed waves (see also de Broglie interpretation of Bohr's standing wave condition of the electron in vol. II). Figure 2. illustrates this aspect. The action potential of a heart muscle cell can be interpreted in terms of a standing wave resulting from the synthesis of the first three harmonics. In fact, the number of superimposed waves is infinite because space-time is infinite. Each material structure or energetic phenomenon results from the superpositon of waves (U-sets), that is, of rotations.

Figure 2: This „right-angle" standing wave is the synthesis of the first three harmonics. Observe the similarity with the action potential of a heart muscle cell.



The LRC_E of muscle cells determines the contraction of the corresponding muscular organ and the effective kinetic work performed by this organ. For instance, the frequency and magnitude of the action potential of heart muscle cells determine the frequency of heart beats (chronotropism) and the magnitude of the ejection fraction of the heart (inotropism). The aggregated product of all cellular action potentials in the heart can be assessed as an *electrocardiogram*, which is the macroscopic electromagnetic manifestation (electric LRC) of the energy exchange of this vital organ. In this case, the P-QRS-T complex is the action potential of the electromagnetic level of the heart as a macroscopic organ. This ECG action potential is the aggregated macroscopic product (wave packet as U-set) of the microscopic action potentials of all heart muscle cells that emerges from their superposition and drives the heart to pump the blood.

We assume in our calculation of the human balance that a plasma potential in the order 120 mV, as observed in heart muscle cells, accounts for the mean action potential of all human body cells because this cell group takes an intermediary position between neurones, which have a higher energy exchange, and the mesenchymal cells, which have a lower energy exchange (for further information see physiology). The frequency of action potentials varies considerably in different muscle cells: from one action potential per second in heart muscle cells at rest up to 20-100 action potentials per second in striated muscle cells. The frequency of excitation is much higher in motoneurones. In addition, facilitations and posttetanic potentiations modulate the frequency of muscular excitation in a non-linear manner. The magnitude and frequency of action potentials in neurones may vary, depending on their type and site. We have for instance the endplate potential (EPP), the miniature endplate potentials or MEPPs on the postjunctional membranes, the excitary postsynaptic potentials (EPSP), the inhibitory postsynaptic potentials (IPSP), which are the result of transient hyperpolarisation (repolarisation), etc. The magnitude of the action potential in neurones also depends on the organisation of the neuronal structure and the synaptic arrangement (number of junctions).

The least investigated cell group in this respect is that consisting of epithelial, mesenchymal, and immune cells. With the introduction of the *nystatin patch-clamp technique*, the amount of information on the energy exchange of these cells has rapidly grown. Some of these cells, such as the renal tubulus cells and mucous cells of the gastrointestinal tract,

may exhibit different potentials and excitation properties at the apical and the basal site of plasma membranes. The average potential that is encountered in this cell group ranges between 60 and 90 mV. There is substantial evidence that the depolarisation of leukocytes and other immune cells is associated with cell stimulation and growth, while repolarisation is associated with cell maturation and differentiation. Mesenchymal cells can appear as quiescent cells at one site (e.g. fatty cells) and as maximally stimulated cells at another site (e.g. renal cells). During an acute reaction after infection, immune cells of mesenchymal origin are stimulated more than 10 000-fold, as manifested by the rapid acceleration in lymphokine concentration in plasma. On the other hand mesenchymal cells do not exhibit action potentials as pronounced as those observed in muscle cells and neurones - their amplitude is usually much smaller, so that the oscillations of the plasma potential of mesenchymal cells are rather difficult to measure. This is most probably the main reason why the electric potentials of immune cells and their modulation by lymphokines and other humoral factors are not seriously considered by immunologists in their efforts to understand the regulation of the immune system (see chapter 2.4).

From this analysis it becomes evident that the definition of the average cell in terms of energy exchange can only be done by means of abstraction. The *definition by abstraction* (H. Weyl) is the universal method of mathematics when it is applied to the physical world[7]. All real numbers are for instance approximations of transcendental magnitudes that can be assessed more exactly by transcendental numbers. However, mathematics has virtually no theory of how to use transcendental numbers - all results in physics and other natural sciences are given in real closed numbers. For instance, the transcendental number *pi*, when given as a real number, e.g. $\pi = 3.14$, is an arbitrary approximation of the transcendental character of the constant space-relationship between the circumference of a circle and its diameter. All space-time relationships are of such transcendental character, even when they are presented as natural constants. Mathematics is thus an adequate reflection of the real world, but only within the inevitable approximations inherent in the application of real numbers. This holds in the first place for all SI units and their reference systems, which are real systems of space-time. To these the

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[7] H. Weyl. Philosophie der Mathematik und Naturwissenschaft, Oldenbourg Verlag, München, 1990.

primary real closed number "1" is attributed in an abstract way and expressed as 1 unit, e.g. 1 meter (space), 1 second (time), 1 joule (space-time), etc. (see vol. I & II).

This elaboration reveals that any assignment of *closed numbers* to real space-time relationships (according to the principle of circular argument all magnitudes are relationships) is a definition by abstraction. Our balance is also based on this kind of definition, which is the only adequate approach to space-time. When this method is applied to an assembly consisting of a large number of elements such as the body, the problem is reduced to finding the mean value of the elements. Feynman's method "sum over the histories" in QED is based on this approach: the speed of photons c is regarded as the mean value of all possible histories, that is, of all possible pathways and velocities of individual photons that reach the detector (for further information see vol. I and II).

The human body is such an assembly. It consists of a huge number of individual cells (10^{14}) that is almost equivalent to the number of stars in our galaxy. Although the energy performance of the individual cells varies, it is nonetheless possible to determine the mean energy exchange of this set of cells from established data. By employing the universal equation to this mean value, we can calculate the total energy exchange in the human body[8]. The more elements in a set, the smaller the deviation from the mean value, this magnitude being an abstract quantity defined within mathematical formalism, just like any other physical quantity. So much for the theoretical aspect of applying mathematics to real systems of space-time such as the human body.

If we now consider that heart muscle cells experience at rest approximately 70 action potentials (heart beats) per minute, we can easily calculate that the total number will be about 100 800 action potentials per day for the average cell at rest. This quantity represents the (absolute) time f of this system, which has a constant energy exchange in the mean. The absolute magnitude of each potential is about 120 mV. This means that

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[8] This method is, for instance, used in the famous *Fisher's equation* of money supply $E = PT$, where P is the mean value of all transactions in a given economy and T is the number of transactions over a given period, say, one year. This equation is an application of the universal equation; it is the point of departure of modern monetarism as propagated by Milton Friedman and the Chicago boys (see the Bulgarian book "Universalnijat zakon", Stankov's Universal Law Press, Plovdiv, 1998).

the average body cell depolarizes completely and restitutes its resting potential with a frequency of $f = 100\,800$ during one day. As the mean metabolic rate of the human body is given per day, we must use the same observation period (definition of an equivalence to make a comparison, principle of circular argument).

We have calculated in equation (14) that the total instantaneous electric energy stored in the resting potential of all cells in the body is 23 J. This amount of energy is transformed into chemical energy or kinetic work and is reconstituted about 100 800 times over the duration of one day. The **effective electric energy (energy exchange, turn-over)** of the organism per day can thus be calculated by applying the universal equation:

$$E_{Eeff} = E_b \times f \tag{15}$$

$$E_{Eeff} = 23\ \text{J} \times 100800 = 2318\ \text{kJ} \tag{15a}$$

We conclude:

> The estimated *effective energy exchange* at the *electric level* of the human body $E_{Eeff} = 2318$ kJ is equivalent to the effective metabolic rate of the human body at rest $E_{meff} = 2500$ kJ, as determined from the basic metabolic rate (4):
>
> $$\boldsymbol{E_{Eeff} \cong E_{Meff}} \tag{16}$$
>
> *Alternatively*: The effective energy of nutrition is completely transformed into the electric energy of biological membranes in the organism and vice versa. This energy level is responsible for the biological regulation of organic matter.

This is a remarkable result that will be elaborated in detail in the present volume. The small difference in equation (16) can be explained in a twofold manner: about 3-5% of the body cells die every day by lysis or apoptosis and have to be restituted by cell metabolism. This additional energy exchange is not considered in our calculation. Hence the somewhat smaller value calculated for the effective electric energy when compared with the initial effective metabolic rate. Another possible explanation of this difference is that our estimate of the electric energy stored in

intracellular membranes may be somewhat lower. Most probably both aspects have contributed to the small difference in the above calculation. However, it does not affect in any way the fundamental importance of the result obtained from the energy balance calculation of human metabolism.

At this point it should be observed that this energy balance was performed for the first time in the history of science in 1994 by myself and prompted the discovery of the Universal Law. This late discovery is quite surprising when it is considered that all the facts necessary for this calculation have been known for more than 60 years. The insight that a simple equation such as $E = E_A f$ is sufficient to calculate the metabolism of the whole human organism, which is considered a system of immense complexity, convinced me that I must have discovered the Universal Law of Nature. Its subsequent confirmation in physics was the logical consequence of this finding. Since then, this equation is called the "universal equation".

The energetic balance of the cell and the organism incorporates the chemiosmotic theory, which is a partial and incomplete energetic approach to cell metabolism. This theory can be regarded as an important precursor of the new General Theory. It has been introduced in this book for didactic and historical purposes, just like the classical laws of electricity and magnetism are still taught in physics, although now fully integrated into Maxwell's four equations of electromagnetism, whereas the latter are applications of the universal equation.

1.3 π-ELECTRON STRUCTURES IN NATURE AND THE SOLITON CONCEPT

Following this introduction to our general energetic approach to metabolism we shall now proceed with the application of the Law to particular levels and systems of organic matter in the cell and analyse them in an axiomatic, that is to say, consistent way. The same approach is employed in physics - the new physical and mathematical axiomatics introduces the primary term, respectively, the Law, in an *a priori* manner before it is applied to all known physical disciplines. This permits the establishment of a unified theory of physics and cosmology which also integrates gravitation (see vol. I & II). Although the competent reader can perform this exercise in the bio-sciences by himself, it is important to observe that the

establishment of the General Theory is based on a collection of further breakthroughs in these various disciplines. Without this background, the reader may not be in a position to develop the General Theory in the same degree of detail as in this volume, and explain the numerous facts obtained in such diverse fields as genetics, microbiology, biochemistry, medicine, and pharmacology in the light of the Law. The advantage of the new outlook is that it integrates science in an axiomatic way and at the same time allows a consistent explanation of any particular experience in experimental research. Thus theory and empiricism become a unity. In this chapter, we shall begin with the **supramolecular level** of the cell and discuss common energetic patterns in the light of the Law.

We begin again with OP in mitochondria. All components of the oxydative chain are integral proteins - they consist of a transmembrane part containing α-helices and intra- and extracellular loops, which are built of α-helices and β-pleated sheets. Integral proteins interact with the lipid bilayer and with each other (cross-reaction), as they are mobile in the membrane (see below). The chemical and spatial configurations of many integral proteins have been elucidated in recent few years. Their detailed description is beyond the scope of the present book. We recommend that the reader scrutinizes the relevant recent publications on this issue. Most of the integral proteins exhibit prosthetic groups with **delocalized π-electron systems**. Common π-electron carriers in biological systems are:

a) Tetrapyrroles in cytochromes, haem, chlorophyll, etc.
b) Flavins, ubiquinones and isoprenoids, which are ubiquitous substances and can be found in all plant cells.
c) Polyenes such as vitamin A, β-carotenoids, and other related substances.
d) Nucleotides such as ATP, GTP, and their derivatives.
e) The three essential aromatic amino acids, Phe, Tyr, and Trp.

Recently, a new branch has evolved from classical chemistry, called *supramolecular chemistry*. While the former deals with *covalent bonding*, the latter unravels the mystery of *weak bonding* in large supramolecular structures. All the supramolecular molecules studied so far, no matter whether they are chemically synthesized or biologically derived, carry extended π-electron systems and can trans-

fer electrons between an *electron donor* and an *electron acceptor*[9]. During this electron transfer, the chemical moieties may undergo conformational perturbations and change their dielectric properties. The most famous substances in this respect are the so-called "cage compounds". Such compounds will sooner or later substitute the present chips in computers. This area of applied physical chemistry is known as "nanomolecular technology". Based on the Law, I achieved a major theoretical breakthrough in nanomolecular technology that will trigger progress in this field. This breakthrough is closely related to the concepts discussed in this chapter. In the General Theory, we define:

> *A functional system* of the supramolecular level consisting of an *electron donor*, an *electron acceptor*, and a *delocalized* π-*electron system* as a "**soliton triplet**".

The reader can imagine the soliton triplet as a kind of *electronic* (*semi*)*conductor* at the *nanomolecular* level. We use the term "**soliton**" as a synonym for a *standing wave* at the supramolecular quantum level. This term was first introduced in biology by the Russian physicist *Davydov.* He suggests that such solitons may occur in amide bindings of integral proteins and may be responsible for the kinetic reactions of organic matter to external stimuli (see below). Subsequently, his approach was further developed and applied to DNA structures. Recent theoretical and experimental evidence has confirmed the validity of the soliton-concept in DNA[10].

I have proved in the new physical axiomatics that the quantum theory used by Davydov in establishing the soliton concept can be derived from the universal equation. It is essentially an application of Schrödinger wave equation which in turn is an application of the Law (see vol. I & II). We shall not discuss the mathematical theory of Davydov in this survey.

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9 Vögtle F. Supramolekulare Chemie, Teubner, Stuttgart, 1992.

10 Baverstock KF & Cundall RB. Are solitons responsible for energy transfer in orientated DNA? Int J Radiat Biol, 1989, 55: 151-53; Swenberg CE & Miller JH. Response to:, Int J Radiat Biol, 1989, 56: 383-86; Baverstock KF & Cundall RB. Solitons and energy transfer in DNA, Nature, 1988, 332: 312-313; Muto V et al. Solitons in DNA, J Biomolec Structure & Dynamics, 1988, 5: 873-94; Khan et al. The possible role of solitonic processes during A to B conformational changes in DNA, Bull Mathem Biol, 1985, 47: 783-89, etc.

Supramolecular chemistry is also called *photochemistry* because most of the supramolecular compounds studied so far are *photo-synthesized*. This fact is extremely important for our subsequent discussion of the basic question of evolution - the emergence of organic life as the final product of the vertical energy exchange between inorganic matter and photon space-time, also circumscribed as the *photosynthesis* of plants (see chapter 1.6). The common feature of supramolecular structures is that they can store information, the term "information" constituting a synonym for the primary term - any information is of energetic character. It is based on the discreteness of space-time - on the existence of action potentials with a specific constant energy for each level or system. Therefore, it is not at all surprising that supramolecular chemistry is also called "molecular informatics" and the photochemical molecules "molecular wires". They can behave as insulators, semiconductors, conductors, or even superconductors (e.g. cage compounds), depending on the electric surroundings. The nature of the signals that such molecules generate is based on various energy exchanges such as: photon/photon, photon/electron, electron/electron, electron/ion, etc. These energy interactions are also found in organic matter, predominantly in structures carrying soliton triplets. Photochemistry is just beginning to emerge as a formal science, but it has already gathered a huge amount of experimental experience with electron/photon/ion transfers in various molecular structures[11]. These experimental data can be cogently explained with the new physical axiomatics, where the energy exchange between photon space-time and the various levels of matter is of central importance. These interactions are also basic to the soliton triplet concept of the General Theory.

The **soliton** concept was proposed by *Davydov* (Kiev) in the early 70s. He correctly emphasizes that the energy of ATP alone is not sufficient to explain how cell metabolism and regulation are *kinetically* driven. His soliton concept is based on Schrödinger wave equation. It is a differential solution for amide-I excitations in proteins. Initially, the concept was developed to explain the excitations in α-helices. Subsequently, Davydov suggested the use of this model to explain the *myosin-actin*

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[11] Chem Rev, 1992, 92: 435-461; Chem Phys Letters, 1982, 90: 136-39; J Phys Chem, 1991, 95: 8434-37; Biochemistry, 1984, 23: 944-955; Nature, 1991, 353: 736-7, Electron transfer in inorganic matter, chapter 5, 71-90; J Am Chem Soc, 1992, 114: 3656-60; Nature, 1987, 327: 508-11; Science, 1988, 240: 440-7; J Phys Chem, 1986, 90: 3673-83, etc.

interactions in muscle cells. Davydov's model assumes the propagation of solitons along the myosin-actin filaments initiated by ATP hydrolysis. These solitons are made responsible for the contraction of the filaments.

However, the soliton model of Davydov does not consider the existence of an electric gradient at the cell membrane. For this reason it does not describe the establishment and propagation of supramolecular solitons in relation to the action potentials of muscle or other cells. Unfortunately, this particular vertical energy exchange, which is basic to cell regulation, cannot be adequately explained without considering the existence of electric action potentials at the cellular level; the latter initiate myosin-actin interactions in muscle cells. Such interactions do not take place under the condition of energetic equilibrium. Thus Davydov's concept of biological solitons exhibits the same shortcomings as the chemiosmotic theory; it is a partial and deterministic approach to biological regulation - this time from the point of view of quantum mechanics. Its chief asset lies in stressing the role of kinetics in proteins and other cellular elements - a fact that is totally ignored in present-day bio-sciences. The negation of motion is typical of modern bio-science, although the idea that organic matter consists of elements which are *movable* and *moving* at the same time is very popular in western philosophy (e.g. Hegel's dialectics) and goes back to *Aristoteles* in antiquity.

When we apply the soliton concept of Davydov by considering the electric LRC of the cell and employ the fundamental axiom of the new axiomatics which states that all systems are U-subsets and contain themselves as an element, we acquire an adequate mathematical device for assessing the cellular energy exchange at the supramolecular level. Recall that mathematics is the only adequate reflection of the physical world, but also that any mathematical application can be substituted by another because mathematics is a transitive system: all mathematical operations can be derived from the universal equation, which is a rule of three. This also holds for the mathematical presentation of biological solitons as suggested by Davydov. This insight introduces the greatest possible simplification in science. Its cognitive background is the Law, which assesses the nature of space-time in mathematical terms (universal equation). The last statement is an inevitable tautology of the principle of last equivalence that reveals the closed character of space-time (see vol. I & II).

Being a creative man, Davydov modified his model in the late 70s

and early 80s. In its latest version, the model assumes the existence of an electron donor and an electron acceptor in the amide sequences, but it fails to specify their actual structures. While showing that minimal changes at one ending of the α-helix may induce profound conformational changes in the whole structure of the integral protein, it still disregards the existence of an electric plasma gradient. The underlying mathematics is based on the time-independent Schrödinger wave function and is rather complex. This hinders the application of the soliton model in biology. In addition, the author is not well acquainted with the major advances in bio-sciences. For instance, Davydov completely neglects the chemiosmotic theory, which has in the meantime become the fundamental bioenergetic framework in biochemistry. This is a major deficiency in all energetic theories developed by biologically orientated physicists - most of them exhibit striking deficiencies in their biochemical knowledge of organic life[12]. This also holds true for the next author.

Fröhlich considers the electromagnetic waves which are triggered by modulations of the electric LRC of the cell and are propagated in the cytosol. He speaks of "biological excitations"[13]. Fröhlich regards the cell as an energetic continuum consisting of biological dielectrics, at best finely grained the size of dipole oscillators, which acquire a continuous flow of metabolic energy. Davydov's model, on the other hand, considers the cell and the energy flow as coarsely grained, that is, as discontinuous.

It is not difficult to perceive that both models are one-sided perceptions of the discrete and continuous character of space-time in the cell and thus reflect the fundamental wave-particle dualism in physics today. I have proved that this dualism is an artefact born in the realm of math-

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[12] Davydov AS. Soltions and energy transfer along protein molecules, J Theor Biol, 1977, 66: 379-387; Davydov AS. Excitons and solitons in molecular systems, Int Rev of Cytolog, 1987, 106: 183-225; Bednar J. Electronic excitations in condensed biological matter, Int J Radiat Biol, 1985, 48: 147-166. Lawrence AF et al. The nature of phonons and solitary waves in α-helices proteins, Biophys J 1987, 57: 785-93; Volobujev AN et al. Nelinejnoe modelirovanie rasprostranenije (non-linear model of distrubution of potential activities) Biophysica, 1991, 36: 546-51, etc.

[13] Fröhlich H. Conditions of coherent excitations in biological systems, Phys Letters, 1982, 93A: 106-7; Fröhlich H. Coherence of biological systems, Collective Phenomena, 1981, 3: 139-46., etc.

ematics and is thus not a property of matter, as is erroneously believed today. Therefore, it is not surprising that some studies have coalesced with Davydov's model, while others fit in more with Fröhlich's model[14].

Davydov's model emphasizes the quantum energy changes in the FUELs (integral proteins), while Fröhlich's model considers intuitively the electromagnetic waves of the oscillating electric LRC, which are propagated in the dielectric medium of the cytosol and drive cell metabolism. Both models assess different levels of the cell, which are U-subsets of space-time and cannot be separated in real terms. These solitary approaches are integrated in the General Theory. Neither of the two models makes any concrete suggestions as to the molecular structures of the solitons. This will be done for the first time in the General Theory.

1.4 THE FUNCTIONAL UNIT OF ENERGY TRANSLOCATION (FUEL) AND THE SOLITON TRIPLET

Integral proteins can be subdivided into three major groups: **receptors**, **ion-channels,** and **ion-motive ATPases (ion-pumps)**. Receptors are usually found in the plasma membrane, but they are also present in inactive form in the membranes of *endoplasmic reticulum* (ER). Ion-channels and ATPases are ubiquitous and are found in plasma membranes as well as in intracellular membranes.

> *Receptors*, *ion-channels*, and *ATPases* are integral proteins that are involved in energy exchange across biological membranes. In the General Theory they are defined as "**Functional Units of Energy transLocation**"**,** in short **FUELs.**

Receptors can be subdivided into various subgroups. Ion-channels are sometimes regarded as receptors when they are directly activated by neurotransmitters, e.g. GABA-receptors, Na^+-channels, etc. At present there is a great deal of confusion in this area because there is no theory of biological regulation. Certain regulatory hormones were found to be-

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[14] Lawrence AF & Adley WR. Non-linear wave mechanisms in interactions between excitable tissue and electromagnetic fields, Neurol Res, 1982: 115-153.

have as integral proteins or to complement membrane receptors. For instance, there are G protein-bound receptors, where G proteins represent receptor-coupled effector systems. Cytoplasmic effector systems are conventionally regarded as receptors, e.g. steroid receptors, although they are not transmembrane proteins. These few examples are paradigmatic for the present confusion in the bio-sciences.

The new definition of the FUEL applies not only to integral proteins, but also to all intracellular proteins, such as enzymes and DNA-regulating proteins, because they also carry soliton triplets. When they exchange energy with the electric LRC through electromagnetism, they propagate solitons at the supramolecular level. These standing waves induce structural perturbations in proteins and trigger their specific activity (see examples below). This fact confirms that space-time is an energetic continuum.

All integral proteins have a transmembrane α-helix part that consists of one or more loops. The α-helix is a very common tertiary structure found in most proteins and is highly specific. α-helices are *amphipathic* moieties: they expose their hydrophilic side chains on the one face and their hydrophobic side chains on the other face of the helix rod.

The α-helix has exactly 3.6 amino acids per turn. All α-helices carry at least one aromatic amino acid residue (π-residues). π-residues are flanked by positively charged amino acids (Arg, Lys) or by negatively charged amino acids (Glu, Asp). Negative residues (–) are electron donors, while positive residues (+) are electron acceptors. Cys and Met may also function as electron donors under certain conditions. However, Cys is seldom found in α-helices:

> An electron donor, an electron acceptor, and a carrier of a π-electron system form a functional unit within the supramolecular structure of integral and cytosolic proteins, called the "**soliton triplet**".

Bacteriorhodopsin, a proton-driving pump in archaeobacter, and *rhodopsin*, a sensory receptor of the human retina, illustrate the operation of the soliton triplet. These integral proteins are highly conservative. Both moieties use *retinal* as a prosthetic group. Its molecule has an extended π-electron system, which is used instead of an aromatic amino acid within the α-helix. For instance, retinal is situated in the middle of the α-helix of bacteriorhodopsin, within the lipid bilayer near Lys-216 (+), and is

flanked by Asp-85 (–) and Asp-96 (–). This soliton triplet functions as a *reversible proton-driving pump* (or semiconductor) that exchanges electrons between the negatively and positively charged amino acid residues when a photon is absorbed by retinal. This interaction is part of the vertical energy exchange between photon space-time and organic matter, or more precisely, between photons of the visible light and the π-electron system of retinal. The reversible electron transport in the soliton triplet drives an opposite ionic transport - in this case, a *proton flow*. The actual mechanism of the soliton triplet will be discussed in detail below. In rhodopsin, the soliton triplet dissipates upon photon activation. Retinal dissociates from opsin after a photon from the visible light interacts with this compound and must be reconstituted in the night.

These two examples illustrate a fundamental aspect of energy exchange at the supramolecular level: *electrons* and *photons* are the action potentials of different quantum levels of space-time that interact within the supramolecular level of the integral protein, that is, with the π-electron anion of the prosthetic group, which participates in the soliton triplet. In volume II, I have proved that the coupling constant of this vertical energy exchange between the electron and photon level, the famous *Sommerfeld's constant of fine structure*, is an absolute constant of vertical energy exchange and can be derived from the Law by employing the new *construction rule* (see chapter 7.9). These derivations of the new physical axiomatics facilitate an understanding of *photosynthesis* in the thylakoid membranes of plants, the transformation of photons into repolarizing action potentials of retinal rods and cones in vision (see below), and the OP in the mitochondrial membrane. These distinct bioprocesses have a common energetic mechanism at the quantum level that can be easily explained by the concept of the soliton triplet.

This fact confirms again that energy exchange involves all levels and systems of space-time. It is a privilege of the human mind to discriminate space-time in a voluntary manner in infinite systems and levels (degree of mathematical freedom). As space-time is discrete, such abstract discriminations always have a correlate in the real world.

Soliton triplets are also encountered in ion-motive ATPases which are ubiquitous. They are subgrouped in three major categories, defined as "P", "V", and "F". ATPases of the "P" class undergo a covalent phosphorylation as part of their pump function. Examples are Na^+/K^+-, Ca^{2+}-, and H^+-transporting ATPases in plasma membranes, and Ca^{2+}-ATPases in sarcoplasmic reticulum (SR) and endoplasmic reticulum (ER).

ATPases of the "V" type are found in vacuoles (hence "V"), lysosomes, endosomes, hormone storage granules, secretory granules, and Golgi vesicles. The "F" class refers to the F_1/F_0 type of ATPases as found in the respiratory chain. The "V" type is similar to the "F" type. Many of the "V" ATPases are involved in the uptake of biogenic amines and amino acids in intracellular granules, or in the uptake (storage) of catecholamines in chromaphin granules. The "P" class needs the presence of Mg^{2+} for the hydrolysis of ATP that drives the pumping of ions against their gradient. ATPases are reversible. They can synthesize ATP in the presence of an electric gradient across the membrane (e.g. F_1/F_0) or hydrolyse ATP to create an electrochemical gradient (e.g. Na^+/K^+-ATPase in plasma membranes).

From this elaboration, it becomes evident that ATPases either create or modulate an electric gradient across a membrane. The specific function of this type of integral FUEL depends on its *orientation* in the membrane, as can be shown in reconstitution experiments. ATP is the key functional component in this kind of integral protein. This nucleotide carries a π-electron molecule (adenine) and an electron donor (phosphate groups), which together constitute a soliton triplet. The ultimate electron acceptor of the ATP soliton triplet is the Mg^{2+} ion. In the absence of this ion, the ATPase cannot function, that is, it cannot expel ions against their gradient. Other metal ions may also assume the function of electron acceptors in the ATP soliton triplet of ATPases or other FUELs. Zinc, iron, or copper ions are further common electron acceptors of soliton triplets that are found at the active site of many enzymes (see below).

From this short exposé, we gather that the ubiquitous molecule ATP constitutes a third common type of soliton triplet in proteins, in addition to the amino acid soliton triplet in α-helices and the mixed amino acid-prosthetic group soliton triplet found in respiratory chain proteins, haem, chlorophyll, rhodopsin, bacteriorhodopsin, and so on. ATP is not a unique molecule in this respect - it is representative of all nucleotides in the cell. For instance, DNA and RNA represent a stack of nucleotides that form extensive macromolecular structures. They carry numerous soliton triplets that store the genetic "information" electronically and operate as *biomolecular wires*. There is growing experimental evidence that the regulation of the genetic code is carried out by complex soliton interactions which will have to be further elaborated in the bio-sciences (see below).

Departing from the concept of the soliton triplet and its chemical structures, we come to an important aspect of all integral proteins that has not been fully comprehended yet. All membrane FUELs such as receptors, ion-channels, and ATPases are **asymmetrically** orientated in the membrane. For each FUEL type, the position of the COO^- and the NH_3^+ groups at the two endings of the protein molecule is fixed once and for all in the membrane and will never change. This is a very important fact that is closely associated with the occurrence of solitons in these FUELs. With respect to the orientation of the FUEL in the membrane, we can define four major types of integral proteins (C for the COO^--ending, N for NH_3^+-ending; "c" is an index for the cytosolic ending and "e" for the extracellular ending of the FUEL) which are indicative of their physiological function:

1. C_cN_e-type,
2. C_eN_c-type,
3. C_cN_c-type,
4. C_eN_e-type.

In addition, there is a mixed type of integral FUELs consisting of the four basic types. The integral proteins of the mixed type are most probably complexes of distinct membrane FUELs that belong to one of the above categories (U-sets).

The orientation of the protein endings determines the function of the integral FUEL. For instance, **C_cN_e-integral proteins** are *depolarizing* FUELs. The group of the *seven-helix-loop receptors* belongs to this type. The **C_eN_e-type**, as represented by the GABA receptor, includes *repolarizing* FUELs. A knowledge of the orientation of integral proteins is indispensable for the determination of their actual function with respect to the electric LRC of the cell. This major breakthrough introduces a great simplification in biochemistry.

The FUEL concept cannot be properly appreciated unless the role of **cholesterol** is analysed in this context. Biological membranes, or more precisely, their lipid bilayers, can be regarded as plate capacitors that exhibit astounding insulating properties. The negatively and positively charged sides of the lipid bilayer allow the establishment of a powerful electric field; according to the new axiomatics this abstract physical quantity has the dimension of acceleration (see vol. I & II). Such an electric field requires extreme insulating properties on the part of the biological membrane.

The lipid bilayer consists essentially of *phospholipids* and *cholesterol* in a molar ratio of about 1:1 that can vary from one cell membrane to another. While phospholipids do contribute to membrane insulation, the key molecule that regulates the dielectric properties of biological membranes is definitely **cholesterol**. This was elucidated for the first time within the General Theory by employing the dipole model. According to it, cholesterol is an *electroneutral* compound, that is, its molecule has virtually no dipole moment. For this reason cholesterol is a unique substance among all biomolecules. The electroneutral character of cholesterol makes this molecule highly mobile in the lipid bilayer, as demonstrated in numerous in vitro studies in membrane research[15].

Another basic fact that has been known for some time, but has remained cryptic to biologists, is also associated with the behaviour of cholesterol. Integral proteins can recover their function only when they are *reconstituted* in lipid bilayers. Such lipid bilayers *must* contain cholesterol. In the absence of cholesterol, the membrane proteins either do not reconstitute their function or do it very poorly. Thus cholesterol is functionally linked to the operation of membrane FUELs and the propagation of solitons along their supramolecular structures. Therefore, this fundamental molecule should always be considered when the function of integral FUELs is discussed.

For instance, the regulation of the organism through *sexual steroid hormones*, which are cholesterol-derivatives, can be properly understood only after the key role of cholesterol in regulating the insulating properties of biological membranes is fully appreciated (see Part 2). The central importance of this molecule in biological regulation is underlined by the fact that various cholesterol-like molecules can be found in all plant cells and prokaryotes and are for instance widely used in Chinese phytotherapy to regulate “homeostasis” in various chronic diseases[16].

This short survey of the various types of FUELs, their specific structure, and function reveals a major motif of organic matter:

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[15] Biomembranes, ed. Shinitzky M, VCH, New York, 1993.

[16] This is a dazzling new aspect of the General Theory that will promote *phytotherapy* as the chief therapeutic strategy of many chronic diseases in the future.

> All organic membranes - plasma membranes and intracellular membranes - incorporate integral proteins as FUELs. They either create an electric gradient across the membrane or modulate it. The energetic interaction between the integral FUELs and the membrane potential is of *electromagnetic* character.

This is a well established fact in biology. However, the implications of this ubiquitous fact are not realized yet. This can be illustrated by listing several basic questions which, in my opinion, should be asked by any biologist who is genuinely interested in unravelling the mystery of biological regulation:

1. Why does nature create an electric gradient (this also includes a pH-gradient) across any biological membrane?

2. Why does the cell consist of a highly complex network of membranes that form extensive intracellular compartments, such as Golgi, ER, SR, lysosomes, and various other organelles?

3. Why do the bio-sciences propagate the idea that each protein exerts a specific function in the cell (e.g. the concept of a specific binding between a receptor and a messenger), while all integral proteins are composed of similar functional units (modules)?

4. Why do all FUELs exhibit a fixed orientation in biological membranes that determines their function?

5. Why can the function of a membrane FUEL be reversed when its orientation in the membrane is reversed - for instance, ATPases operate as ATP-synthases and vice versa?

6. Why do we find in organic matter proteins that are similar in structure, but different in function, depending on the site of occurrence - for instance, the ubiquitous integral proteins *cytochromes* are involved in biotransformation in liver cells and in the oxydative burst in lymphocytes?

When these questions are answered properly, one inevitably arrives at the conclusion that **there is a universal functional pattern in all FUELs**. Indeed, these integral proteins seem to be variations on the same theme. All integral FUELs either create or modulate an electric gradient across a biological membrane by propagating ionic and electron currents across the lipid bilayer. The same mechanism of charge transport is also observed in cytosolic FUELs. The simultaneous occurrence of ionic and electron transport in supramolecular structures (charge transport) is a typical property of the soliton triplets which all FUELs carry. The soliton triplets are comprised of structurally different, but functionally related, components that exhibit the same fundamental properties. Each soliton triplet has an electron donor, an electron acceptor, and a π-electron system that acts as a charge conductor between the two. The propagation of a soliton along such structures can be regarded as an action potential of the energy exchange at the supramolecular level of the FUEL. This is a quantum process.

Soliton triplets can be found not only in integral proteins where soliton-specific amino acids are part of the sequences of transmembrane α-helices or binding sites that contain various prosthetic groups, but also in DNA, RNA, DNA-regulatory proteins of the loop-helix-loop-type, cytoplasmic enzymes (e.g. Tyr-kinases), myosin-actin filaments, microfilaments of the cytoskeleton, tight junctions, histones, etc. In fact, soliton triplets can be found in <u>every</u> protein or enzyme structure in the cell. The evidence is overwhelming and is exponentially growing with our knowledge of the structure of new proteins.

Obviously, organic matter "employs" several highly conservative patterns of energetic regulation. The bewildering diversity of chemical structures traditionally presented in the bio-sciences reveals one fundamental leitmotif of energy exchange at the supramolecular level:

> Energy is propagated in the cell along *supramolecular structures* that carry **soliton triplets**. These functional systems of the supramolecular level of the cell interact with the electric LRC of the cell. This vertical energy exchange between the electric level and the supramolecular chemical level of organic matter is responsible for the kinetic and structural (metabolic) *regulation* of the cell and the organism.

Before we proceed with our elucidation of biological regulation, we must first present the soliton concept from a physical point of view for the purposes of the bio-sciences, that is, descriptively. The underlying theory is, however, based on mathematics.

Solitons are *standing quantum waves* that are propagated along supramolecular protein structures. They have the propensity not to disperse when they move along chemical structures which carry extended π-electron systems with delocalized electrons. π-electron systems are unique in their propensity to accommodate additional *unpaired* electrons. Such systems form a **delocalized π-electron anion**. According to the soliton concept, such electrons occupy with a high probability localized, energetically favourable positions, called "**midgaps**", which dwell in the π-electron system. This term was first applied to polyene structures. The midgaps are mathematical solutions of Schrödinger wave equation. It is important to observe that this application of the universal equation can only describe *areal integrals* within geometry. Therefore, the midgaps are mathematical solutions with respect to quantum topology at the supramolecular level.

Midgaps can move freely along the supramolecular structure. This displacement is described as a standing wave - a **soliton**. Recall that *motion* is the universal manifestation of space-time. This may seem trivial for a single electron, as conventionally presented in classical electricity, but when one considers the delocalization of π-electrons over long conjugated-carbon chains, this energy exchange is a qualitatively new step in the organisation of organic matter[17]. The behaviour of unpaired electrons in the "midgap" states is fundamentally different from that in metals, where common electrons are shared between atoms. For instance, when polyenes are "dotted" with oxydative compounds, e.g. with NH_3^+-groups, metal, or other ions, electrons are readily released from the "midgaps" because of the higher energy state they experience in this position.

When an unpaired electron is released, the "midgap" does not disappear, but is transformed into a localized positive charge - a **proton**. This

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[17] The basic energetic difference between the two forms of matter, organic and inorganic, is elucidated in vol I. A proper understanding of this difference will permit the development of effective superconductors that will not be brittle and will work at normal temperatures. These superconductors will imitate the energetic organisation of soliton triplets in membrane FUELs.

is an application of the axiom of CAP for this specific energy exchange: the electron and the proton can be regarded as two action potentials belonging to different quantum levels that interact (U-sets). Before we proceed with this elaboration, let us recall for the sake of clarity that both terms, "electron" and "proton", are circumscriptions of standing (superimposed) waves at the quantum level. The (+) and (−) signs traditionally attributed to these particles in physics are a purely mathematical convention that expresses the condition of constructive or destructive interference of waves. This knowledge is of eminent cognitive importance.

The positively charged "midgap" now moves freely along the π-electron system, just like an unpaired electron does. The direction of its movement is opposite to that of the electron. Thus the exchange of positive and negative charges occurs *simultaneously* in the soliton triplet. Therefore, every electron transport is associated with an opposite proton transport and vice versa. In the new axiomatics, we clearly state that every energy exchange takes place in both directions. This is also true for this particular energy exchange at the quantum level. Here, it is important to observe that charge is a synonym for the *cross-sectional area* of the system - therefore positive and negative charges do not really exist. They are mathematical circumscriptions for the condition of constructive and destructive interference when applied to standing rotational waves (solitons, phonons, particles, etc.), and merely reflect the reciprocity of space and time (see vol. I & II).

The energy exchange through soliton triplets seems to be quite similar to that observed in superconductors. Experimental evidence confirms that the charge transfer in biological supramolecular structures may also be superconductive[18]. In this area, the application of the Law allowed a major theoretical breakthrough that also eliminates the shortcomings of the BCS theory. It will permit the construction of cheap and non-brittle superconductors that will work at normal temperature (see also footnote 17). This will revolutionize the economy and society and solve mankind's energy problem once and for all.

Finally, it should be observed that *positively charged groups* which are adjacent to the π-electron anion of a soliton triplet "**melt**" the midgaps and disrupt the propagation of the soliton in the protein. In this case, positively charged groups such as amino groups fulfil the condition of destructive interference with respect to the negatively charged, unpaired

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[18] Science, 1993, 262: 1025-1029.

electrons that are localized in the midgaps of the π-electron systems. This kind of energy interaction at the quantum level impedes the physiological function of any membrane or cytosolic FUEL.

We shall prove that the vast majority of drugs which are currently employed inhibit the propagation of solitons in membrane and cytosolic FUELs in this very way. **They carry at least one or more positively charged groups.** Their pharmacological effects - or more precisely, **adverse effects** - are based on this energy inhibition at the supramolecular level. This unphysiological interaction establishes the condition of destructive interference, which ultimately leads to cell lysis. For this reason such drugs are called "**cell-inhibiting**" (see chapter 2.1). When we say that cell-inhibiting drugs infringe upon the Law, we actually mean that they cause a dissipation of cells by destructive interference:

> **Every interaction that leads to destructive interference infringes upon the Law** - it diminishes the life of the system.

We shall show in chapter 2.9 that such drugs increase morbidity and mortality in chronically-ill patients when given over a long period of time or at high doses.

When the FUELs expel localized positive charges (protons) on the one side and electrons on the other side of the membrane, this affects the electric LRC of the cell. The function of each integral FUEL contributes to the electric LRC of the cell (U-subsets). The electric LRC of the cell is the aggregated product, the total set, that results from the function of all FUELs in the membrane. At the same time, the function of each particular FUEL is linked to the function of all other FUELs through the electric LRC. This is the principle of delocalized coupling, as first perceived in the chemiosmotic theory. For instance, a tiny modulation of the LRC_E caused by one FUEL may open many other membrane channels, conventionally called "voltage-gated channels", which, in turn, trigger a rapid (total) depolarisation of the cell. This outlook effects another great simplification in our understanding of biological regulation.

We have shown that electron transport in soliton triplets is always associated with an ionic transport, e.g. with an opposite proton transport. This phenomenon can be observed in all ion-channels. The channel may be ion-specific, depending on the tertiary structure of the α-helices in the membrane. The α-helices are assumed to form a *hydrophilic channel*

across the lipid bilayer that can be kinetically opened by the propagation of solitons along these α-helices. The hydrophilic faces of the α-helices are adjacent in the membrane and form a hydrophilic channel, or rather a hydrophilic milieu, in the hydrophobic lipid bilayer that surrounds the transmembrane part of the protein. The α-helices of all integral proteins expose their hydrophobic (lipophilic) sides to the lipid bilayer. This orientation is energetically driven (U-sets) and fulfils the condition of constructive interference. Since different ions have different sizes, the lumen of such channels can be ion-specific. This is, however, a mechanistic simplification of the real conditions in the membrane.

Activated soliton triplets in receptors are also involved in charge transfer. However, there is still no evidence that they function as direct ion-channels; most probably, they simply exchange electrons and protons through their soliton triplets. In this way they depolarize or repolarize the membrane gradient and open various *voltage-gated* channels. As these systems are U-sets, it is practically impossible to determine with current techniques the precise kind of ionic transport in each individual membrane FUEL under physiological conditions. This important fact should be taken into consideration when conventional papers on this issue are interpreted.

For instance, the propagation of solitons in ATPases leads to the separation of charges against their gradient. This active process is maintained by the continuous supply of ATP which is reversibly hydrolysed in this process. This is basically the function of soliton triplets and FUELs in the light of the General Theory. An extensive analysis of particular structures and functions was performed on the basis of numerous publications and confirmed the above elaboration. A detailed discussion of these results is beyond the scope of the present volume. Selected examples will be presented below.

1.5 THE UNIVERSAL LAW OF BIOLOGICAL REGULATION

Modern biological research has evolved around two major issues: the *biochemistry* of the metabolic web and *genetics*. Both have produced a number of concepts that hinder an understanding of biological regulation. Metabolic research has introduced the "*lock-and-key*" concept, later modified as the "*induced fit*". The extensive advocacy of this idea in

ligand-receptor binding studies and saturation kinetics studies leads to an erroneous interpretation of most of the experimental results in this field and should be eliminated from bio-science. Recall that all wrong ideas in science are of non-mathematical character.

Another popular concept in biology is the "*energy-rich*" ATP, considered to be the universal carrier of energy in cell metabolism. Although this concept is criticized from various conventional points of view, none of them has elucidated the simple fact that a single chemical compound cannot be a universal carrier of interconvertible energy *per se* that is immediately and universally accessible to all components of the cell, e.g. in rapid reactions to external stimuli.

Another flaw which can be summarized as the "*message notion*" has emerged from genetics. This flaw is further propagated as the "*first messenger*" and the "*second messenger*" concept. The "messenger" idea has been successfully inhibiting any progress in an understanding of cell regulation over the last 30-40 years. Since the main stream of biological research does not regard regulation in the context of self-organisation, various metaphysical concepts have been introduced, such as the "invisible hand" borrowed from economics (Adam Smith) or "Maxwell's devil" from physics. Recently, the "hypercycle" notion was put forward in the evolution theory of M. Eigen to explain the motive force of genetic evolution (see chapter 1.6).

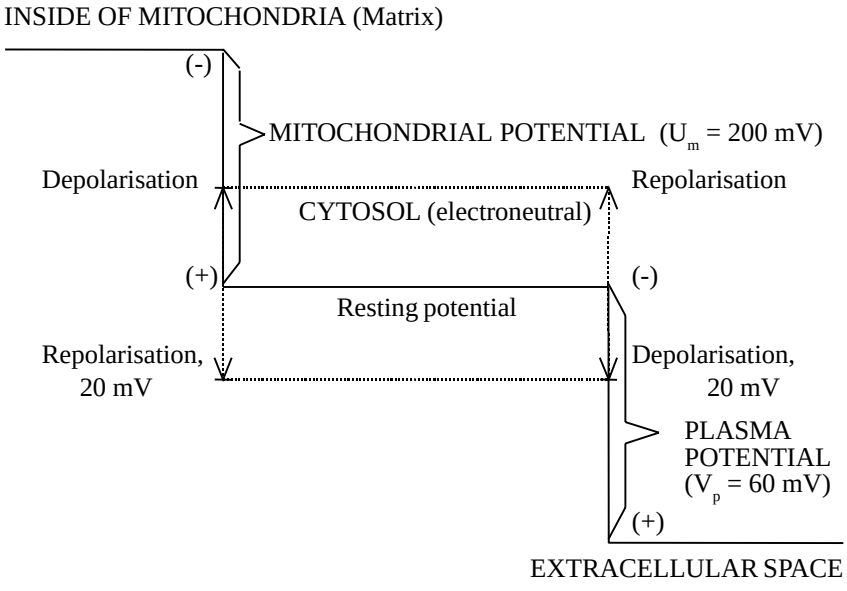
At this point, we shall summarize the core of The General Theory in the light of the Law - **the mechanism of dislocated energy coupling across two biological membranes in the cell.** This new interpretation of biological regulation rejects the aforementioned concepts as false ideas.

The energy used for cell metabolism and regulation is predominantly produced in mitochondria during OP. This pathway represents the final step of the metabolic redox cascade in the cell. The final products are electrons and protons, as summarized in the general equation of respiration (1). These ions are separated across the outer membrane of the mitochondrion to produce an electric LRC. The electrons are transferred by the π-electron systems of the prosthetic groups in the respiratory chain proteins. The electrons dwell in the "midgaps" of the π-electron systems and form a delocalized anion. When such electrons are transferred to an adjacent electron acceptor, the "midgaps" acquire positive charges, protons, which can now move along the π-electron system. In this respect,

H_2O should be regarded as the ultimate acceptor of protons produced by OP. During this charge transfer, protons are expelled from the matrix side (N-side) to the cytosolic side (P-side) of the mitochondrial membrane. The mitochondrial potential that is established by the proton extrusion drives the ATP synthesis in F_1/F_0.

It is a well established fact that all cells exhibit an electric gradient across the plasma membrane, ranging from 60 to 110 mV depending on the cell type. All plasma potentials are negatively charged inside and positively charged outside. Thus both the mitochondrial and plasma potentials have the same direction. The two membranes can be regarded as **serially coupled capacitors,** so that their potentials can be added (see Fig 3.). The gradients of other organelles are *serially* coupled to the plasma potential and are thus *parallel* to the mitochondrial potential.

Figure 3: Electromagnetic coupling via the cytosol between plasma potential and mitochondrial potential in the cell according to the principle of electroneutrality (membrane potentials as serial capacitors).



It is said that cell cytoplasm is subjected to the *principle of electroneutrality* - the distribution of charges is considered equal in the mean at any place in the cytoplasm. All electrophysiological considerations in biology depart from this principle (e.g. Nernst's equation). This principle is of statistical, abstract character and is of the same origin as the *cosmological principle*. Both are applications of the principle of last equivalence for the parts. The principle of electroneutrality is a mathematical definition by abstraction and does not exclude the existence of local charge disparities at the supramolecular level as observed in soliton triplets.

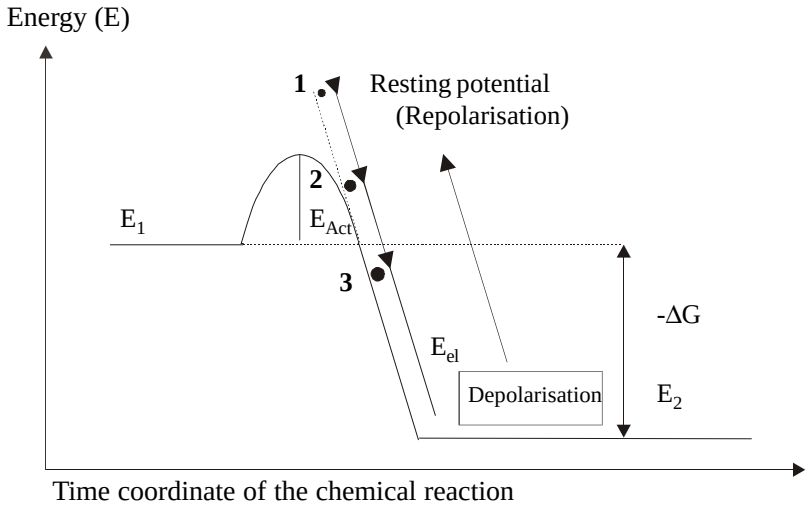
The principle of electroneutrality states that any macroscopic region of a solution must have an equal number of positive and negative charges. According to it, the charge on the mitochondrial P-side is identical to the charge on the negative cytosolic side of the cell membrane when both magnitudes are regarded as statistical mean values. We can regard the ionic cytosol as a conductor that connects the two serial membrane capacitors. Any depolarisation of the plasma potential leads to an increase in the positive charge on the cytosolic side. According to the principle of electroneutrality, the P-side of the mitochondrial membrane will also exhibit an equivalent and immediate increase in its positive charge when the cell is depolarized and vice versa. Both potentials are serially coupled by the electroneutral ionic cytosol that operates as a conductor between the two membrane potentials (for further details see physics).

Consider now a plasma potential of –60 mV (negative inside) as observed in leukocytes (see Fig. 3). A depolarisation of about 20 mV will lead to a new cell potential of –40 mV. In this case, the mitochondrial potential is simultaneously repolarized in the same order from the initial 200 mV to 220 mV. In terms of the chemiosmotic theory, any increase in the mitochondrial potential leads to an equivalent increase in the proton-motive force. This causes an increase in the production of ATP. The chemiosmotic theory assumes an equilibrium between the mitochondrial potential as represented by the proton-motive force (proton gradient) and the production of ATP on the one hand, and between these two magnitudes and the redox potential of the respiratory chain (OP) on the other. According to this theory, they are coupled in a delocalized manner. It is believed that this coupling is achieved by the proton-motive force. In fact, it is the result of the fluctuations in the mitochondrial potential that simply follow the de- and repolarisation pattern (action potentials) of the plasma potential, to which it is serially coupled. The action potentials of

the plasma membrane are triggered by external, extracellular factors, which we subsume under the term "**supracellular regulation**" (see below). This coupling is confirmed by numerous experiments.

It can be shown that ATP has a high affinity to F_1/F_0 and can be set free when a potential spans the mitochondrial membrane. An increase in the mitochondrial potential releases a greater amount of ATP, which is actively transported in the cytoplasm. This phenomenon sheds light on a very important aspect of biological regulation that is common to all FUELs. Figure 4 summarizes this aspect of energy exchange between the electric LRC and the biochemical reactions in the cell which are systems of the metabolic level. It is closely associated with the current energetic approach in chemistry and involves basic energy quantities, such as *activation energy* and the *free energy* of *exergonic* and *endergonic* (bio)chemical reactions. These terms can be derived from the primary term of space-time. Below, we shall present in a concise form the regulation of biochemical reactions in the cell by the electric LRC.

Figure 4: The regulation of biochemical exergonic reactions in the cell through the electric LRC (cell potential)



It is an established fact in chemistry that an exergonic reaction, during which a free energy, called *Gibb's energy* -ΔG, is set free, can only take place after the *activation energy* E_{Act} is circumvented by a supply of external energy. Under equilibrium conditions, the initial substrates do not usually react because they cannot overcome the energetic barrier described as an activation energy. The additional energy that should be supplied to initiate the chemical reaction must be at least equivalent to E_{Act}, whereby the kind of imported energy is of no importance. It can be thermal (heat), chemical (other coupled chemical reactions), mechanical (pressure), or electromagnetic (photon energy). This conventional presentation of the mechanism of chemical reactions is an application of the axiom of CAP.

Let us now assume that we have only two substances that participate in an exergonic reaction. This is an application of the axiom of reducibility for two chemical systems (U-sets). For this purpose we can select any redox reaction in the cell. As cell metabolism is essentially a redox cascade, any biochemical reaction in the cell will do. In chemistry, the two limbs of a redox reaction, called *reduction* and *oxydation*, are regarded as a particular (horizontal) energy exchange between two chemical systems that occurs in both directions under the condition of energy conservation. In biochemistry, it is assumed that cell metabolism is a cascade of coupled exergonic and endergonic reactions of the redox type, whereby one reaction supplies the necessary energy to overcome the activation energy of the next reaction coupled to it. In particular, ATP hydrolysis to ADP and P is considered the universal supplier of energy in the cell. The initial substrates are biochemical substances from food supply. The total free energy of the redox process is transformed during chemiosmosis into the electric energy of membrane potentials as specified above.

In this sense, the attributes "exergonic" and "endergonic" are relative terms, because any reaction can be exergonic and endergonic at the same time, depending on the system (reaction) of reference. This fact is not fully realized in biochemistry. Let us now demonstrate the logical fallacy of present biochemical thinking with a simple example - it is an application of *Hilbert's finite procedures* in mathematics, which are based on deductive logic. These procedures are, in turn, an application of the principle of circular argument, which is the only cognitive principle of science (see vol. I & II).

Conventionally, all metabolic pathways in the cell are regarded as *closed* cycles that are interrelated by feedback mechanisms. Cell metabolism is imagined as a closed loop, to which the law of conservation of

energy is applied. This is an intuitive perception of the closed character of space-time that is erroneously attributed to the parts, while the nature of the whole (space-time) is ignored. This is a principal flaw in science that has hindered the discovery of the Law. According to this view, the whole metabolic cascade would continue to operate for ever if only one exergonic reaction from the redox cascade received additional external energy to overcome its activation energy (see also the current concept of superconductivity in the BCS theory, vol. I & II). This exergonic reaction will then release sufficient free energy to drive the next coupled endergonic reaction and so on. In this context, ATP is regarded as the universal carrier of free energy in the metabolic web of the cell. This is the current explanatory principle in biochemistry. However, this approach contains a basic paradox that is closely associated with the one-sided perception of "growing entropy" in the second law of thermodynamics. This law is eliminated in the new axiomatics as an erroneous idea.

Suppose now, we have an organism that receives food supply. The energy it needs to maintain its existence is obtained from the degradation of food substrates, such as carbohydrates, fatty acids, and proteins. However, before the organism starts with the first redox reaction in the closed metabolic loop, it needs an artificial energy supply from outside to overcome the activation energy of the first metabolic reaction that will release the free energy which is necessary to trigger the redox cascade of cell metabolism. The choice of the first reaction is in this case arbitrary - in a closed loop, any reaction can assume the role of a first reaction. In other words, in any closed metabolism there is at least one reaction that cannot be energetically triggered by any other metabolic reaction, but rather needs an external supply of energy (1st conclusion). Where does this initial energy supply come from, given the theoretical presumption that food supply to the organism is unrestrained (which in fact it is not)? From God? The situation is additionally aggravated by the fact that any biological organism emits a vast portion of the gained metabolic energy as heat to the surroundings, which is irreversibly lost. This is the topic of the 2nd law of thermodynamics (see vol. I & II).

Surprisingly enough, the problem concerning the initial energy supply that "ignites" organic life is not of theological character, but of purely mathematical origin. It was astutely anticipated by *K. Goedel* in his famous theorem (1931), with which he challenged the validity of mathematics and threw this discipline into a *foundation crisis* that has lasted to the present day (see vol. I & II). Goedel proved that in any axiomatic

system of mathematics, e.g. in a mathematical algorithm, there is at least one statement (axiom) that cannot be derived from any other statement of the system by finite procedures (deductive logic), as was advocated by Hilbert in his programme on the axiomatization of mathematics. Therefore, in any mathematical system there is always one statement that is an "object of thought" (Dedekind), and cannot be verified by means of mathematics - it can only be proven in the real physical world (proof of existence), which is space-time (2nd conclusion). Observe the logical equivalence between the first and the second conclusion.

As this primary statement of the mind can be voluntarily defined, we always arrive at a basic paradox when we apply the principle of mathematical formalism advocating an inner consistency of any categorical system of the mind. This basic paradox is called *Russell's antinomy* and is embodied in the famous *continuum hypothesis* of mathematics. The chief conclusion from Goedel's theorem is that this hypothesis cannot be solved within mathematics, but only in the real physical world. This was achieved in the new physical axiomatics on the basis of the discovery of the Universal Law. The solution is extensively discussed in the first two volumes. The basis of this solution is that we must first define the nature of the primary term, which is energy = space-time (principle of last equivalence), and only then derive any other scientific term axiomatically from the primary term. For instance, all physical quantities can be derived from energy/space-time within mathematics and are thus abstract concepts (U-subsets) of the primary term. They are objects of thought. As already mentioned, the only operational principle for deriving new secondary terms or quantities from the primary term is the *principle of circular argument* (PCA). It is an application of the principle of last equivalence for the parts.

When we apply this principle to cell metabolism, which is a particular energy exchange in space-time, it postulates that we must first take into consideration the total energy exchange in the organism with respect to the surroundings (nutrition, thermal radiation), while the latter is a synonym for space-time, and only then describe any particular energy interaction in the cell. This is precisely what we did when we calculated the energy balance of the cell and the organism in chapter 1.2. Such a global approach should also include the intricate relationship between electric LRC and metabolic LRC in the cell, which is a manifestation of the reciprocity of space and time. Present-day biochemistry, however, completely ignores the role of stored electromagnetic energy across bio-

logical membranes. Paradoxically, this cognitive malaise is still not questioned, despite the fact that the existence of electromagnetic action potentials in cells is basic knowledge in any standard textbook on physiology, not to speak of such fundamental diagnostic procedures as ECG and EEC in medicine, which are simple macroscopic electromagnetic interactions at the organ level.

For this very reason present-day biochemistry cannot explain the *displacement of energy equilibrium* in all metabolic reactions in the cell. In organic matter there is a permanent supply of external energy to all biochemical reactions. This energy supply results in the biochemical reactions being far removed from the equilibrium point which is observed for the same reactions under normal physical conditions. Inorganic reactions are characterized by the existence of E_{Act}. The external energy supply in the cell is obviously much greater than the activation energy of metabolic reaction, so that all biochemical processes run spontaneously to minimal external stimuli.

The electric energy of the membrane potential LRC_E is precisely this external (superimposed) energy that displaces all biochemical reactions in the cell in a uniform manner away from the equilibrium point observed in inanimate matter. This energetic difference is precisely elaborated in volume I through the derivation of several new fundamental constants of the vertical energy exchange in the cell (see also discussion above). We shall now interpret this energetic difference between organic life and physical matter with respect to the modulation of biochemical reactions in the cell under the influence of the superimposed electric LRC.

As Figure 4 illustrates, the resting potential LRC_E is maximal during repolarisation. All reactions in the cell are in a state of extreme disequilibrium because they are subjected to the extremely high electric field E_{el} (acceleration) of the plasma resting potential that is imposed on the cell. Due to the existence of this superimposed electric LRC, the activation energy E_{Act} of metabolic reactions is completely repressed and is of no importance for the regulation. This follows from the axiom on the reciprocal behaviour of the LRCs of two contiguous levels in a system. As the magnitude of the resting potential (position 1) is much higher than E_{Act}, the biochemical reactions can commence spontaneously, as soon as the cell potential is depolarized and the disequilibrium point moves downslope (positions 2 and 3). Each biochemical reaction has a specific threshold of activation. The set point of each reaction is finely

tuned with the set points of all other reactions in the cell, no matter whether they are exergonic or endergonic (axiom of CAP).

This direct relationship between the magnitude of the electric LRC and the displacement of the energetic equilibrium in all biochemical reactions in the cell can be illustrated by the following fundamental evidence. When an electric potential *dP* in the order of the proton-motive force in mitochondria is generated across SMPs that carry F_1-ATP complex, the binding affinity of ATP to F_1 dramatically decreases. The *dissociation constant* K′ of ATP from F_1 is increased in the order of 10^7-10^8. Under equilibrium conditions ($dP = 0$), ATP is almost completely found in the bound form at the catalytic site of F_1. Within the new axiomatics, dissociation constants, such as those introduced in chemistry, are absolute constants of vertical energy exchange that can be obtained by the novel construction rule (see vol. II).

At the same time, we have calculated in chapter 1.2 that the *electric field* of the mitochondrial potential is in the order of $E_m = [1d\text{-}space\text{-}time]\ f = 11 \times 10^7\ [ms^{-2}]$. We can now define the electric field of inanimate matter which behaves as an electroneutral assembly as a reference system and assign it the primary number "1", as is done within the SI system of physics: $E_0 = [1d\text{-}space\text{-}time] = 1$. In this case, we obtain for the energy displacement in the mitochondrion the absolute constant of $K = E_m/E_0 = 10 \times 10^7$. This dimensionless constant is of the same magnitude as the dissociation constant of ATP from F_1. The ratio of ATP/ADP is generally regarded as paradigmatic for the displacement of all biochemical reactions in the cell. In fact, the magnitude of the dissociation constant K′ of ATP from F_1 merely reflects the superimposed electric LRC_E of the cell with an electric field of the same magnitude $K' = K = E_m/E_0 \cong 10^7$.

This is indeed a remarkable result; it proves that the electric LRC_E is responsible for the observed disequilibrium in all biochemical reactions in the cell. In addition, it reveals a basic fact in experimental research. As space-time is a closed entity, we can depart from any energy exchange and obtain the absolute constants of any other energy exchange. This was proven for all known natural constants in physics, which were derived from the mass and charge of the basic photon. In this process we demonstrated that photons also have a mass (energy relationship) and charge (cross-sectional area) and thus rejected a basic dogma in physics (see vol. I & II). In the present case, we can either depart from the dissociation constant of ATP from F_1 under *dP = proton-motive force* or from

the electric field of the mitochondrial potential to obtain the absolute constant of vertical energy exchange between the electric and metabolic level in the mitochondrion, which is in the order of 10^7-10^8.

As we see, the disequilibrium (LRC_c) of all metabolic processes in the cell is determined by the magnitude of the electric LRC that alters during an action potential. For instance, in the state of maximal depolarisation the reactions run at full pace and the free energy -ΔG released is maximal. This is also convincing proof that cell metabolism is stimulated during depolarisation and repressed during repolarisation. During the state of maximal repolarisation, the electric LRC is much higher than the activation energy E_{Act} and is orientated in the opposite direction (axiom on the reciprocal behaviour of the LRC of two contiguous levels). We say that the set point of cellular activation is higher under repolarisation - this inhibits the biochemical reactions in the cell in a global manner. This is actually the whole "shebang" of cellular regulation when the electric plasma potential is considered. However, a full comprehension of this intricate vertical and horizontal energy exchange in the cell seems to pose substantial difficulties to the traditionally trained biologist. The only adequate methodological approach to this aspect of high level abstraction is the consistent application of the three basic axioms of the new axiomatics.

From this elaboration, it becomes evident that an energy gradient is required at the plasma membrane to maintain all FUELs in their *proactive* state. Under this electric LRC, the FUELs assume a different energetic state from that observed under equilibrium conditions (LRC = 0). Their spatial configuration (tertiary and quaternary structure) is different from that of proteins under normal experimental conditions, which represent a state of energetic equilibrium. Recall that space is a constituent of space-time and behaves reciprocally to energy (see also theory of relativity in vol. I & II).

Whenever an electric gradient is spanned on proteins, they behave in a specific manner; they change their configuration and move with a specific velocity in the electric field[19]. For instance, the *electrophoresis* of

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[19] This behaviour is observed not only with proteins, but also with any kind of chemical substances. For instance, electrolysis, Hall effect, etc. are particular manifestations of the vertical energy exchange between electromagnetism (described as a field) and matter, the chemical level of which is a particular U-subset.

proteins is based on this interaction. The speed of displacement depends on the charge (cross-sectional area) Q = SP(A)[2*d-space*] of the proteins and determines the specific action potential, as presented in the new space-time symbolism E_A = SP(A)[2*d-space*] *f*. This vertical energy exchange between proteins which are systems of the biochemical level and the level of electromagnetism is broadly used in bio-science and medicine for experimental and diagnostic purposes. However, bio-scientists have absolutely no idea of what the biologically active configuration of the FUELs looks like in the powerful membrane potential, because this aspect has been overlooked.

The role of the electric LRC for the physiological function of integral and cytosolic proteins is beyond any doubt and can be easily demonstrated by the behaviour of ATP in the cell. For instance, the dissociation constant of the F_1-ATP complex is about 10^{-12} when no gradient is applied. Under equilibrium conditions, the F_1-ATP complex is almost completely in the bound form. When a gradient is generated across the mitochondrial membrane carrying the F_1-ATP complex, the binding affinity of ATP to F_1 dramatically decreases and ATP is released. Thus a transient repolarisation or depolarisation of the mitochondrial potential affects the biochemical (binding) properties of the transmembrane protein F_1 - and its *association kinetics* with ATP. This interaction is a chemical reaction. The dissociation of ATP from F_1 is finely tuned to the magnitude of the mitochondrial gradient. This phenomenon is quite common in applied electricity, for instance in the work of semiconductors, which can be "opened" when a threshold voltage is imposed on them.

At present, the biochemical reactions in the cell such as the association of ATP to F_1 are evaluated under the aspect of "Gibb's free energy of activation". It is the only epistemological principle employed in biochemistry today with which the regulation of cell metabolism is explained from an energetic point of view. This approach was initially applied to chemical reactions in inanimate matter that take place in a state of energetic equilibrium (no external electric LRC). However, it makes no sense to use the same approach in organic matter, where the FUELs operate under the direct impact of a powerful membrane LRC_E, which determines the chemical properties (e.g. affinity and dissociation kinetics) and the space structure of all cellular components.

This aspect of biological regulation has not been comprehended yet. It is central to our understanding of the biological regulation of cell metabolism in the light of the Law. The vertical energy exchange be-

tween the electric LRC and the chemical LRC of the cell can be precisely described by the axiom on the reciprocal behaviour of the LRCs of two contiguous levels in a system and by the axiom of CAP. We shall present this interaction once again in a more general way, so as to promote a better understanding of this central aspect of biological regulation.

During an action potential, the resting potential is depolarized and the magnitude of the electric LRC is diminished. According to the axiom of CAP, the electric energy that is set free during this period is completely transformed into the energy of the adjacent level; this means that the chemical LRC increases in the same amount. This is an aspect of the closed character of space-time, as manifested by the systems which are open. All known physical laws abide by this axiom and can be easily derived from the universal equation. The cell is a real system of space-time and can also be assessed by the two axioms. The electric LRC can be regarded as the stored energy that is immediately available to the cell for its regulation.

During the depolarisation phase, an ion-coupled symport of substrates takes place across the plasma membrane following the ion currents responsible for this depolarisation (for details see physiology). At the same time, when the electric LRC of the cell decreases, the cell receives a net supply of chemical energy (substrates) from the surroundings that boosts its metabolism. The final product of the metabolic redox cascade in the cell are protons and electrons, which are expelled across the mitochondrial membrane and establish an electric LRC that is serially coupled to the plasma membrane potential. During cell depolarisation, the mitochondrial LRC is repolarized in the same order and more ATP is released from F_1. We can therefore regard ATP as the final biochemical product of cell metabolism - it *reflects* the behaviour of the chemical LRC of the cell (U-set). We conclude:

> When the electric LRC (plasma potential) of the cell decreases, its chemical LRC (ATP production) increases.

This reciprocal behaviour of the two LRCs in the cell takes place through infinite intermediary steps of cell metabolism which are an object of study in biochemistry. As all metabolic pathways are U-subsets of space-time, they can be aggregated into these two levels. Thus the electric and chemical LRCs include the total metabolism of the cell, as was proven

by the energy balance calculation above. This is an application of the axiom of reducibility.

The axiom of CAP says that energy exchange occurs in both directions - that is, once the chemical LRC reaches its maximal value, it begins to diminish and the electric LRC begins to grow in a reciprocal manner. We shall now follow the principal steps of this reciprocal energy exchange in the cell. The increased production of ATP during depolarisation provides a net supply of ATP to the ATPases, e.g. to Na^+K^+-ATPase at the plasma membrane, that operate as ion-pumps. In the presence of more ATP, the ATPases begin to expel ions from the cytosol (predominantly Na^+, K^+, and Cl^- ions) against their gradient and to re-establish the plasma gradient. The observed repolarisation of the cell is the aggregated product of the pump-function of these integral FUELs. During this phase, the electric LRC of the cell continuously grows, until it reaches the maximal amplitude of the resting potential, while at the same time the chemical LRC continuously decreases - ATP is hydrolyzed by the ATPases and its concentration decreases in the cell.

These processes are well described in biochemistry and have now become amenable to consistent dynamic interpretation in the light of the Law. This cyclic energy exchange in the cell is manifested by the action potentials as observed in muscle cells and neurones, and can be documented by ECG and EEG charts. The same holds true for mesenchymal cells - however, the modulations of the plasma potentials in this type of cell are less pronounced. The transformation of electric energy into chemical energy and vice versa takes place about 100 000 times per day in the mean. In neurones, the frequency of energy exchange is about 1 000 000 times. These are the essentials of biological regulation within the General Theory. This pattern can be traced down to every particular subset of energy exchange in cell metabolism, respectively, in space-time.

The interaction (serial coupling) between the plasma potential, which is subjected to external regulation, and the mitochondrial potential, which is the final product of cell metabolism, is crucial because cell respiration, called oxydative phosphorylation, takes place in the mitochondrion. This is the energetic link which Nature has established between the environment and cell metabolism. The coupling between the two potentials is of **electromagnetic origin** and occurs with the speed of light. It can be described as a horizontal energy exchange between two electromagnetic systems - between two serially connected capacitors. This physical out-

look of cell regulation effects a great simplification in the bio-sciences. The actual energy exchange takes place at the quantum level and involves the numerous membrane and cytosolic FUELs which interact simultaneously with the electric LRC. They are elements of the chemical LRC of the cell.

Depolarisation and repolarisation of membrane gradients in the cell can be registered as electromagnetic oscillations, also called *weak radiations*. This effect was first measured by Russian biophysicists by using the method of *Kirlian photography*, and only later confirmed by western scientists. Fröhlich's excitations are based on this phenomenon. Although Kirlian radiation of the body is often interpreted in a rather metaphysical way, there is nothing extraordinary about this electromagnetic phenomenon triggered by cellular action potentials. It is of the same origin as EEG or ECG. It is the aggregated product of electromagnetic energy exchange at the cellular level.

1.5.1 Cell Metabolism is Regulated by Depolarisation and Repolarisation of Plasma Gradient

The above elaboration elucidates that the cell is regulated by recurrent depolarisation and repolarisation phases of plasma and intracellular potentials; the latter are serially coupled via the cytosol. As we can only measure the plasma potential, while the intracellular potentials are directly coupled to it, we shall only consider the plasma potential (U-subset) of the cell from now. These two potentials are the aggregated product of the function of all FUELs, such as ion-channels, ATPases, and receptors, that are expressed on cell membranes at any time.

The function of the FUELs is effected by soliton triplets at the supramolecular level. These quantum systems of space-time reveal a simple recurrent pattern of energetic structure and function. For didactic purposes, we may regard the cell as the macroscopic level of organic matter and the soliton triplets as the microscopic (quantum) level thereof. As space-time is closed, the infinitely small contains the infinitely great and vice versa (U-sets). This is an aspect of the reciprocity of space and time. This simple view of the physical world also holds for organic matter. It leads to the following axiomatic conclusions in bio-science and medicine:

The axiom of cell regulation:

Depolarisation and *repolarisation* of cells represent the **action potential** of energy exchange at the cellular level:

a) *Enhanced depolarisation* of plasma potential leads to cell stimulation, including increased metabolism, protein synthesis, cell growth, cell proliferation, lower degree of FUEL expression, etc.

b) *Enhanced repolarisation* of plasma potential leads to decreased metabolism, protein synthesis, cell maturation, cell differentiation, and prolonged expression of FUELs.

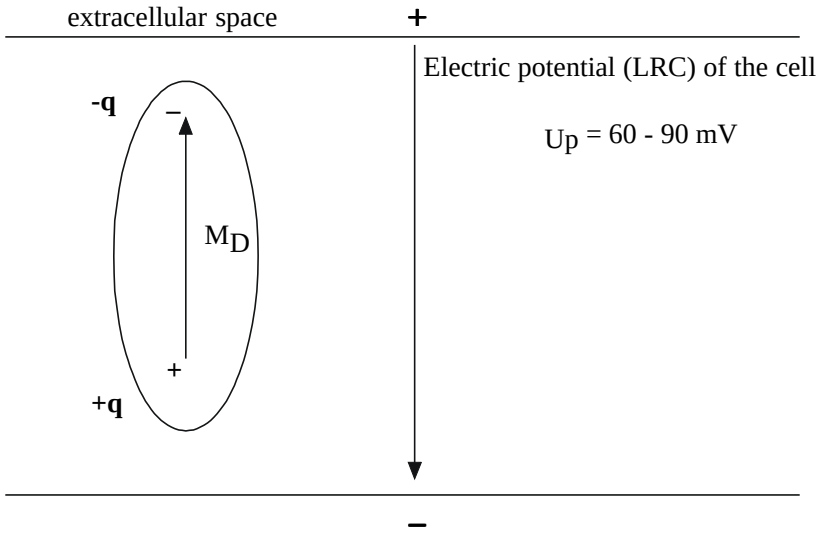
This axiom is confirmed by all experimental data in bio-science and medicine. There is no exception to this axiom. It is the fundamental axiom of the General Theory. We shall present some basic facts confirming its validity. All physiological factors, such as *hormones*, *neurotransmitters*, or *humoral* (*immune*) *factors*, are either **depolarizing** or **repolarizing** agents. They contribute to the generation of action potentials in the cell.

As cells are open systems, they interact with any chemical moiety that is introduced into the body either in the form of a nutritional component or a drug (see Fig. 5). All chemical substances that interact with the cell have a specific energy structure as determined by the *dipole moment* within electricity. The initial interaction between an extracellular compound and a cell occurs in the plasma membrane and involves integral FUELs. This interaction is immediately "sensed" by the electric LRC. Any external chemical moiety first comes in contact with the cell membrane and modulates its plasma gradient according to its dielectric properties. The degree of modulation depends on the *dipole moment* of the molecule. This interaction follows the axiom on the reciprocal behaviour of the LRCs of two contiguous levels.

The dipole moment can be determined from the supramolecular structure with the help of electromagnetic and quantum derivations of the universal equation (see vol. I & II). These mathematical applications of the Law are summarized in the "dipole model" - it is a simple mathematical and physical device that meets the modest needs of biochemistry and pharmacology. With this model, the pharmacological effects of any chemical compound can be precisely determined or predicted from its struc-

ture (see below). This application of the Law will revolutionize pharmacology and the pharmaceutical industry in the next few years.

Figure 5: Molecular dipole M_D in the membrane potential. The electric dipole moment of a chemical moiety builds an intrinsic gradient that is opposite to the plasma potential and diminishes its magnitude by the amount of the dipole energy (axiom on the reciprocity of the LRCs of two contiguous levels of a system).



When this model was applied to 4000 drugs (chemical entities) currently available on the market, it was found that the dielectric properties of most drugs enhance an **inhibition of the energy exchange in soliton triplets of transmembrane and cytosolic FUELs**. Therefore, they cause a global inhibition of cell metabolism. The pharmacological effect of such drugs is a global impairment of all cellular functions. The clinical manifestations during chronic treatment with cell-inhibiting drugs are:

> **Occurrence of various adverse effects, decrease in life-quality, increase in morbidity, and mortality.**

The toxicity of cell-inhibiting drugs is confirmed by many pivotal clinical trials that have been performed in the last few years. Until now their results could not be explained in an appropriate way because there was no general theory of biological regulation (see chapter 2.9). Most of these drugs are synthetically produced and are not of biological origin. We say that such drugs "infringe upon the Law" when they are applied to biological organisms.

From this we can conclude that modern pharmaceutical research, as it has evolved on a world-wide scale after the Second World War, has been essentially misguided by false theoretical presumptions. Due to the lack of a consistent theory of biological regulation, the international pharmaceutical industry has developed drugs on the basis of erroneous pharmacological models. Considering the deleterious effects of such drugs on millions of patients world-wide (premature death and high level of chronic morbidity of iatrogenic origin), this deplorable situation of imminent ethical significance should be immediately redressed.

As cell-inhibiting drugs do not show any significant therapeutical effects when they are evaluated by appropriate statistical methods (see chapter 2.9), this has prompted the search for new principles of pharmacological action. Recent developments in cell-stimulating drugs of biological origin, such as *interleukins, interferons*, etc., point in the right direction - the use of cell-stimulating drugs for therapy (for further details see chapters 2.7 and 2.8).

Cells are open systems. This means that there is a free supply of energy and substrates that flow in a co-ordinated manner in the cell during regulation. The energy exchange in the cell is effected by action potentials (modulations of LRC_E). As already mentioned, the supply of substrates follows exactly this principle. Depolarisation is mainly achieved by Na^+-influx and K^+-efflux, because these ions are essentially involved in the generation of plasma potentials in organic matter (see Nernst's equation). All animal cells exhibit Na^+-coupled import of amino acids and glucose[20]. Repolarisation goes hand in hand with the expression of proteins, some of which are secreted and participate as components in the supracellular regulation of the organism. *Hormones*, *neurotransmitters*, and *humoral factors* belong to this group. They are secreted in the interstitial fluid and become part of blood and lymph circulation.

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[20] Proton- and Cl^- coupled symports were also described; Nature, 1994, 368: 563-566.

As we see, the import of substrates into the cell and the export of regulatory factors from the cell is self-regulated and coupled to the depolarisation or repolarisation phases of the cellular action potential. Depolarisation leads to cell stimulation and enhanced metabolism, as a net supply of substrates is provided in the cell by Na^+-symport. During repolarisation, the opposite events are observed. At any time, there is an optimal synchronization between the degradation of electric energy associated with substrate supply on the one hand and metabolism on the other. This bioenergetic view of organic matter allows the establishment of a coherent theory of biological regulation. In order to demonstrate the qualitative leap of the new theoretical approach in terms of cognition, we shall introduce in a concise form the present bioenergetic approach to cell metabolism and then interpret it within the General Theory.

The present bioenergetic outlook is centred around *ATP balance* in the cell. The "energy charge" used in conventional bioenergetics was first employed by *Atkinson*; it is given as the *ATP/ADP ratio*, which is calculated to be 0.9 in the cell. Under normal conditions, that is, at energy equilibrium, the ratio of ATP/ADP is 4×10^{-8}. The substance is almost totally found in hydrolysed form as ADP. This means that the cell maintains an ATP/ADP ratio that is displaced from equilibrium in the order of 2.25×10^7. In the new axiomatics, this ratio is a natural dimensionless constant that assesses the horizontal energy exchange between the two chemical systems - ATP and ADP. It is of the same origin as the dissociation constant K′ of ATP from F_1, as presented above.

As anticipated, this natural constant corresponds perfectly to the magnitude of the mean plasma potential when it is calculated as an *electric field* $E_c = 4.5 \times 10^7$ [V/m] = [ms^{-2}] (9). In the new axiomatics, the electric field is a synonym for acceleration in electromagnetism E = a = [1*d-space-time*] *f*. It is a U-subset of space-time defined within mathematics. In the view of classical mechanics, acceleration determines the force $F = ma$ (Newton's second law) and energy (work) $E = Fs = sma =$ = SP(A)[2*d-space-time*]. This also holds for the electric field. Within mathematics, this quantity can be expressed as a dimensionless constant of energy exchange when it is given as a quotient to the reference electric field of inanimate matter $E_0 = 1$ (see above). These correct mathematical operations are subsumed under the fundamental cognitive concept of the new axiomatics, called "degree of mathematical freedom" (see vol. I & II).

Thus the ATP/ADP ratio as measured in cells gives the actual magnitude of the electric LRC. This result is consistent with our axiomatic conclusion that this ratio is indicative for the displacement of the chemical LRC from equilibrium, as observed in inanimate matter. Being subjected to the electric LRC of the cell, the hydrolysis of ATP is also displaced in the order of 10^7-10^8 and is thus a mirror image of the magnitude of the cell membrane gradient. Both the electric and metabolic LRCs are equivalent in absolute terms (axiom of CAP), but opposite in their direction because they are U-sets (axiom of reciprocal LRCs of contiguous levels in a system). The ratio observed for ATP/ADP is shared by all other biochemical processes. This becomes obvious when we consider the fact that this nucleotide is involved in any major pathway in cell metabolism.

At present, it is believed that the ATP/ADP ratio is the primary event that determines the "disequilibrium" observed in biochemical reactions in the cell. In the light of the Law, this disequilibrium is the result of the electric LRC that encompasses all elements of the cells and determines their behaviour in a global manner[21].

Within the General Theory, ATP represents a common, incomplete *soliton triplet* that is part of most proteins. The adenosine ring builds a cyclic π-electron structure; the three negatively charged P-groups of this compound function as an electron donor. In this case, Mg^{2+}-ions, without which ATP-associated proteins cannot operate, act as an electron acceptor. Other ions may also behave as electron acceptors. The binding of ATP to proteins is reversible. ATP is hydrolysed to ADP and dissociates from the protein complex when the cell is activated, that is, when it is depolarized. The hydrolysis is accompanied by an electron and proton transfer within the ATP-protein complex. During this quantum process, a soliton occurs that induces conformational changes in proteins and triggers further biochemical and/or kinetic reactions (see below). A transient increase in the intracellular concentration of ADP and a decrease in ATP/ADP ratio is always observed during depolarisation when the cell is stimulated. During repolarisation, the ATP/ADP ratio is increased. The ATP synthesis or hydrolysis is thus driven by modulations of the electric LRC. The oscillations of the ATP/ADP ratio are synchronized to the

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[21] In this context, we use the word "disequilibrium" in the sense of a chemical gradient. In the new axiomatics, the term "disequilibrium" is critically reassessed in classical mechanics and is eliminated as a confusing pleonasm (see vol. I & II). As this term is quite common in chemistry, we still use it in this area.

action potentials, but are displaced in time. This is confirmed by numerous experiments. In terms of wave theory, we say that they are "out of phase".

Every element in the cell is influenced by this regulation - it is moved or changed; at the same time it triggers further motion or conformational changes in adjacent elements. Every system of space-time is in motion and induces motion - motion is the only manifestation of space-time and is thus of closed character. This ubiquitous fact rejects the principle of causality, which is the current explanatory approach in the bio-sciences. The total set of motions in the cell is so complex that it makes no sense to describe every single event in a deterministic way as a causative chain (e.g. first and second messenger), as is done in present-day bio-sciences. This leads to a deadlock. We should bear in mind that any effect is a result of energy exchange, which is open and is thus at once vertical and horizontal. This knowledge also rejects the principle of causality. In this context, we remind the reader that any particular energy exchange, respectively, motion, obeys the Universal Law.

Notwithstanding these principal considerations, we shall present some typical examples that illustrate the kinetics of cellular regulation. For instance, the action potentials are propagated as electromagnetic waves (oscillations) in the cell and influence the various processes in the nucleus and ER, such as DNA-replication, transcription, RNA synthesis, protein synthesis, targeting of proteins, and their expression, in a similar delocalized manner as that observed in the production of ATP in the mitochondrion. We shall discuss these complex processes on various occasions below so as to convince the reader that all phenomena of biological regulation, including all future data, can be succintly explained in the utmost detail. These epistemological breakthroughs in bio-science and medicine establish the edifice of the General Theory.

The present deterministic approach in these disciplines departs from the principle of causality, which is rejected in the new axiomatics (space-time is closed)[22]. The search for a "full cause for a full event" has predetermined the fallacy of the bio-sciences in explaining biological regulation. For instance, cell regulation is explained as a causative chain of

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[22] The principle of causality was rejected by many thinkers in the past, above all by Hume, the ardent protagonist of modern scientific empiricism. Paradoxically, this school of thought dwells on this very principle. This is, indeed, the most puzzling aspect of modern scientific outlook.

several “primary messengers” such as cAMP and a collection of “second messengers”, such as PIP_3-cascade, DAG, cAMP, etc. When these ideas are critically reassessed, it becomes evident that they cannot explain the global behaviour of the cell, and in particular, its global kinetic response to external signals, including the dynamic replication of DNA in the nucleus and the coding of vital proteins. The large body of awkward explanations and apparent inconsistencies which one regularly encounters in numerous publications on bio-research are overwhelming evidence for the cognitive deadlock in these disciplines. This should be cogent to any logically thinking specialist.

In the General Theory, the “messengers” are common substances or pathways in the metabolic web that are activated by the action potentials in the same way as any other metabolic process in the cell. Thus, the role of the messenger as a “carrier of information” is a subjective, one-sided anthropocentric interpretation, as the term “information” is a synonym for energy. In this respect, it is important to iterate a basic conclusion of the new axiomatics: space-time is termless. It is a privilege of the human mind to “populate” the physical world with scientific terms. When such terms are axiomatically derived from the primary term, they are always correct; when not, they are almost certainly erroneous ideas that should be excluded from science. This is a radical consequence of the Law when applied to any human intellectual endeavour and, in particular, to the historical heritage of collective human thinking in science.

To underline this fact, we shall present one single example of great cognitive and experimental relevance that illustrates the validity of the Law in cell regulation. In the new axiomatics, an action potential is defined as the amount of charge (cross-sectional area) that is transported per time in a conductor, whereby any system can play the role of a conductor: E_A = SP(A)[2*d-space*] *f*. This equation also holds for the cellular action potential. In this case, the (absolute) time *f* represents the frequency of the action potentials for each particular cell type. When a cell is excessively stimulated, it has only two possibilities to respond to this relative increase in energy exchange - either by augmenting time *f* (frequency of action potentials) or by increasing the cross-sectional area (charge) that is transported per time across biological membranes. For instance, in muscle cells *f* goes up under physical strain as measured by the increased pulse of the heart (chronotropy): $E_A \approx f$.

Cells can also adapt to an increased energy exchange by augmenting the surface (area) of their membranes, through which the ions of the

action potential are transported. This phenomenon is particularly pronounced in mitochondrial membranes, where the proton-motive gradient is responsible for the production of ATP. When cells are excessively stimulated, they eventually need more ATP. Such cells exhibit a greater number of mitochondria and their membranes develop more cristae than usual. Muscle cells for instance are responsible for the contraction of the actin-myosin filaments. Physical work and any motion of the organism are based on this interaction at the quantum level. Muscle cells are thus highly stimulated body cells. For this reason they are formally stacked with mitochondria: the cross-sectional area/charge of the electric action potential is highly augmented in this histological cell type as $E_A \approx [2d\text{-}space]$, when f = cons.

An increase in the time f and cross-sectional area (= charge) of the system leads to an increase in its energy exchange. When cells are quiescent, that is, when their metabolic energy exchange is low, the opposite histological effects are observed. Quiescent cells such as mesenchymal cells have a few mitochondria and their cristae are less pronounced than those of muscle cells. These morphological findings can be microscopically demonstrated. There is no exception to this rule. They are powerful experimental evidence for the ubiquitous validity of the General Theory. For the first time in the history of the bio-sciences, we are in a position to explain any morphological feature in organic life in a consistent way in terms of energy function.

1.6 THE UNIVERSAL LAW IN THE EVOLUTION OF THE GENETIC CODE

The Law leads to a derivation, called the "Evolution Law". It says that the structural complexity K_s = SP(A)[2*d-space*] = *area* is proportional to the energy exchanged and grows with the square of conventional time $K_s = Et^2$. This equation is not a separate law, but an application of the universal equation from a static point of view (see vol. I & II). At present, the evolution of organic matter is closely linked to the development of the genetic code. The latter is, however, a particular structural complexity within the cell and not the origin thereof. For this reason we shall discuss this issue of central cognitive importance in the present chapter.

Organic life emerged from physical matter, but only after it was in a

position to establish and maintain a constant electric gradient at the cellular level. The cell with its electric LRC is thus a new level of matter; it differs from inorganic matter in its ability to respond to external stimuli and to behave in a co-ordinated kinetic manner. The response is *electrically* driven. The *neurones* and their *axons* form the nerves and can be regarded as electric wires. The same holds true for the central nervous system (CNS). The development of electric gradients and circuits is the actual prerequisite for the evolution of organic life from inorganic matter. The importance of the electric LRC can be substantiated by the fact that we are in a position to construct robots from inorganic matter, which are driven electrically and can imitate more or less adequately certain human movements. The difference between a robot and a human organism lies only in the higher degree of electromagnetic complexity of the latter. It is a quantitative difference which leads to a new quality. The underlying law is, however, the same - it is the Universal Law.

The structural complexity that evolved from the energy exchange between the electric level and the chemical level of the cell led to the evolution of the genetic code. In this respect, the genetic code is not a unique *a priori* structure from which organic life has evolved, as is generally believed today, but just a particular chemical system (U-subset) which is intrinsic to the structural complexity of the cell. It is a product of the electric LRC of the cell, or more precisely, of its vertical energy exchange with the chemical level of inorganic matter, as described by the Evolution Law: $K_s = Et^2$. This simple outlook eliminates most of the "shebang" surrounding biological evolution, e.g. the survival of the fittest, Eugen's supercycles, and such like, which one encounters in present-day literature.

In anticipation of the following discussion, we may be permitted to draw the reader's attention to a basic observation: the genetic code cannot operate apart from the cell; it is, so to say, "electromagnetically driven" within the cell. For instance, when DNA is mechanically manipulated by various biotechnologies, it has to be reinserted into the cell before it produces new "gene-technical" products. The genetic code cannot reproduce by itself - it cannot survive without the cell and its electric LRC. This clearly indicates the priority of the cell over DNA.

The occurrence of electric gradients in the early stages of biological evolution can be easily perceived and experimentally confirmed. Electric potentials can only occur across biological membranes, which are

lipid bilayers. Such bilayers consist essentially of phospholipids, saturated, and unsaturated fatty acids, and cholesterol, respectively, cholesterol derivatives. Due to their aliphatic character, phospholipids spontaneously join in aqueous solution and form lipid bilayers, also called "black membranes". This is the actual organic solution we find on the earth. Therefore, it is correct to assume that water is a prerequisite for the development of organic life. In the meantime, a lot of evidence has been accumulated that water and carbon dioxide, which are considered precursors of organic substances, are very common in the universe. This makes the existence of other non-aqueous forms of organic life in the universe quite improbable when the cosmological principle is applied. The occurrence of organic life everywhere in the universe is an axiomatic conclusion from the Universal Law postulating that all levels of space-time are of the "power of the continuum". This is also true for organic life and consciousness.

What were the probable pathways of biological evolution at the very beginning? To answer this question, we must depart from the energy exchange between matter and photon space-time which is central to the new axiomatics. The single fact of importance is that the initial energy interaction leading to the emergence of organic life was that between photons and chemical compounds. We find this kind of energy exchange in most primitive species, such as *archaeobacters* which are light-harvesting prokaryotes, as well as in plants living on *photosynthesis.* While *archaeobacters* are generally believed to be one of the most primitive species from which organic life emerged about 4.5 billion years ago, plants have enriched the atmosphere with oxygen through the process of photosynthesis. This energy exchange enabled the development of breathing organisms, while the evolution of the latter led to the emergence of human consciousness and science as a metaphysical manifestation thereof (space-time is closed). The stoichiometric equation of *photosynthesis*

$$12\ H_2O + 6\ CO_2 = C_6H_{12}O_6 + 6\ O_2 + 6\ H_2O$$

does not reveal the basic redox process - the cleavage of the water molecule into electrons and protons, which are then separated across the thylakoid membranes of plant cells in the same manner as in mitochondria to produce an electric gradient. This process was recently explained in detail (see the determination of P_{700} by Deisenhofer, Huber, and Michel, Nobel prize 1988).

In this context, it is important to observe that plant cells are eukaryotes, just like animal cells, and thus have common mechanisms of regulation. This is confirmed for the genetic code and the type of proteins involved in basic metabolic pathways. Their molecules are highly conservative and exhibit striking similarities in their amino acid sequences. In this respect, it is intriguing to speculate on the first steps of biological evolution. The discovery of the soliton triplets and their mechanism of action provides us with a clue.

The building of lipid bilayers in aqueous solution in the form of vesicles is a ubiquitous phenomenon that can be experimentally demonstrated. The first organic substances which are believed to have emerged from inorganic matter, when the results of Miller's experiment are taken into consideration, are aliphatic compounds that can spontaneously associate in aqueous solution to form such vesicles. This is, however, not sufficient for the emergence of organic life. To advance the evolution of these primitive vesicles into complex cells, it is necessary to establish an electric gradient across the lipid bilayer. Such a gradient can only emerge when an energy exchange between the lipids, being systems of organic matter, and photon space-time takes place.

We have already explained that all conjugated carbon chains, e.g. all unsaturated fatty acids, can form extended π-electron systems that interact with photons. This is the foundation of modern *photochemistry* that can also be applied to evolution. The underlying energy exchange in photosynthesis is the photon-electron-proton interaction, from which an electric LRC is generated in plant cells. The same holds true for *archaeobacters*, where a single proton-driving FUEL, bacteriorhodopsin, is sufficient to generate an electric gradient from photon energy. As we see, it is only necessary to take a fresh look at biological phenomena to recognize the intrinsic web of the Universal Law that links inorganic to organic matter.

We can now imagine that the first substances that carried π-electron systems were not very effective in transforming photon energy into electric energy, but that they were still in a position to separate charges on both sides of the lipid bilayer upon interaction with photons (as some crown substances do). Spontaneous discharges might have led to modulations of this primitive electric gradient. In the following, the number of light-harvesting molecules, such as carotenoids, retinal, vitamin A, etc., began to grow in the vesicles. These compounds were products of the first photochemically driven redox reactions of cell metabolism. This

process abided by the Evolution Law, which solves a growing structural complexity with the square of conventional time. With this growing structural diversity, the inorganic substances that were enclosed in the lipid vesicles began to evolve, predominantly by participating in redox processes, until they reached their present state of complexity. Evidence for this scenario can be deduced from the behaviour of the two basic groups of membrane components, the phospholipids of the lipid bilayer and the light-harvesting substances with extended π-electron systems. These compounds are amphipathic and avidly self-assemble in aqueous solution to form closed compartments. In addition, they are photochemically active and readily interact with photons from the visible light to form new compounds.

It is generally assumed that the *prebiotic* atmosphere on earth was quite similar to that assumed to exist on Venus; it contained plenty of water vapour (see also Oparin's theory on evolution). Light photons interacted with the prebiotic π-electron-carrying substances in the atmosphere to produce an electric gradient across the lipid bilayers of the first primitive vesicles. The synthesis of lipids and other π-electron-carrying molecules was the first prerequisite for the establishment of an electric LRC in inorganic matter that led to its gradual transformation into complex organic matter. The maintenance of an electric LRC at the vesicular level could only have been achieved by modulating it, that is, by establishing an effective energy exchange with the underlying chemical level (all systems and levels are open). In this way *nucleotides* were created within the lipid vesicles by *autocatalysis*. Following the Evolution Law, the nucleotides began to interact with each other and to acquire the complexity of the genetic code, as observed in DNA and RNA today. This process was driven by the energetic constraint of the electric LRC in prebiotic vesicles. The emergence of the genetic code cannot be separated from the emergence of proteins, which drive the genetic code as DNA-regulating proteins or as membrane FUELs via the electromagnetic waves of the plasma potential. This is a closed circle.

It is important to stress that the scenario proposed in this chapter does not set out to solve the question of which organic molecules were first synthesized, as was endeavoured in Miller's experiment, but only to unravel the Universal Law behind the evolution of organic life from inanimate matter. The conclusion from this survey is that both inorganic and organic matter obey the Law, so that there is no principal difference between the two levels of space-time. The actual energetic difference be-

tween the two levels is elaborated in the German volume I, p. 611, and will not be discussed any further here.

From this we conclude that the emergence of organic life on the earth was only possible in closed compartments formed by lipid compounds that carried π-electron prosthetic groups similar to *retinal* in bacteriorhodopsin or *tetrapyrroles* in chlorophyll. Probably less effective, these prototypes of present FUELs could transform photon energy into electric potentials by transporting electrons and protons across lipid membranes, as is accomplished by many *crown substances*, and establishing an adequate electromagnetic gradient inside the prebiotic vesicles.

The Universal Law repudiates the current concept postulating that the genetic code was the initial event that triggered biological evolution. This highly idealistic and deterministic view, propagated by most genetically orientated biologists, ignores the energetic background of organic matter. This erroneous outlook has led to the current deadlock in this discipline (see also discussion on AIDS).

The General Theory reveals the role of electric gradients across biological membranes as the driving force behind evolution. The complexity of the cells evolved under the **energetic constraint** of their electric LRC, that is to say, the cells evolved out of themselves, until they finally reached the necessary structural complexity to self-organize in multicellular organisms. This evolutionary process is ongoing. The development of consciousness at the level of *homo sapiens* and its active intervention in the mechanisms of the genetic code open a new era of rapid biochemical transformation with an open end - an infinite development or annihilation of organic matter on earth. In this sense, the discovery of the Law is a milestone in the biological evolution on earth and may contribute to the survival of mankind.

The Law is space-time and thus part of every system or level of space-time such as cells, organisms, and consciousness. This is the simple truth of Nature that eliminates the ridiculous religious idea of an omnipotent God dwelling outside space-time - the Creator of human and other beings (genesis). God is simply the “word”, Logos - the **primary term** of the new axiomatics - and man is the only demiurge of his own destiny. This is the principle of last equivalence applied to human mankind as a particular biological system of space-time. Religion(s) is thus part of the new axiomatics - a historical U-subset (precursor) thereof with no genuine scientific interest in comprehending Nature. Its destiny will be to

dissolve in the scientific monism of the Law and disappear as a distinct area of thinking.

This conclusion is extremely important, as it also challenges the theory of Darwin, which assumes that the environment is the external constraint of evolution. This concept is modified in the "hypercycle" theory of M. Eigen. Both concepts are essentially mistaken and unduly over-estimated. None of the current concepts on evolution explicitly emphasizes the importance of the energetic constraint of the electric LRC in the cell as the driving force of biological evolution. Scientists do not fully realize that evolution is an **energetically driven process** - that is, it is an aspect of energy exchange. Nor did they develop any ideas as to how this constraint actually operates at the cellular and biochemical level to explain the "evolution of species" in coalescence with the bulk of biological evidence[23]. This is a privilege of the General Theory.

This new approach to the genetic code allows a consistent interpretation of its function. This opens up some dazzling new perspectives. For the first time since the discovery of the genetic code we can read the DNA-syntax in a meaningful way and explain the role of mutations in cell metabolism. The General Theory also allows a consistent interpretation of all recent results in this field. For instance, there is growing experimental evidence that the nucleotide sequences of DNA and RNA exhibit complex soliton patterns[24]. Cell-inhibiting carcinogenic drugs seem to exert their effects on DNA and RNA by impairing the solitons of the genetic code[25].

The General Theory explains the structure and function of solitons participating in the regulation of the genetic code (see below). The role of *histones* and helix-loop-helix proteins in the regulation of DNA-cod-

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[23] Prigogine, for instance, introduces the term "internal constraint" for dissipative systems without appreciating their energetic character. He assumes that Darwin's idea of evolution as a product of adaptation to external constraints is a sufficient argument in support of the irreversibility of organic matter. In the so-called "Brusselator" model, the self-regulation of energy and supplies is not truly considered. The "chemical clocks" used in this model are kept working by an artificial supply of substrates.

[24] J. Biomed. Structure & Dynamics, 1988, 5 (No 4): 873-894; Bio Systems, 1993, 30: 31-48; Medical Hypothesis, 1993, 40: 326-328.

[25] Physiol. Chem Phys & Med, 1992, 24: 227-236; Molecular Basis of Cancer, 1985, ed. AR Liss, Inc. p. 343-356.

ing, especially, is elucidated in detail. The soliton-specific structures of these biochemical moieties abide by the Law. Further interactions within the genetic code are also suggested. It can be proven that regulation and mutations of the genetic code are energetically driven. Thus the General Theory rejects the "central dogma" in biology postulating that messages go from DNA and RNA to proteins, but never vice versa. This deterministic approach can no longer be sustained. The function of the genetic code and the electric LRC of the cell are involved in a recurrent input-output process with the surroundings, which is space-time and thus closed - hence the idea of energy conservation.

As we see, the operation of the genetic code depends on an intact energy exchange in the cell as manifested by the electric action potential. Numerous experiments confirm that prolonged stimulation through depolarisation enhances transcription, while prolonged repolarisation slows down or inhibits transcription. In reality, both states correspond to different sets of transcription patterns. Dissipation of the electric gradient stops transcription and causes cell death. Any inhibition of the vertical energy exchange between the electric and chemical levels creates a condition of destructive inteference in the cell and imposes a strong energetic constraint on the genetic code to counterbalance this impairment through mutation. This intrinsic matagenic property of the cell embodies **the energetic mechanism of transformation to cancer cells** (see chapter 2.3). The external sources of inhibition can be radiation, chemotherapy, the use of immunosuppressive drugs, or cytostatics (see chapter 2.9).

Cells with an impaired energy exchange mutate to produce abnormal quantities of *growth factors*, *proto-oncogenes*, or other FUELs that enhance an *autocrine stimulation*. Transformed cells (cancer cells) no longer depend on the supracellular regulation, but are *self-sufficient*. Cell transformation represents a qualitative jump to a new energetic level of cellular behaviour. Recall that all qualitative changes are energetic differences. Normally, the cell can compensate an impairment of energy exchange within a certain range, beyond which it changes profoundly (see chapter 2.3). Impaired energy exchange may proceed for a long time at the cellular level, but this change may not be perceived at the level of the organism where the diseases are manifested.

The time which has to elapse before two states in a dissipative system are perceived as being different is called *Ljapunov time*. Ljapunov time is a reciprocal quantity of time $\tau = 1/f$. This quantity can be employed to

explain the emergence of different species of common biological origin during evolution. It also plays a central role in the proper evaluation of clinical trials based on the primary endpoints, healing and mortality (see chapters 2.8 & 2.9). Both parameters assess the Ljapunov time, after which a profound change in energy exchange at the cellular level is manifested at the level of the organism. This is the basis of biological evolution.

PART 2

MEDICINE AND PHARMACOLOGY

PROPAEDEUTICS

In Part 2 we shall outline the basis of the General Theory in medicine and pharmacology. Special attention will be paid to the following major aspects:

a) For pharmacological and medical purposes, the so-called "**dipole model**" has been developed. It is based on the new theory of *electromagnetism* and *quantum mechanics*. This model can be presented in a simple way at the biochemical level, to serve the needs of bio-scientists. It can be used to explain and predict the mode of action of all pharmacological drugs and all physiological factors from their supramolecular structure. This model will replace the current heterogeneous and contradictory chemical models in pharmacology (chapter 2.1).
b) The regulation of the *endocrine*, *immune*, and *nervous systems* will be presented in the light of the Law. It will be shown that these three systems are U-subsets of organic matter (organic space-time) that cannot be separated in real terms, as is done in present-day medicine. This will be substantiated by some typical examples (chapter 2.2).
c) The **pathogenesis of cancer** and the role of the Law in the transformation of normal cells to carcinogenic cells will be elucidated in chapter 2.3.
d) The regulation of the immune system will be explained. Special emphasis will be put on the development of **self-tolerance** and **alloreactivity**. Many examples from recent biochemical research supporting the General Theory will be presented (chapter 2.4).

e) The **bioenergetic pathogenesis** of AIDS, rheumatoid arthritis (RA), multiple sclerosis (MS), Alzheimer's disease (AD), atherosclerosis (AS), which are paradigmatic for the pathogenesis of other chronic diseases, will be outlined (chapters 2.5 & 2.6).
f) The pharmacological profile of **Nystatin** (Nys), **Amphotericin B** (Amp), and the group of polyenes will be discussed in the light of the Law (chapter 2.7)
g) Current therapeutic approaches will be critically reassessed. Effective new strategies with cell-stimulating drugs will be suggested (chapters 2.7 & 2.8). Clinical evidence confirming in an irrevocable manner that **cell-inhibiting drugs increase mortality and morbidity in humans** will be presented (chapter 2.9)

2.1 THE DIPOLE MODEL

Current pharmacology consists of a heterogeneous collection of conflicting models which are incapable of explaining in a consistent and irrevocable manner even the most common pharmacological and clinical phenomena. This "state of the art" of clinical pharmacology becomes evident whenever any standard textbook on the subject is consulted. The specialized publications in this field are even more confusing.

The "dipole model" suggested in the General Theory is based on an evaluation of the *dipole moments* of individual chemical compounds in the powerful electromagnetic field of cellular potentials. For the purposes of pharmacology, the dipole moments of chemical substances can be easily described with conventional applications of the Universal Law in electricity, while the mathematical approach at the quantum level is less feasible for the purposes of biology, pharmacology, and medicine. For this reason I shall restrict myself in this survey to a purely descriptive presentation of the dipole model. In this sense, the dipole model of the General Theory is conceptually similar to the *covalent bonding* and *molecular orbit* in chemistry. Both concepts are simple geometric abstractions of complicated solutions of Schrödinger wave equation that fulfil the modest demands of chemistry. The underlying theory behind these metaphysical concepts is quantum mechanics, but this fact is usually ignored by chemists. In the following, the dipole model will be introduced with respect to the soliton triplet.

As already pointed out, all FUELs carry soliton triplet(s) in their transmembrane α-helices. In addition, they may exhibit soliton triplets at the extracellular binding site, e.g. in most immunoreceptors. The same holds true for cytosolic proteins that function as enzymes - they also carry soliton triplets at the active site. The soliton triplet consists of an electron donor, an electron acceptor, and an extended π-electron system that connects the two poles as a semiconductor. Thus the soliton triplet can be regarded as a classical dipole that is embedded in the supramolecular structure of proteins. The integral proteins can also be regarded as huge dipoles that consist of numerous smaller dipoles - the soliton triplets. This knowledge is of great importance when one considers the fact that these FUELs are subjected to the powerful electric field of membrane potentials. In addition, we encounter a variety of chemical substances in the body, or more precisely, in blood circulation and interstitial fluid, which are of non-proteinic origin but also exhibit more or less pronounced dipole moments and can interact with the soliton triplets of integral FUELs. This interaction is immediately sensed by the electric LRC, as all systems of the cell are U-sets that cannot be separated from each other in real terms - they exchange energy simultaneously.

Typical substances of this kind are *steroid hormones*, which are derivatives of cholesterol. We shall show below that cholesterol is the chief insulating molecule in the lipid bilayer and is responsible for the maintenance of the immense electric potentials observed at the small distance across the lipid bilayer of biological membranes. The dipole moments of steroid hormones vary substantially, depending on the lateral groups at the two endings of the cholesterol moiety, but their magnitude is always greater than that of cholesterol, which has virtually no dipole moment (see below).

Another typical non-proteinic group of physiological substances with a pronounced dipole moment consists of peripheral and central *neurotransmitters*, such as acetylcholin, dopamine, norepinephrine, epinephrine, etc. It is important to observe that the last three adrenergic catecholamines are synthesized from *tyrosine* (Tyr), which is one of the three hydrophobic amino acids with a cyclic aromatic ring; they participate in the formation of extended π-electron systems in soliton triplets. This example reveals the common energetic origin of neurotransmitters and transmembrane FUELs and confirms the new approach to evolution. We shall often come across similar common patterns that have remained unnoticed by biologists.

From these examples we learn that the pharmacological effects of all chemical moieties can be easily explained with the dipole model, as is illustrated in the case of steroid hormones and neurotransmitters. Some steroid hormones are also administered as drugs or contraceptives, however at higher doses than usually found in the organism. They exert pronounced clinical effects that can be explained with the dipole model in the context of cell regulation, that is, with the energy exchange between the electric and biochemical levels in the cell. This aspect of eminent medical importance is beyond the scope of this survey - it will be partially covered when steroid-associated disorders are discussed below.

According to the dipole model, adjacent **positively charged groups** of chemical moieties that interact with cell membranes and their FUELs may interfere with the wave function of the π-electrons in the soliton triplets of FUELs. They quench the "midgaps" occupied by unpaired electrons. The most common organic group that is positively charged is the amino group NH_3^+. Amino groups "melt" the "midgaps" of π-electron systems in soliton triplets and thus interrupt their energetic continuum. In the context of the dipole model, we say that the FUELs temporarily lose their dipole character (dipole moment) in the presence of NH_3^+-groups and become inactive. In terms of quantum mechanics, we say that their propensity to propagate solitons is impaired because the adjacent positively charged groups establish a destructive interference with the negatively charged "midgaps" and destroy them energetically.

At this point, we should recall that the terms "positive charges" and "negative charges" are mathematical circumlocutions for standing waves. When a positive and a negative charge interfere, they fulfil the condition of *destructive interference*, that is, the two standing waves are "out of phase" and destroy themselves upon *superposition.* This interpretation in terms of wave theory can be universally applied to all levels and systems of space-time, as is proven in the new axiomatics (see vol. I & II). It is of great cognitive and epistemological importance. An underlying discovery is that all systems are U-sets and contain themselves as an element. They can also be described as rotations that reflect the closed character of space-time. This is the maximal possible simplification that can be achieved in science. However, this approach demands a great deal of intellectual discipline, which is the basis of any logical (axiomatic) thinking.

Most drugs currently available on the market carry one or more positively charged amino groups and do not have any negatively charged groups or extended π-electron systems to counter-balance the former. Such drugs have a very weak or no dipole moment. When they associate with biological membranes, their positively charged amino groups interact with the π-electrons of the FUELs (weak forces) and inhibit their function. As these interactions are reversible, the FUELs can recover their dipole moment, i.e. their propensity to propagate solitons, as soon as they dissociate from the drug molecule. In most cases, the drug molecules are transported into the cell by endocytosis (or by active ionic symport), where they are either eliminated by biotransformation, e.g. in liver cells (hepatic clearance) or by renal tubulus cells (renal clearance). However, when such drugs are chronically applied, the function of the cell FUELs is continuously inhibited. This leads to a global impairment of the energy exchange in the cell. As cell performance is based on an intact energy exchange between the electric and metabolic levels, such drugs depress the function of the cells in a global manner. This energetic blockade results in various adverse effects, as may be observed in the case of virtually all drugs currently available on the market (see official drug information sheets).

Most drugs primarily exert their pharmacological effects in the plasma membrane. The same is true for most physiological factors. After cellular intake, drugs may also exert intracellular effects on DNA, RNA, and enzymes for a short period of time, before they are metabolized in the redox cascade. Since soliton triplets are found ubiquitously in DNA, RNA, enzymes, regulatory proteins, and other intracellular FUELs (e.g. in cytochromes), the intracellular mode of action of drugs is in principle equivalent to that observed in membranes (see below). In real terms, it is impossible to distinguish whether a drug exerts its action at the cell membrane or in the cell. The effect is always global and depends exclusively on the dipole moment of the molecule and not on the site of action. The cell itself is a unity and always responds in a global manner to external interaction.

According to the dipole model, all drugs and physiological factors can be characterized with respect to their dipole moment. From this, their principal mode of action is determined. The basic conclusions of the **dipole model** can be summarized as follows:

1. Drugs carrying *more than one amino group* (or other positively charged groups) and having no or a very *weak dipole moment* are defined as **cell-inhibitors**. There is no exception to this rule. We leave it to the competent reader to check this conclusion by himself. We proved this rule by analysing 4000 chemical entities used for therapeutic purposes. Such drugs interact with the FUELs and, depending on their dielectric properties, inhibit the soliton triplets to a greater or lesser extent. The FUELs are inactivated by this interaction and the energy exchange in the cell is inhibited in a global manner. The vast majority of current drugs belongs to this category. This includes all β-blocking agents, Ca-antagonists, antiarrhythmic drugs, anti-ulcer drugs, cytostatics, immunosuppressive drugs, antibiotics, etc. The names already suggest the cell-inhibiting properties of these drug groups. The putative specificity of such drugs, as propagated by their manufacturers in brochures and uncritically advocated by many pharmacologists, depends only on the types of FUELs expressed in each particular cell line and is merely a function of the threshold of activation of the individual cell (recall that all qualities are energetic differences).

The pharmacodynamic behaviour of drugs in the human organism is mainly determined by their concentration at the site of action. At sufficiently high concentrations, all cell-inhibiting drugs exhibit deleterious effects in all cell types and FUELs. Contrary to the general belief in pharmacology, such drugs are not specific. The specificity that is ascribed to these drugs is an artefact born in the realm of human (pharmacologist's) imagination - it is an athropocentric flaw with grievous consequences for the patient's life.

This flaw is introduced during clinical research in the following way: one of the deleterious cell-inhibiting effects of a drug is arbitrarily defined as a positive (intended) therapeutic effect due to wishful thinking. However, this hypothesis is not tested in long-term, double-blind, placebo controlled trials based on mortality, but in small non-controlled, short-term studies based on non-validated, surrogate endpoints. More than 90% of all registered drugs world-wide, especially those registered before 1985, are not proven for efficacy and safety to appropriate statistical standards.

This deficiency is known to all national and international registration authorities. For instance, the German registration authority demands from drug manufacturers further efficacy verification for more than 16 000 registered drugs (in reality, their number is much greater). This clearly

indicates that these drugs were not appropriately tested for efficacy and safety prior to registration. When this is done in an immaculate statistical manner after registration, one always finds that cell-inhibiting drugs, as defined by the dipole model, are deleterious to the organism when compared to placebo - they increase morbidity and mortality in humans and have no positive therapeutic effects on the disease for which they are registered (see examples in chapter 2.9).

2. Drugs having a *pronounced dipole moment* usually include an extended π-*electron system* and no more than one positively charged group (e.g. amino group) that is counter-balanced by a negatively charged group (e.g. carboxyl group). Such drugs are defined as "**cell-stimulating**". Chemical moieties with a pronounced dipole moment modulate the dielectric properties of biological membranes towards a greater permeability and trigger the propagation of solitons along the FUELs. The π-electron systems of cell-stimulating drugs either interact directly with the π-electron systems of the FUELs to enhance electron transfer, or do this indirectly by operating as autonomous depolarizing FUELs (see polyenes in chapter 2.7). Cell-stimulating compounds can either be depolarizing agents, such as Nys and Amp, or repolarizing agents, such as GABA and GABA-like drugs.

The overwhelming majority of *physiological factors* are **cell-stimulating**. Most of them are depolarizing agents. This includes all growth factors, insulin, most lymphokines, such as IFN-α, IFN-β, and IL-8. The rest are repolarizing agents. This group includes somatostatin, IL-1, TNF, and IFN-γ (for details see below). Depolarizing factors promote cell growth, proliferation, and protein synthesis. Repolarizing factors promote cell maturation, cell differentiation, and prolonged expression of FUELs. None of the physiological factors inhibits the FUELs by unspecifically quenching the "midgaps" of their delocalized π-electron systems, as is done by cell-inhibiting drugs. This would infringe upon the Law. Evolution is a prestabilized harmony of energy interaction, where only systems that comply with the condition of constructive interference "survive" - the rest is destroyed by destructive interference. This is the simple logic of space-time evolution.

The dipole moment of drugs can be easily calculated by applying the Law in electricity. When we apply this method to the two polyenes Amphotericin B (Amp) and Nystatin (Nys), we find that it is in excellent

agreement with experimental data. The **energy** of the **dipole moments** of Nys- and Amp-molecules in the electric plasma gradient of leukocytes are:

$$E_{nys} = 1.4 \times 10^{-19}\ [\mathrm{J} = \mathrm{m}^2\mathrm{s}^{-2}]$$

$$E_{amp} = 1.7 \times 10^{-19}\ [\mathrm{J} = \mathrm{m}^2\mathrm{s}^{-2}]$$

The dipole energy of Nys and Amp, or any other molecule, is opposite to the energy of the electric LRC (see Fig. 5). This follows from the axiom on the reciprocal behaviour of the LRCs of two contiguous levels. The electric gradient is diminished (depolarized) by the amount of the dipole energy of each molecule that interacts with the plasma membrane. The dipole energy of Amp is about 18% greater than that of Nys. This means that Amp is slightly more effective than Nys. This is consistent with the extensive experimental data which show that Amp is slightly more effective than Nys in stimulating eukaryotes or killing yeasts in vitro. Thus the calculation of dipole moments of structurally related drugs can provide valuable information not only on the principal character of their pharmacological effects, but also on their potency. This method can be further developed in quantum mechanics.

2.2 THE UNIVERSAL LAW IN HEALTH AND DISEASE

All physiological factors enhance energy exchange in eukaryotes, either as depolarizing or repolarizing agents. The three major regulatory systems, *immune, hormonal,* and *nervous* system, are defined as the level of **supracellular regulation:**

> The common mechanism of biological regulation through *hormones, humoral factors,* and *neurotransmitters* is the **modulation of the electric LRC** of cells. This is called "**supracellular regulation**".

Thus any physiological factor that belongs to one supracellular system is able to affect cells which are predominantly regulated by the agents of another supracellular system and vice versa. Indeed, there is growing evidence that humoral factors, e.g. cytokines and eicosanoids, stimulate

nerve cells in the CNS, and participate in the regulation of body temperature in hypothalamus[26], while hormones, e.g. anaesthetic steroids, can interfere with the peripheral neurotransmitter systems and modulate energy transduction in postsynaptical junctions. Neurotransmitters can affect the immune system and so on.

The "communication" between these systems is still a mystery, as the generally accepted "second messenger" concept does not provide for a common effector level of regulation (N-set). This stance in bio-science is in apparent contradiction with the growing experimental evidence of "common pathways of energy transduction"[27] in cells, as reported in many publications in the recent years. The interpretation of this data is entirely deterministic. The application of the Law to the energy exchange in the cell eliminates this conceptual deficiency. The new axiomatics postulates that all systems are U-sets that cannot be separated in real terms, but only in the mind by employing mathematics. While all physiological factors regulate the cell by the same Law, the three supracellular systems exhibit certain peculiarities in their self-organisation that should be described in the light of the new axiomatics.

The **nervous system** suggests a highly hierarchical and immobile structure. However, this hierarchy does not apply to the energetic organisation of the brain. The synaptic interactions between brain neurones are highly dynamic and depend on stimulation. This process is known as "connectionism" and plays a central role in the conceptual development of artificial intelligence. The establishment of new synapses between neurones is based on cell-stimulation through depolarisation (growth) and repolarisation (maturation). Whenever neuronal pathways are inhibited, for instance through injury or experimental dissection, an atrophy of the affected part of the nervous system and of the corresponding organ is observed. This finding fits in perfectly with the General Theory - the self-organisation of cells and organisms is energetically driven.

The peripheral innervation is essentially based on the depolarisation of neurones (afferent innervation) and target organ cells (efferent innervation) by peripheral neurotransmitters. GABA and other inhibitory (repolarizing) neurotransmitters are found in much higher concentrations

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[26] Adam D & Stankov G. Eur J Pediatr, 1994, 153: 392-402.

[27] This term has become quite popular in the bio-sciences in the last few years. Unfortunately, it is intuitively used and is not properly defined.

(more than 10 times) in the CNS (brain and postsynaptic membranes) than in the neural periphery. This can be explained by the self-organisation principle of the nervous system. Afferent information generated by depolarizing cell-stimulating agents in the periphery can be more adequately processed (modulated) by further repolarisation rather than by additional depolarisation. In this way a higher discrimination in the afferent information flow can be achieved. In addition to established central neurotrans-mitters, the depolarisation in the CNS may be triggered by a variety of biological molecules, such as amino acids, nitric oxide, or external factors.

Neurones exhibit the biggest energy exchange among all body cells. This is evident from the fact that, under oxygen deficiency, it is the brain which is damaged first. The greater the energy exchange of a system, the more rapid and pronounced the effects of its interaction with external factors. Anaesthesia or drug addiction is a typical aspect of the higher energetic turn-over in CNS. The same holds true for poisons, such as curare, that affect the peripheral nervous system. Curare is a generic name for a mixture of alkaloids used as poison arrows that cause a peripheral paralytic action at the junctions between nerves and muscles. Curare alkaloids usually carry two or more amino groups; tertiary groups increase the cell-inhibiting potential of these compounds. Curare primarily inhibits peripheral neuronal FUELs in the junctions, which are enhanced by the cell-stimulating peripheral neurotransmitter *acetylcholin*. This compound has a pronounced dipole moment, as can be perceived from its chemical formula when the dipole model is employed:

$$(CH)_3 - N^+CH_2 - CH_2O - (C = O)^{(-)} - CH_3$$

However, curare alkaloids inhibit not only nerves and muscle cells but also any kind of cells because they are potent cell-inhibiting drugs that interact with any membrane FUEL. They inhibit the soliton triplets by melting the midgaps of the π-electron anion with their positively charged amino groups.

The *classical antagonism* between *sympathicus* and *para-sympathicus* at the target organ, as is postulated for didactic purposes in pharmacological textbooks, appears to be a pure abstraction when the facts are scrutinized within the General Theory. This idea is based on the principle of causality. In reality, the notion of a biological antagonism is an intuitively correct perception of the axiom on the reciprocal behaviour

of the LRCs of two contiguous levels in a system. Depending on the target organ and the expression of specific FUELs in its cells, stimulation through depolarisation may be manifested as dilatation, relaxation, and increased secretion on the one hand, and as suppression, constriction, contraction, and decreased secretion on the other. Thus a particular regulatory effect of the supramolecular regulation depends on the initial energetic condition of the cells and the instantaneous composition of depolarizing and repolarizing agents at the site of action. Observe that all these physio-logical phenomena are circumscriptions of the reciprocity of space and time, or space and energy. We leave the detailed elaboration to the competent reader. At present, there is a profound confusion in this area - a typical example is Goodman & Gilman's The Pharmacological Basis of Therapeutics (latest edition). The new approach will allow a more clear-cut classification of the various effects triggered by innervation.

The **immune system** is a rather mobile system of cell-stimulation that is distributed all over the body. Like any other system of space-time, it is a U-set, that is, it contains all biological levels as an element. The energy interactions between immune cells and with the rest of the body cells are transmitted by *humoral factors*, also called *immune factors*. These factors are transported by blood circulation, but they also appear in a membrane-bound form. The mode of cell activation is an additive stimulation (potentiation) through depolarisation or repolarisation based on the principle of constructive interference at the chemical level in plasma and interstitium.

The peculiar situation in the humoral system is that immunocompetent cells are distributed throughout the whole organism or harboured in distinct lymphatic organs. This circumstance necessitates delocalized interactions. On the other hand, immune cells must be recruited in a quick and effective way at the site of infection. A quick response, known as "acute reaction", is achieved by superimposing the humoral activity of numerous immune cells that leads to a rapid potentiation of their effects. Immune cells secret humoral factors of the depolarizing and repolarizing type that exhibit overlapping pleotrophic effects. During the acute reaction, their concentration is increased a thousand-fold (10^4-10^5). This phenomenon is usually described as a "humoral cascade", which is a synonym for constructive interference at this particular level. The immune response at the chemical level is quite similar to the rapid depolarisation

of an electric action potential at the cellular level. Another term from wave theory that adequately describes this phenomenon is *resonance* (see vol. I & II).

The high mobility of immune cells is another specific aspect of this system. The motion of cells is usually referred to as "*migration*" or "*chemotaxis*". In the new axiomatics, motion is the only manifestation of space-time: it is equivalent to the primary term. So far, the mechanism of chemotaxis has not been unravelled. The greatest mystery of organic life - its "**intentional motion**" - can be explained for the first time in the light of the Law. The motion of immune cells to the site of infection is *energetically driven*. Many humoral factors that are secreted by immune cells are *chemotactic* agents, that is, they cause the cell to move (migrate) in the organism. Such factors are potent dielectrics that create an electrochemical potential in the body fluids, such as interstitium and plasma. This gradient drives the immune cells, which can be regarded as charge points (see Coulomb Law as an application of the Universal Law in vol. I & II), along its electromagnetic field (acceleration), which is a system of photon space-time. This energy interaction, defined as chemotaxis or migration, is very similar to *electrolysis* (see also Hall effect). The field of the supramolecular chemoattractants interacts with the electric LRCs of the immune cells and triggers their motion (migration). This particular energy exchange can be precisely described with the axiom of reducibility. The mechanism of motion at the cellular level is chiefly investigated in bacteria. As expected, it involves the proton-motive gradient across the bacterial membrane. In flagella bacteria such as *E. coli* or *S. typhimurium* the flagellas are driven by a proton gradient. This gradient causes the flagellas to rotate.

This kinetic mechanism is similar to that observed in actin-myosin interactions, which are driven by the action potentials of muscle cells. This energy interaction also involves the transformation of electric energy into mechanical work, and can be precisely described with the Law. Indeed, there is nothing remarkable about this energy exchange, that can be studied in any electric motor at the macroscopic level. The electrically driven flagellas rotate and push the bacterium forwards and backwards; myosin-actin filaments contract and induce a parallel translation. The proton (ionic) gradient of cells, bacteria, and other organisms interacts with the electrochemical gradient in the body fluid, which is essentially an electromagnetic interaction. Such interactions are always associated with motion (charge displacement), as postulated by all conven-

tional laws of electricity and magnetism, which are in turn precursors of Maxwell's four equations of electromagnetism. The latter are differential and integral derivations of the universal equation when it is presented as a classical wave function (see vol. I & II). Recall that all electromagnetic fields are photon systems (U-sets) that propagate infinitely in space-time and thus encompass the whole body (see also the electromagnetic principle of superposition in vol. I & II). For instance, the electromagnetic field of the heart can be measured as an ECG by using limb leads. This fact demonstrates how an electrochemical gradient in the body fluids drives the migration of immune cells throughout the whole organism.

This electrochemical gradient is established by the secretion of humoral factors in high concentration during the acute reaction. It points towards the site of infection because the largest number of secreting immune cells can be found in the vicinity of an inflammation. The electrochemical gradient in the fluid induces an electromagnetic field that can alter its direction. When this field is imposed on the electric LRC of immune cells, it can modulate the latter by influencing the velocity and direction of charge motion across their cell membranes. This energy interaction is described in physics as quantum Hall effect and can be expressed with the universal equation (see vol. I & II). This modulation determines the action potential and the direction of cell motion. Thus the migration of immune cells is an energetic process that involves all levels of organic matter. It can be precisely assessed at the level of electromagnetism.

For instance, the proton-driving pumps in bacteria are highly conservative proteins, and resemble those found in the respiratory chain in mitochondria. Both groups of proteins are related to the group of *cytochromes*, which are made responsible for the *oxydative burst* in lymphocytes. For this reason, it has been suggested that mitochondria were primitive prokaryotes that were incorporated by eukaryotes during the evolution of organic matter from monocellular to multicellular organisms. Hence our claim that prokaryotes and eukaryotes operate in symbiosis, that is, their serially coupled electric LRCs operate under the conditions of constructive interference, as transmitted by the ionic cytosol (see chapter 1.5). This straightforward energetic interpretation of the "intentional motion" of cells in the organism effects another significant simplification in our view of biological regulation.

All humoral factors are potent depolarizing or repolarizing substances. The functional antagonism that is attributed to the immune system is

thus an intuitive reflection of the reciprocal behaviour of its LRCs. We leave the detailed elaboration of this aspect to the reader (see above), helping him with the following suggestions and examples.

The various lymphocyte types and clones may express different FUELs and effector systems, e.g. various receptors of the IgG superfamily, cytochromes for oxydative burst, DNA-regulatory proteins, etc., in different quantities at the cell membrane. The initial energetic conditions are thus specific for each particular immune cell and line and this determines the kind of cellular response. For instance, a functional antagonism can be observed between some repolarizing cytokines such as IFN-γ that stimulate the maturation of immune cells and depolarizing cytokines such as IFN-α and IFN-β that stimulate cell proliferation. Some leukocytes produce more IFN-γ, others more IFN-α and IFN-β. The same functional antagonism can be observed in quiescent and stimulated (primed) polymorphonuclear lymphocytes, PMN. While the former respond to chemotactic stimuli, the latter are usually refractory to this kind of stimulation. Primed PMN are excessively depolarized, so that their electric gradient is too low to respond to the chemotactic, electrochemical gradient in the fluid. Thus the kind of cell regulation depends significantly on the initial energetic conditions of the individual body cell and these can vary infinitely.

The overall efficacy of the immune system depends on the efficacy of each individual cell (principle of superposition). The energy of each system is the U-set of the energy of all elements of the system (conservation of energy). Although this axiom sounds very simple, its practical consequences are not realized in immunology. The efficiency of each cell is determined by its propensity to exchange energy between the electric and the metabolic levels. This energy exchange is the aggregated product of the function of all FUELs in the cell. The efficiency of the individual cell is lowered when there is a functional impairment in one or more FUELs. These effects may add up (U-sets). We shall substantiate this with a key example based on recent experimental research.

It is established that certain alleles of the ubiquitous MHC molecules exhibit a functional deficiency that is associated with the development of various immunogenic diseases. Typically, these alleles involve amino acid sequences of soliton triplets, that is, they include point mutations of soli-ton-specific amino acids that are substituted by other amino acids. This leads to a disruption of the soliton triplets in MHC molecules and inhibits the occurrence of solitons in these FUELs. Such mutations cause

an energetic deficiency in the MHC molecules, which are ubiquitous integral proteins and are expressed in all body cells (HLA). The exact analysis of such genetic defects at the supramolecular level is rather comprehen-sive and time consuming. We shall present some typical cases in chapter 2.4.

This example illustrates the close interrelation between quantum effects in the cell and clinical symptoms in the patient. As all levels are open U-sets that interact, any functional impairment at the quantum level can be manifested as clinical symptoms at the level of the organism. In medicine, we usually see the clinical symptoms first and only then perform specific diagnostic procedures at the molecular level. If they are sophisticated enough, they may also include a partial genetic analysis (see Humphrey's case in chapter 2.9). There is growing evidence that most diseases are associated with *inherited* or *acquired genetic mutations*. We shall show that these defects always involve soliton triplets that indicate an impaired energy exchange at the quantum (supramolecular) level. Thus, future medical diagnostics should consistently analyse a disease from the quantum level to the level of the organism by following the Universal Law. This will dramatically improve our knowledge of the pathogenesis of diseases. This aspect will be covered in chapters 2.4 to 2.8. No doubt, this new trend will necessitate a profound new scientific education in medicine.

This is a fundamentally new approach that is being introduced for the first time in medicine and bio-science. It will revolutionize these disciplines and will enable the effective early treatment of many incurable chronic diseases. The rationale behind this approach is rather simple and straightforward. Energy exchange is discrete and occurs in constant quants (action potentials); these are specific for each level and system: $E = E_A f$, where $E_A = cons$. This is the basis of modern quantum mechanics (see Bohr model and de Broglie's wave-particle dualism). In bio-science, the discreteness of space-time is often circumscribed with the vague term "threshold". This word implies that an event (recall that all events are action potentials) can only occur when a certain threshold is reached. This kind of terminology obscures the scientific view of nature; it is discussed at this point with the sole objective of eradicating this idea from science.

The pathology of all chronic diseases (see examples below) begins with an *inborn genetic error* or *acquired deficiency*, most often caused by a spontaneous mutation at the quantum level. This defect is mani-

fested at the amino acid sequence level of the coded protein and usually involves soliton triplets. The site in the amino acid sequence pertaining to soliton triplets is the most important one for the function of the FUEL because it is responsible for the propagation of solitons along the supramolecular structure of the protein. Many of these defects can be compensated at the cellular level, so that they never become manifest at the level of the organism. However, when such genetic defects *aggregate*, they may lead to a manifest disease. For instance, an inapparent inborn error of the genetic code can be aggravated by environmental pollution or radiation leading to further spontaneous mutations. These acquired deficiencies may aggravate the energetic imbalance in the cell and cause an exacerbation of the disease, for instance the development of cancer.

The expression of the disease depends on the overall efficacy of the body cells. With ageing, the energy exchange in the body cells gradually decreases, so that inborn errors can no longer be compensated by further energetic mechanisms at the supramolecular level and the disease becomes manifest (long Ljapunov time[28]). Most chronic diseases in the elderly, such as diabetes, arteriosclerosis, etc., exhibit this kind of energetic pathogenesis. The most relevant mechanisms that lead to a gradual decrease in the energy exchange in the body cells and organism and cause chronical diseases will be elucidated below. This novel understanding of ageing will revolutionize our medical approach to this phenomenon and will contribute to a dramatic improvement in life expectancy in the elderly. This is a highly ethical perspective of the General Theory.

The discovery of the Law focuses on the fact that each system has a constant lifetime f (in the mean) and then dissipates under the condition of destructive interference; this condition can be precisely defined within mathematics (see vol. I & II). The human organism has an energetic peak between the second and the third decennium that gradually decreases until exitus. In the light of the Law, death is an energy exchange, in which the organism as an action potential is completely transformed into the action potentials of the underlying biophysical levels (axiom of CAP).

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[28] The long Ljapunov time of most diseases explains why it is very difficult to establish a correlation between radiation and an increase in cancer in exposed populations. In most epidemiological trials of this kind, the period of observation is much shorter than the Ljapunov time. This is a basic deficiency that should be eliminated in the future.

This outlook eliminates the whole religious "shebang" that has been obscuring the collective consciousness of mankind for centuries. The fundamental question that arises is how we can improve the "inner harmony" of energy exchange in the cell and prolong human life. This will be the topic of chapters 2.7 and 2.8.

Here we shall point out another principal flaw in medicine that vitiates the interpretation of basic immunological phenomena. At present, it is generally believed that a higher recruitment rate of immunocompetent cells (e.g. PMN) at the site of inflammation indicates a more potent reaction on the part of the organism. For this reason, allergic and other impaired immunogenic reactions are interpreted as "over-reactions" of the body that should be therapeutically inhibited. This a grievous mistake that is causing a lot of harm in present-day medicine. The most astounding fact is that this belief is rejected by the overwhelming experimental evidence. We must now correct this flaw if we want to stop the further iatrogenic murdering of patients by treating them with immunosuppressants (see chapter 2.9).

In the light of the Law, the more efficient the immune cells in terms of energy exchange, the fewer will be required to combat an infection, e.g. a bacterial infection. This axiomatic conclusion is confirmed by all the facts. *Sepsis* is associated with a higher number of PMN, while a benign outcome of a gastrointestinal infection (most lethal infections in ICU patients are of this kind) is associated with a lower number of recruited PMN. This phenomenon is also encountered in chronic diseases with an immunological involvement, where elevated counts of T- and B-cells are regularly found at the site of inflammation. It is a common error to interpret this histological finding as a sign of over-response, an over-reaction of the immune systems, that should be inhibited by immunosuppressive drugs. In fact, the reverse is true - such drugs only augment mortality in these patients (see chapter 2.9).

The immune response can be compared with a battle: the more efficient each soldier, the smaller the proportion of the army actively engaged in the battle, and the fewer the victims when the victory is won - this can be defined as the "Gulf war" phenomenon; sepsis is more like a "Pyrrhic victory". The explanation of this phenomenon is quite simple - it is based on the correct interpretation of the reciprocity of energy and space.

Let us assume that the energy exchange in the immune cells of a patient is reduced due a defect at the quantum level. In this case, the number

of immune cells involved in an inflammation should be larger than normal in order to compensate for this deficiency. Therefore: the lower the energy exchange (metabolism) of each individual cell, the greater the volume of immune cells necessary to combat the infection. Most immunogenic inflammations such as chronic polyarthritis are of this kind. This is the classical reciprocity of energy and space (volume). There are other equivalent interpretations of this phenomenon, which also depart from the axiom on the reciprocity of energy and space. We leave their elaboration to the reader.

Finally, the immune system is involved in the regeneration of the organism. All cells have a finite lifetime. This is true for all systems of space-time. It is estimated that each day about 3-5% of all body cells die and have to be restituted. The organism undergoes an incessant energy exchange, although it may not alter visibly. This aspect is generally ignored in medicine. The cell exchange in the body is effected by immune cells, which are actively involved in all kinds of *repair mechanisms*. The stimulation of cell growth, proliferation, maturation, and differentiation is accomplished by the excretion of the depolarizing and repolarizing agents of supracellular regulation. The high mobility of immune cells enables their presence at any site in the body. The renewal of body cells is exemplified by the immune system itself. Immune cells have a very short lifetime and the efficiency of the system depends decisively on cell proliferation in immunologically competent organs. Whenever this proliferation is impaired, the immune system is deficient and the organism tends to dissipate. The irreversible depletion of T4-cells in AIDS (acquired immune deficiency syndrome) leading to death is a typical example that will be discussed in detail in chapter 2.5.

The **hormone system** regulates cell metabolism and cell growth. This includes the regulation of substrate transport in and out of the cell, sexual activity, and *embryogenesis*. The hormone regulation is believed to be circular through feedback mechanisms (e.g. the hormone axis involving hypothalamus, hypophysis, and target organs), but this interpretation does not consider additional, cross-linked pathways of interaction with the other two supracellular systems. For instance, β-blocking agents affect predominantly adrenergic neuroreceptors, but they also induce impotence, which is considered a domain of steroid hormones. The steroid effects are exerted through the regulation of cholesterol homeostasis in biological membranes (see below), while the activity of membrane FUELs de-

pends on the lipid composition of the membrane and so on.

In the new axiomatics, we exclude all ideas that are N-sets. An N-set is the set of all sets that do not contain themselves as an element. The distinction between neural, immune, and hormone systems is such an abstract N-set. While this discrimination may be appropriate in terms of didactics, it is completely erroneous in terms of epistemology: it leads to a cognitive deadlock.

From this discussion we learn that an adequate cell function depends on the appropriate maintenance of energy exchange. This is the purpose of the supracellular regulation in any multicellular organism. We conclude:

> The energy exchange between the electric and metabolic levels is the U-set of all activities of all FUELs and other elements in the cell. The **supracellular regulation** is the aggregated product (U-set) of the energy exchange of all body cells.

Each cell type has a genetically pre-determined condominium of FUELs that is energetically regulated. The pluripotent cell from which the various cell types evolve contains all possible alternatives of energetic development. Its growth, proliferation, and differentiation is the result of the energetic evolution to which the foetus is subjected during embriogenesis. *Embriogenesis* is an accelerated version of the evolution of organic life on earth. The changing composition of the supracellular regulation in the female during pregnancy (e.g. peaks of sexual hormone levels) gives us a clue to the optimal concentration of the de- and repolarizing agents that belong to the three aforementioned systems. This is a highly complex optimization process, which can only be solved within mathematics by interdisciplinary research and the development of new types of computers in the future. The ultimate objective of this research will be the prolongation of human life.

A possible methodological approach to the evaluation of optimal supracellular regulation and the effects of externally induced energy interactions (drugs, radiation, etc.) can be borrowed from the theory of *social welfare function* in economics. The most difficult task in establishing the optimal policy of social welfare is to determine the personal betterment of all individuals. This presupposes interpersonal comparisons which

are impossible to obtain, as there is no way to judge objectively an improvement in the welfare of each individual. In biology, it is impossible to judge an optimal supracellular regulation, because at present there is no way of determining the optimal energy exchange for each individual cell. The **biological health function** is thus in principle identical to the social welfare function.

In economics, the problem is tackled by introducing the so-called *Pareto criterion.* It is a simple common sense idea stating that any change in social welfare policy that makes at least one individual better off and none worse off is an *improvement* in social welfare. A change that makes none better off and some worse off is a *worsening* of social welfare. In this concept, no statement is made concerning a change that makes some better off and others worse off, although this is what usually happens in reality. This does not mean that we are indifferent to a situation in which some are better off and some are worse off; we simply admit that we cannot make any judgement in this case.

Welfare judgements based on the above criterion are said to be *Paretian***.** A configuration of the economy such that nobody can be made better off without someone else being made worse off is said to be *Pareto-optimal*. The future task in medicine will be to determine and maintain Pareto-optimal energy exchange in the human organism in all phases of development and medical treatment. The approach should be essentially mathematical (stochastics, Markov's chains, optimization processing) by employing the Law.[29]

Present-day medicine is not in a position to give quantitative information on the energy exchange of each individual cell or tissue because this problem is not appreciated. At present, physicians judge an optimal supracellular regulation mainly on the basis of selected parameters that assess the energy exchange in an organ, tissue, or the whole organism. In

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[29] It can be shown that current mathematical approaches to solving complex optimization problems of practical relevance, such as the *travelling salesman problem* (TSP), depart intuitively from the Law and achieve much better and quicker results than standard procedures (Toleranzschwelle und Sintflut: Neue Ideen zur Optimierung, G. Dueck et all., Spectrum der Wiss., März 1994, 42-51). One can solve the problem in a simple way by applying the universal equation (under preparation for publication). This is the departing point for the development of a new applied mathematics based on the Law, which will be in a position to solve a variety of practical optimization problems of great relevance to society.

fact, physicians can rather subjectively discriminate between health and disease. The border between the two energetic states is voluntarily set, as is the case with the normal ranges of clinical parameters in internal medicine. The discrimination between these two states depends on the sophistication of the diagnostic method and the correct interpretation of the measured parameters. The latter is a basic problem in medicine. Almost none of the clinical parameters measured for diagnostic purposes in medicine at present are compared to primary endpoints, such as death (mortality), healing, or life-expectancy. This application of the principle of circular argument, being the only cognitive and operational principle in mathematics and science, is conventionally known as "validation of parameters". An appropriate judgement can only be based on validated endpoints. This circumstance explains why true judgements are rare in present-day medicine. From this it becomes evident that the more we know about the various integral proteins and their structure, the more exactly (or the earlier) we can discriminate between health and disease. The General Theory as outlined in this volume will be a *vademecum* in this respect (see examples below).

The supracellular regulation can be regarded as *optimal* in health. In the context of the social welfare function, the term optimal is reserved for a situation in which nobody can be made better off without someone else being made worse off. There is sufficient evidence that the supracellular regulation operates in an optimal way. The incessant turn-over of tissue cells indicates that at any point in time some cells are optimally stimulated, while others are less so and die (for further examples see chapter 2.4). This phenomenon is observed in any tissue or organ. From this we conclude that the supracellular regulation in health is *Pareto-optimal*.

The Pareto criterion is a valuable approach that can be employed in the evaluation of current therapeutic strategies. This can be illustrated by the following examples. A change in the supracellular regulation in which every individual cell could be made better off without considering whether every individual cell has been made so in fact is defined as *efficient* in the context of the Pareto criterion. A therapy with depolarizing cell-stimulating drugs such as Nys and Amp (see chapter 2.8) is thus considered efficient because all body cells are stimulated. The energy exchange is augmented in an overall manner in the organism. However, we cannot exclude the possibility that some cells are over-stimulated and die (by lysis), nor can we consider the fact that they might have died without this

therapy. The reason for this uncertainty is that we cannot make appropriate quantitative comparisons between the two states at this level of diagnostic sophistication. This situation will gradually change in the future. The two concepts "efficient" and "optimal" are related in the following way: an optimal situation is necessarily efficient, but an efficient situation is not necessarily optimal.

Chemotherapeutic drugs are potent cell-inhibiting drugs. They interrupt the energy exchange at the plasma membrane and in the cell and cause cell lysis. The idea behind chemotherapy is to inhibit the uncontrolled proliferation of cancer cells by accepting its deleterious effects on healthy cells in the body. The obligatory *alopecia* after chemotherapy is representative of the cell-inhibiting effects (inhibition of hair growth) of these drugs - hair cells represent a highly proliferative tissue that is the first to be damaged by cell-inhibition. As immune cells are also highly proliferative, this also holds true for this system. However, an immune deficiency always leads to morbidity and premature death, as exemplified by AIDS. Below, we shall present further clinical evidence that substantiates the deleterious effects of chemotherapy in patients.

When chemotherapy is applied, physicians intuitively speculate on the propensity of the healthy body cells to recover from the cell-inhibiting shock to which they are subjected during this kind of treatment. This *quasi* religious belief in the recuperative properties of the human organism is disastrous for the patient, as recent double-blind, placebo-controlled trials clearly indicate (see chapter 2.9). From an ethical point of view, this deplorable situation can only be excused by the uncertainty of the physicians concerning the consequences of their therapy. This uncertainty stems from the absence of an objective theory of biological regulation which medical doctors can consult. In this context, it is important to observe that until now it has not been statistically proven that chemotherapy prolongs life, whereas there are numerous results confirming that it significantly decreases life-quality by causing various severely adverse events. In addition, there is growing cumulative evidence that chemotherapy may decrease life-expectancy (see below). Thus the chemotherapeutic approach is neither based on any theory of regulation, nor does it consider experimental evidence.

For instance, it is a well known fact that chemotherapy increases the risk of mutation and cancer. The mechanism of mutation due to cell-inhibition can be precisely explained in the light of the Law. All chemotherapeutics carry one or more positively charged groups (mainly amino

groups) and have a very poor dipole moment. Such chemical moieties readily inhibit the soliton triplets in DNA, RNA, and the regulatory proteins of the genetic code and thus induce an impaired transcription that leads to point mutations. When these genetic defects involve soliton specific amino acids, they initiate the transformation of normal cells to cancer cells (see chapters 2.3 & 2.9). In the context of the Pareto criterion, chemotherapy leads to a **worsening** in the supracellular regulation.

2.3 THE PATHOGENESIS OF CANCER IN THE LIGHT OF THE LAW

The local-deterministic approach in medical research has prevented scientists from grasping the pathogenesis of cancer, chronic immunological diseases, viral infections, atherosclerosis, etc., and from developing effective therapies. This is deplorable when one considers the immense resources that have been allocated for this purpose during the last 50 years. The classical deterministic approach in the bio-sciences presupposes a full cause for a full event as reflected in the key-lock idea or the messenger concept. The principle of causality is not seriously challenged in experimental bio-research, although this principle was convincingly rejected by the most outstanding protagonist of empiricism - Hume - a long time ago. Therefore, it is not surprising that the regulation of cells poses insurmountable problems to both geneticists and cancer researchers, as illustrated by the following quotation:[30]

> "The striking feature is that the pathway (leading to transformation of cells) is activated by different means in each case (appropriate to the individual system) and it has different end effects in each system, but many of the intermediate components can be recognized as playing analogous roles. It is much as though Nature has developed a *signal transduction cascade* that can be employed *wholesale* by means of connecting the beginning to an appropriate effector. Several of the components of this pathway (in mammals) are proto-oncogenes, which suggests that the aberrant activation of this pathway at any stage has a powerful potential to cause tumours."

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[30] B. Lewin. "Genes V", Oxford University Press, 1994, p. 1210.

In this chapter, we shall only outline the basic mechanisms that lead to the development of cancer. A comprehensive survey including recent results in genetics, biochemistry, and medicine has been performed, but it is beyond the scope of this survey.

Cancer has four characteristic properties: a) it develops from a single transformed cell (*clonality*); b) cell stimulation, growth, and proliferation of the tumour cells elude the physiological supracellular regulation and are subjected to auto-stimulation (*autonomy*); c) there is no normal cell differentiation (*anaplasia*); d) the tumour cells can leave the cell, aggregate, and disseminate (*metastasis*).

The four characteristics of cancer can be explained by the Law in a consistent way. It is important to observe that at present there is no comprehensive theory which is capable of explaining the basic features of cancer on the basis of a single regulatory principle. The underlying energetic mechanism will now be briefly presented.

The transformation of normal cells into carcinogenic cells is always the result of a decreased energy exchange - due either to insufficient cell-stimulation by the supracellular regulation or to genetic deficiencies in the cell. Decreased cell-stimulation is usually *acquired*. For instance, environmental toxins such as nicotine, tar substances, asbestos, chronic therapy with cell-inhibiting substances such as cyclosporin, various other immunosuppressants, or radiation, are all highly carcinogenic (see chapter 2.9). These external factors interact with the body cells and inhibit the optimal energy exchange between the electric potential across the cell membrane and the biochemical metabolism in the cell.

The mechanism of inhibition can be explained very simply with the help of the dipole model. In the case of radiation (e.g. gamma radiation), high energy photons $E = hf = E_A f$ interact directly with the solitons of the genetic code and the corresponding regulatory FUELs. Such photons interfere (superimpose) with the electromagnetic waves of the cellular action potentials that are propagated in the cell and regulate the solitons in the DNA-RNA-regulatory protein-complex in a delocalized manner. When this non-physiological superposition of electromagnetic waves takes place under the condition of destructive interference, the gene transcription in the nucleus is profoundly impaired. Such wave interactions result in a higher entropy in the cells, that is, the energy of the thermodynamic, kinetic level of organic matter is increased. Traditionally, entropy is used as a synonym for “disorder”.

I have proved that the term “entropy” (S) is a synonym for the molecu-

lar action potential of the thermodynamic level $E_{A,thermo} = k_b = S$. An increase in the thermodynamic energy leads to an increase in the *degree of freedom* (Z) of the particles; the latter is a physical quantity of space. A higher entropy in the cell means that the average kinetic velocity $K_{(ave)}$ of biomolecules in the cell augments, as measured by the root mean square velocity v_{rms}. This quantity can also be measured by the mean free path λ of the particles. In this case, the "degree of freedom" is a circumscription of the mean free path $Z = \lambda$; the ratio Z_1/Z_2 gives the absolute time of this level, which is assessed by the temperature in thermodynamics $T = f = Z_1/Z_2 = [3d\text{-}space]_1/[3d\text{-}space]_2$. Exactly the same approach is used in Lorentz' theory of electric conductivity to assess the space-time of the electron level of matter. The relationship Z_1/Z_2 is conventionally employed in the probabilistic presentation of the second law of thermodynamics: $\Delta S = R/N_A \ln p = R/N_A \ln Z_1{:}Z_2 = 3/2 k_b T = E_A f$ ($k_b = E_{A,thermo} = Boltzmann\ constant$ and $T = f$), which is another mathematical iteration of Boltzmann's law (see vol. I & II). Before the discovery of the Law, the term "entropy" was interpreted as a quantity of disorder. In this sense, an increase in entropy can be interpreted as an increase in the disorder in the cell. However, we can no longer follow this line of argumentation, although it is an intuitively correct notion of the Law at the thermodynamic level.

The German volume I contains a consistent explanation of the role of thermodynamic energy in cell regulation (see pages 611-622). The basic difference between organic and inorganic matter lies in the existence of a powerful electric gradient (= energy) at the cellular level in the order of 10^{-14} J (10a). When the energy of the membrane gradient is compared with the energy of the electron (1.9×10^{-20} J), given as a charge e that interacts with this gradient $E = eU$ (axiom of reducibility), we obtain the absolute coefficient of energy exchange between these two levels. We also called it the **absolute electric constant of the cell $L_{E,cell}$**. It is in the order of $L_{E,cell} = 10^6$.

The energy of the electrons, as calculated from their root mean square velocity v_{rms} in Lorentz' theory, determines the *activation energy* that should be circumvented by the kinetic energy of the particles, as calculated from their v_{rms} in the *Boltzmann's distribution function*, before they undergo chemical reactions. This traditional interpretation is an application of the axiom of CAP for these two levels of matter. In the cell, the magnitude of the electron energy (1.9×10^{-20} J) is almost equivalent to the kinetic, thermodynamic energy of the biomolecules

$K_{(ave)} = 0.64 \times 10^{-20}$ (J) These absolute constants were derived for the first time as a consequence of the discovery of the Law. This led to the development of the so-called "*derivation rule*"; with this mathematical formalism we can derive infinite absolute constants of vertical energy exchange (see vol. II, chapter 7.9). The peculiar situation at the cellular level is that the energy of the plasma gradient is in the order of 10^6 greater than the kinetic, thermodynamic energy of the particles in the cell and thus almost equivalent to $L_{E,cell}$:

$$K_{e,t} = E_{el} / K_{(ave)} = 10^{-14} \text{ J} / 0.64 \times 10^{-20} \cong 10^6$$

In inorganic matter, on the other hand, there are no measurable electric gradients similar to those observed at the cellular level, unless they are artificially imposed by humans, e.g. electric potentials in wires. This didactic simplification excludes spontaneous discharges in the stratosphere or the existence of an electromagnetic field around each body in motion such as the earth. The composition and structure of most inorganic matter complies with the *principle of electroneutrality* - most chemical moieties interact according to this principle and form new electroneutral compounds. The two basic terms *molecular orbit* and *covalent bonding* reflect the principle of electroneutrality in inorganic matter. We leave the detailed elaboration of this aspect as an exercise for the reader. As previously stated, this principle is of abstract mathematical character.

Due to this energetic situation in inorganic matter, the absolute coefficient between the kinetic energy of particles and the energy of the electron level is in the order of 10^5 in favour of the kinetic energy:

$$L_{TE} = K_{(ave)} / E_{el} = 0.9 \times 10^5$$

As we see, we find exactly the reverse situation in inorganic matter compared to organic matter, which consists of the cellular level. In inorganic matter, the kinetic energy is much bigger than the electric energy of the particles that determines the activation energy of chemical reactions. In terms of conventional chemistry, the kinetic energy of the molecules is regarded as the driving force (energy) behind all chemical reactions. This prevailing mechanistic approach assumes that the molecules collide as a result of their kinetic energy and form chemical substances by surmounting the activation (repulsive) energy of the electrons. This aspect of chem-

istry is covered in the new axiomatics by the axiom of CAP (see vol. I & II).

The circumstance that the kinetic energy of the particles is usually much greater than the repulsive energy of the electrons in inorganic matter explains why most inorganic particles occur in the bound form as molecules. In the cell, the electric LRC is much greater than the kinetic energy of the biomolecules and thus dominates the kinetics of all metabolic interactions. The electric potential is the "long range correlation" that determines the pace of biochemical reactions in the cell in a global manner. During repolarisation, the electric LRC augments and the rate of chemical reactions decreases. In this phase the cell maturates and differentiates, as can be histologically observed. During depolarisation, the electric LRC diminishes, and the rate of chemical reactions increases. Depolarisation always leads to cell-stimulation and proliferation. This dynamic relationship reveals the reciprocal character of the LRCs of contiguous levels in a system. With the help of this axiom we can explain any energy interaction in a dynamic way. Hence its central didactic importance in the General Theory.

When the energy exchange between the electric LRC and the chemical LRC is inhibited, as is the case with carcinogenic compounds, this leads to a significant increase in the thermodynamic, kinetic energy in the cell. In this energetic state, the biochemical compounds interact in a random way (hence the term "degree of freedom") and not in the ordered way, as is the case under the condition of constructive interference, which is physiologically regulated by the cellular action potentials. This increases the rate of carcinogenic mutations (see below). This descriptive presentation for the sake of bio-scientists can be further formalized within mathematics and physics.

From this we conclude that the thermodynamic, kinetic energy is augmented in the cell when carcinogenic agents, such as radiation or cell-inhibiting compounds as found in tobacco smoke, impair the electric LRC and its energy exchange with the intracellular biochemical LRC. Tobacco smoke for instance contains about 6000 substances, many of which are highly carcinogenic. The substances with the highest carcinogenic potential can be determined by the dipole model. In the first place we have compounds that carry one or more positively charged amino groups and have a very weak dipole moment. These are: N-nitrosodiethylamine, N-nitrosodimethylamine, N-nitrosonanabasin, N-nitrosopiperidin, etc. Polycyclic aromatic hydrocarbons with extended α-electron struc-

tures, but without an electron donor and an electron acceptor, such as dibenz(a,h)anthracene, dibenz(a,j)anthracene, dibenz(c,g)carbazone, etc., are also highly carcinogenic.

As we see, the transformation of normal cells into cancer cells is always a result of an insufficient stimulation caused either by external factors (chemical carcinogens and radiation) or hereditary deficiencies in the genetic code. From this elaboration we can draw the following axiomatic conclusion on the **energetic pathomechanism of cancer development**:

> An *impairment of the energy exchange* between the electric and thermodynamic levels of the cell is the actual mechanism of **carcinogenic transformation**. It causes an increase in the thermodynamic LRC and a decrease in the electric LRC. This impairment is an energy interaction at the supramolecular level. It takes place under the condition of destructive interference and can be caused by numerous internal factors (e.g. genetic defects) or external procedures (e.g. treatment with cell-inhibiting drugs such as cytostatics and radiation).
>
> The development of *cancer cells* represents a compensational (evolutional) mechanism to this energy inhibition that allows the affected cells to survive: cancer cells are characterized by an excessive auto-stimulation through depolarisation, as caused by an over-production of growth factors or a transformation of proto-oncogenes into oncogenes. These mechanisms reverse the initial condition of destructive interference at the supramolecular and cellular level, but at the same time create a destructive interference at the level of the organism - e.g. the patient dies prematurely in a state of marasmus.

This is the simple energetic basis of cancer pathogenesis that will be substantiated by numerous facts in this volume. Many genetic defects that cause cancer have been elucidated in the last few years. We shall present some of the most common disorders below. The reason why normal cells transform into cancer cells can be explained for the first time in the General Theory. This is a major breakthrough considering the numerous cancer research centers world-wide that have failed to develop a

consistent theory of cancer pathogenesis. The transformation of normal cells into cancer cells abides by the Law. The underlying processes have been analysed in great detail. We shall present some insights into the ubiquitous validity of the General Theory.

Cancer cells are characterized by an over-production of growth factors and transformation of *proto-oncogenes* into *oncogenes*. These changes result from acquired mutations, although genetically inherited mutations may also contribute to cell transformation. Usually, more than a single, energetically caused modification of the cellular energy exchange is required before the cell transforms. Such mutations are the product of increased thermodynamic energy in the cell due to a reduced cell-stimulation, as outlined above. Mutations can occur in both directions - they can be energetically advantageous or deleterious to the cell. In the second case, the cell dies by lysis (dissipation). The over-production of growth factors or the transformation of proto-oncogenes into oncogenes represents a favourable mutation that improves the energy exchange in the cell which is initially inhibited. Most growth factors produced in great quantities by cancer cells are potent depolarizing agents. For this particular reason they carry the name “growth factors” - they stimulate cancer cells through depolarisation and thus trigger their excessive growth and proliferation. The excessive production of own growth factors improves the energy exchange of cancer cells to such an extent that they now become auto-sufficient: they can reproduce by themselves and no longer need the cooperative supracellular regulation of adjacent tissue cells. Cancer cells are, in contrast to normal cells, *immortal* in vitro, that is, they can reproduce infinite times in cell cultures. Thus two of the characteristics of cancer - *clonality* and *autonomy* - can be consistently explained with the new energetic approach of the General Theory.

The unrestrained self-stimulation of cancer cells by growth factors and oncogenes leads to an excessive depolarisation of their plasma gradient. This results in a reduced differentiation (recall that repolarisation leads to differentiation and maturation) and increases the endocytosis of integral proteins in such cells. **Endocytosis** is an important energetic process in the cell that is not well understood. In the light of the Law, we can give a simple and consistent explanation of this key process.

It is a well established fact that when membrane FUELs, for instance receptors expressed on the surface of immune cells, interact with humoral factors or antigens, they undergo conformational changes and dis-

appear from the membrane. This particular motion of membrane FUELs is circumscribed with the term "**endocytosis**". However, this vague term is not defined from a physical point of view.

In the General Theory, such conformational changes in proteins are explained with the occurrence of solitons in the soliton triplets of the FUELs. Solitons are propagated along the supramolecular structure of transmembrane proteins when the latter are activated by modulations in the electric LRC. Such interactions at the quantum level may open ion-channels for a short period of time, expel ions against their gradients in ATPases, or influence adjacent systems in receptors. In the course of these interactions, the integral FUELs acquire metastable configurations that allow them to leave the membrane and enter the cell along the electric LRC. This motion is called **endocytosis**.

Their exact destiny in the cell is not known at present. Some authors believe that integral proteins reappear on the membrane after some time, while others assume that they are metabolized. When the *targeting of proteins* is thoroughly scrutinized in the light of the Law, one soon comes to the conclusion that the second alternative is correct. We leave the elucidation of this key process in the cell to the competent reader and suggest that the reader follow the line of argumentation that will be presented in the following chapters.

The excessive auto-depolarisation of cancer cells by their own growth factors leads to an increased endocytosis that involves all transmembrane FUELs. This also holds for a group of important transmembrane proteins that form "**tight junctions**" between adjacent cells. Tight junctions are indispensable integral FUELs for the self-organisation of the tissue, which can be regarded as another level of organic matter. The role of the tight junctions is still not well understood. Notwithstanding this fact, there is growing evidence that cells connect their intrinsic *cytoskeleton* structures through tight junctions at long distances to form a specific tissue. The proteinic filaments of the multicellular cytoskeleton operate in the same way as any other biochemical structures in the cell: they carry soliton triplets and propagate solitons throughout the whole tissue along the tight junctions. This mechanism is very similar to the contraction and dilatation of actin-myosin filaments in muscle cells or the propagation of electric action potentials in neurones and synapses. This explains the intrinsic co-ordination of tissue cells.

Tight junctions are always expressed in normal cells. In cancer cells, the tight junctions are either not expressed, or appear to a much lesser

extent on the cell surface than in normal cells. The reason for this is that cancer cells are excessively depolarized, so that their tight junctions are incorporated into the cytosol by enhanced endocytosis. Cells without tight junctions lose their capacity to adhere to neighbouring cells (recall that motion is the only manifestation of energy) and to differentiate into specific tissue cells. This explains the state of anaplasia observed in cancer cells. Such energetically transformed, anaplastic cells readily leave the original tissue and cause metastases in the body. Thus the occurrence of metastases in poorly differentiated cells at distant sites - this riddle of cancer - finds a consistent explanation in the light of the Law. The same holds true for the other characteristics of cancer - clonality and autonomy; - they are further manifestations of the altered energetic state of transformed cells that is induced by quantum defects in the soliton triplets of common FUELs, such as growth factors and proto-oncogenes.

We can conclude that an excessive autocrine stimulation of cancer cells through depolarisation leads to an increased endocytosis of membrane FUELs, including the tight junctions. This altered energetic state determines the poor differentiation of tumour cells when compared to normal tissue cells. Cancer cells no longer follow the supracellular regulation; instead they can proliferate at distant sites by generating metastases. In terms of wave theory (cells are systems that produce action potentials which are electromagnetic waves), cancer cells evolve under the condition of destructive interference with respect to normal cells. The final outcome of this disruption of the prestabilized harmony in the organism is its ultimate dissipation, called “death”. Recall that all systems of space-time have a *finite* lifetime and dissipate under the condition of destructive interference.

It is, indeed, breathtaking to find all the problems associated with cancer solved by a single principle of energy exchange - the Universal Law. This also holds for the following common phenomenon in cancer cells. Due to their excessive auto-stimulation by growth factors, cancer cells proliferate at a higher rate than that of normal cells. However, the growth rate of cancer cells is often over-estimated. Most cancer cells do not grow much faster than normal cells, they just grow in an uncoordinated manner, that is, they do not obey the physiological supracellular regulation because they are energetically self-sufficient.

2.3.1 Current Treatment of Cancer

Principally, there are two possibilities of destroying cancer cells: by inhibiting the energy exchange between the electric and metabolic levels in the cell and enhancing **cell lysis;** by an excessive stimulation that causes their **apoptosis**. Both cell lysis and apoptosis are aspects of the same physical phenomenon - the artificial induction of destructive interference at the cellular level.

The first mechanism is the only one presently employed in cancer therapy. According to the dipole model, all *cytostatics* are potent cell-inhibiting substances - they cause lysis to both normal and cancer cells in an unspecific manner by dissipating their electric LRC. Since immune cells exhibit a high rate of proliferation, cytostatics preferentially depress the immune system. All cytostatic drugs are potent *immunosuppressants*. Unfortunately, the immune system is the strongest natural defence of the organism that impedes the occurrence and growth of cancer cells. Although this fact is deliberately ignored by most specialists (with the objective of promoting the sales of many cytostatics that were developed in the 70s and 80s), the eminent importance of an intact immune system for the inhibition of cancer growth is now generally recognized. The evidence is overwhelming. Paradoxically, this has not led to a withdrawal of cytostatics from the market. The reason for this ambiguity is the absence of a general theory of biological regulation and the inherent ethical inconsistency of present scientific bio-research, which is susceptible not only to the theoretical dogma of empiricism, but also to the pecuniary interests of the international pharmaceutical industry (see conclusions).

Immune cells impede cell transformation by destroying newly produced cancer cells. The physiological mechanism of cell destruction is **apoptosis.** Immune cells trigger the apoptosis of cancer cells either by *excessive depolarisation* or *excessive repolarisation*. The apoptosis can be mediated by humoral factors, e.g. by immunoglobulins of B-cells, or can be cell-mediated, e.g. by killer T cells (for further details see chapter 2.4). Both mechanisms trigger energetic modulations of the cellular action potential. It is an established fact that in every organism there is a baseline rate of transformation from normal cells into cancer cells, that is, every second the organism produces some cancer cells that have to be eliminated by the immune system. Therefore, an intact immune system is an indispensable prerequisite for the prevention of cancer growth and distribution (metastasis).

The correlation between an impaired immune function and the occurrence of cancer is confirmed by clinical evidence. Immunosuppression in transplanted patients causes a higher rate of cancer (50 to 100 times) than without it. Patients with hereditary immune deficiencies develop cancer much more frequently than healthy subjects. The same holds true in patients with acquired immune deficiencies such as AIDS or immunosuppression associated with radiation. Some outstanding recent clinical results will be presented in chapter 2.9. Their list can be extended *ad infinitum*. Nevertheless, cytostatic drugs and radiation are still the therapy of choice in the treatment of cancer.

This practice has grievous consequences for the patients. By employing cytostatics and radiation, physicians consciously accept the suppression of the natural immune defence in cancer patients as a severe, though "inevitable", adverse effect of the treatment. Quite apart from the fact that this common argument on behalf of this kind of cancer therapy is a logical blunder, it is also ethically deplorable, as the clinical outcome under cytostatic treatment and radiation does not support this medical strategy. Statistical meta-analysis of large cancer trials performed in the last few years do not confirm any positive effect of cytostatic drugs and radiation on long-term mortality. Instead, there is strong cumulative evidence that these treatments increase mortality when compared to "no treatment" (see chapter 2.9). Notwithstanding this powerful clinical evidence, cytostatics and radiation are still not seriously questioned by physicians.

2.3.2 New Treatment Strategies of Cancer According to the Law

The mechanism that is physiologically used by immune cells to destroy cancer cells is apoptosis. The same mechanism is also employed in the selection of immunocompetent cells in the organism (see chapter 2.4). Immune cells are regularly found in the vicinity of tumour cells. Some tumours are encapsulated by lymphocytes and grow slowly (non-invasive tumours). This is an energetic reaction on the part of the immune cells. The attraction of immune cells by tumour cells (migration) can be energetically explained. The mechanism is *chemotaxis* as discussed above. Immune cells produce lymphokines and other depolarizing or repolarizing agents at a high rate and thus trigger the apoptosis of cancer cells by

excessive de- or repolarisation. For this purpose they also employ cell-bound proteins, which interact with selected integral proteins of the cancer cells. For instance, killer T cells bind with their immunocompetent FUELs to the FUELs of cancer cells. This energetic interaction also triggers apoptosis. Since cancer cells are more stimulated than normal cells in adjacent tissues, the excess stimulation by immune cells results in a selective apoptosis of cancer cells.

From this we conclude that there is only one effective strategy in the treatment cancer that is predetermined by Nature - it is the energetic support of the immune system. At present, we are not in a position to eliminate cancer specifically by inducing in the organism a particular energetic condition of selective destructive interference to cancer cells only. This would presuppose that we can discriminate between the different energetic states of body cells. The solution to this problem is beyond the technical and theoretical potential of present-day medicine. In fact, physicians are light-years away from even grasping the problem. Therefore, future cancer research should focus on the solution of this central medical problem.

In the near future, any effective anticancer therapy will be mediated by the immune system, which has been specialized for this job throughout evolution. From an energetic point of view, the most feasible possibility of boosting the immune system is to use cell-stimulating drugs. Other energy interactions should also be considered. The new physical theory of the Law will be a *vademecum* in this respect. In chapter 2.7 we shall show that Nys and Amp are the most potent immunostimulators currently available on the market and are effective in the treatment of cancer patients. The therapeutic effects of depolarizing drugs in cancer and other common chronic diseases will be presented in chapter 2.8. Their mode of action can be summarized as follows:

1. Depolarizing agents stimulate the immune cells of the body and these destroy the cancer cells by apoptosis at a higher rate than would otherwise occur.

2. Such drugs directly depolarize cancer cells and destroy them by apoptosis. This effect can be observed in vitro. For instance, Nys and Amp are powerful ionophores and can depolarize any kind of cells. The rate of lysis is proportional to their concentration and incubation time. When given to cancer patients, Nys results in a remission and

encapsulation of liver and lung metastases. Presently, there is no drug available for the treatment of liver and lung metastases. This also holds true for any other mesenchymal organs, such as ovary and endometrium.

3. Depolarizing agents improve the supracellular regulation of healthy cells and inhibit their transformation into cancer cells. For instance, the cell-stimulating effect of polyenes decreases the risk of new metastases at distant sites.

4. The overall stimulation of energy exchange in the body improves the quality of life and life-expectancy. For instance, most cancer patients die from marasmus which can be counter-balanced by polyenes.

Cell-stimulating drugs should be given chronically in cancer patients both for therapy and early prophylaxis. However, they cannot eliminate large tumours. In this case, a combination with palliative surgery is recommended.

2.4 THE ENERGETIC REGULATION OF THE IMMUNE SYSTEM

The Law determines the regulation of the immune system. The specific functions of T and B lymphocytes, immunoglobulins, MHC molecules, receptors, and lymphokines, as well as their intricate interplay are energetically regulated. In this chapter we shall discuss the basic immunological interactions which lead to the development of the two manifest properties of this system: **self-tolerance** and **allo-reactivity**. We shall begin with the traditional views in immunology and show how they can be integrated into the General Theory. Further on, we shall present some basic examples that confirm the validity of the *soliton-triplet concept*. Without this idea it is impossible to understand the structure of the FUELs involved in immunological interactions and the regulation of this system at the cellular level.

2.4.1 Elements of the Immune System

The immune system has three fundamental aspects: *humoral immunity*, *cellular immunity*, and *secretion of proteins* (e.g. lymphokines) and other substances (e.g. eucosanoids) that act as humoral mediators between immune cells. The humoral immunity includes *immunoglobulins*, also called "*antibodies*", and the *complement cascade*. Immunoglobulins, complement, lymphokines, eicosanoids, and some additional physiological factors are called "*humoral factors*". According to the dipole model, they are cell-stimulating agents. In addition, there are many integral FUELs expressed on the plasma membrane of immune cells which are involved in specific immunological reactions such as *MHC molecules*, *T cell receptors*, etc. Their specific effects can be explained in the context of the Law.

Antibodies are said to have a high-binding affinity to specific antigens. Weak forces such as *hydrophobic forces*, *ionic forces*, and *van der Waals forces* are made responsible for these interactions. These forces are of electromagnetic origin and can be described by the application of the Law for electromagnetism. They can be regarded as distinct levels of matter that interact with the particles beneath. For this reason they cannot be disentangled from the underlying quantum processes. Only when we consider this vertical energy exchange can we explain the building of complex supramolecular structures and the occurrence of *solitons* at this level. In the light of the Law, **solitons are the action potentials of the supramolecular level of organic matter**. The amino acid sequences and steric structures of the FUELs involved in immunological reactions will be discussed in this context.

The site in an *antigen* which an antibody binds is called *determinant*. There may be many identical determinants in one antigen molecule that occur as repeated structures, e.g. in virus particles. In this case, the antigen is said to be *multivalent*. By attaching a small molecule onto the surface of a protein, a new determinant can be created, called a *hapten*. A specific antibody can be produced against this hapten. For instance, when dinitrophenol is incorporated into a protein, the antibody that reacts with the dinitrophenol-conjugated protein binds poorly a trinitrophenol-conjugated protein. This is interpreted as proof of the "specificity" of antibodies. On the other hand, there may be different antibodies that react with different determinants on the same antigen. For instance, there are *superantigens* that can activate various humoral or cellular antibod-

ies and cells. These facts demonstrate that the specificity of antibodies is rather "degenerated", that is to say, the interactions of antibodies with antigens are not specific, as is maintained in present-day immunology. The above examples illustrate that any deterministic interpretation in biology is an abstract and erroneous concept (N-set) of the real world. This is a basic motif of the current survey. A major objective of this chapter will be to correct such erroneous ideas in immunology. We begin with *immunoglobulins* because they are central to the view which prevails at present.

Immunoglobulins: All immunoglobulins (antibodies) have a *variable binding domain* and a constant *effector domain* that includes the transmembrane α-helices of the *light* (L) and *heavy* (H) *chains*. A specific set of effector domains is common to most antibodies, while a given binding domain is found only in a very small set of antibodies. The conservative transmembrane domain of immunoglobulins reflects its specific role in propagating solitons across the membrane. The amino acid sequences of this domain in immunoglobulins are similar to those of other humoral FUELs. We shall show that the variable domain of immunoglobulins also carries repeating sequences that participate in the building of soliton triplets.

The central problem of immunology is to explain the mechanisms of **self-tolerance** and **allo-reactivity** of the immune system, that is, its ability to respond to various foreign antigens, but not to the body's own biochemical structures. Both properties are regarded as intrinsic to the immune system. It is assumed that the system possesses a kind of memory stored in the immune cells that has evolved throughout evolution. Many haptens, against which antibodies are immediately built, are synthetic products of chemistry. However, during the long evolution of vertebrates no animal outside a laboratory has ever encountered a dinitrophenol-conjugated protein. How does the immune system develop the capacity of producing a specific antibody to an unknown antigen? The propensity of the immune system to meet unprecedented challenges is the greatest epistemological challenge to modern immunology, to which it has given no adequate answer.

The present dilemma of this discipline can be summarized as follows: although the immune system is a product of evolution, not all the genes that code specific antibodies could have been selected during evolution because not all the determinants recognized by antibodies could

have been previously encountered. This becomes cogent when one considers the numerous synthetic compounds that have been produced in the last fifty years.

Self-tolerance and allo-reactivity are not only restricted to antibodies - these phenomena also include T cell receptors, which are similar to immunoglobulins in their structure and function, and MHC molecules; the latter are central to the immune response. These FUELs are membrane-bound. Self-tolerance and allo-reactivity are thus properties of the whole immune system - they are manifested by all elements of the immune reaction (U-sets). Therefore, the central question which the General Theory has to solve is to explain the common mechanism leading to self-tolerance and allo-reactivity.

Traditional immunology has forwarded several partial explanations for this problem. Initially, the *instructive theory* was put forward with respect to the alleged "antibody specificity". It suggested that one antibody protein could be induced to fold in different ways by combining with the antigen as a structural template. Later on, this theory was disproved; subsequently, the *clonal selection theory* was introduced. The clonal selection theory, as put forward by *Niels Jerne* and *MacFarlane Burnet*, postulates that: 1) the organism continuously proliferates B lymphocytes that carry immunoglobulin molecules 2) all surface immunoglobulins on a cell have the same binding specificity 3) for any one antigenic determinant only a very small subset of the entire pool of B cells will carry surface antibodies that will bind. This means that a foreign antigen combines with a pre-existing immunoglobulin on the surface of a few B cells. The interaction between an antigen and an antibody on the B cell surface stimulates the B cell to proliferate and to produce daughter cells, which in turn synthesize and secrete an antigen-specific antibody. It is postulated that an antigen has the capacity to select from the B cell pool the one carrying an appropriate antibody.

Two different phases are distinguished in this theory: the *antigen-independent phase* and the *antigen-dependent phase*. Before any interaction between an antibody and an antigen takes place, a large number of B cells are produced. Each cell has a different antigen-binding specificity. In the antigen-dependent phase the cell is activated: it grows, proliferates, and excretes a specific antibody. At the same time, memory B cells are produced. The first response is dominated by the production of IgM, while the second response is dominated by IgG and to a lesser extent by IgA. The memory cells produce mainly IgG and IgA. During a second

encounter with an antigen, these cells respond much faster and effectively to the infection. These are the essentials of the clonal selection theory as generally accepted today. However, it does not solve the problem of the self-tolerance and allo-reactivity of the immune system.

There are at least three further hypotheses trying to explain the self-tolerance and allo-reactivity of T lymphocytes, but not of the whole immune system. It is believed that they describe three complementary mechanisms. Firstly, the hypothesis known as *clonal deletion* suggests that potentially allo-reactive T cells are eliminated from the repertoire in secondary lymphatic organs. Secondly, auto-reactive T cells can be present in the periphery, but they are rendered non-responsive (*clonal anergy* or *functional inactivation*). Thirdly, the function of autoreactive cells can be inhibited by other cells (*suppressor cells*). We shall show that these three hypotheses can be summarized under one single energetic mechanism of lymphocyte selection based on the Law.

T cells and their receptors: While B cells carry surface immunoglobulins and can be activated to secrete them as humoral FUELs, T lymphocytes carry membrane-bound T cell receptors (integral FUELs) and do not secrete antibodies in the serum. Essentially, there are two fundamental types of T cells: *cytotoxic T lymphocytes* (CTL), also known as *killer T cells* (*killer cells*), and *T helper lymphocytes* (*T helpers*). T lymphocytes carry specific membrane FUELs that are functionally involved in the immune response. CTLs carry predominantly CD8 surface protein, while T helpers express preferentially CD4. Killer cells and T helpers can be distinguished by these markers. In reality, these two types of T cells express various other FUELs, most of which await further elucidation. The division of T cells into subpopulations is based on qualitative parameters which are highly arbitrary. This common practice merely takes into consideration the different *initial* energetic conditions of the lymphocytes in each subpopulation; these differences determine the “specific” function of selected T cell lines. Each lymphocyte type carries a specific condominium of membrane FUELs, which are energetically selected during its cell growth and differentiation; they modulate the electric LRC of the lymphocyte in a specific manner. Recall that each particular quality which we attribute to a system of space-time represents a quantitative energetic difference, e.g. the colours of the visible light which we perceive as distinct qualities result from differences in the wave frequency.

Like immunoglobulins, T cell receptors are highly variable proteins

which are believed to be "antigen-specific". The antigen must be presented to the T cell receptor as part of a complex with a specific self-molecule, called *MHC class proteins* (see below). The CTL receptor recognizes the complex consisting of a self-MHC and a foreign antigen, but never the antigen alone. This phenomenon is central to the alleged specificity of T cell response. For this reason one usually speaks of "*MHC-restricted T cell response*". The underlying energetic mechanism has not been elucidated yet. Thus, T cell receptors are closely related to immunoglobulins with respect to their structure. However, they differ in the site of occurrence: while the T cell receptors are expressed on the cell surface of lymphocytes (integral FUELs), the antibodies exist in two forms: as cell-surface immunoglobulins (integral FUELs) and as soluble-secreted molecules (humoral FUELs).

Killer cells (CTLs) and T helpers carry the same family of receptors consisting of two chains which are very similar to those of immunoglobulins. This indicates a common mechanism of action of these FUELs. The chains of the most common receptors are designated as α and β; they are glycoproteins that consist of two domains, a *variable* and a *constant* one. Immunoglobulins are glycoproteins too. In fact, this is true for all proteins (see below). T cell receptors, MHC molecules, and membrane-bound immunoglobulins are integral FUELs that operate in the same energetic mode as discussed for ion-channels, ATPases, and other receptors: they modulate the membrane gradient and affect the energy exchange in the lymphocyte in a global manner. The membrane-bound FUELs of immune cells propagate solitons at the supramolecular level and undergo conformational changes upon activation. This energy exchange triggers further kinetic processes, such as endocytosis, migration, and gene coding (see below). The interactions between the immune cells are effected by these FUELs. For instance, T helper cells interact with B cells and stimulate them. As the immune system is open, the same FUELs are also involved in interactions with other cells in the organism. For instance, the T cell receptor on CTLs can bind foreign MHC molecules; in this way they kill foreign cells and reject grafts in transplantation patients (host-versus-graft reaction). Although CTLs are normally tolerant toward self-MHC molecules, they may interact with various body cells and destroy them by *apoptosis*.

MHC molecules: The *major histocompatibility complex* or MHC includes genes that code a large number of membrane FUELs; the latter

can trigger rejection of transplanted organs (foreign MHC as antigens). There are three classes of MHC. The first two are referred to as *MHC antigens* or **alloantigens** because they can be recognized by the immune system during rejection. One of the most important features of MHC molecules is their *polymorphism*. Within each class of molecules, even at one locus, a large collection of variants is present in the human population. Each individual expresses a specific MHC type (**HLA type**). It is important to observe that each individual has a restricted set of different MHC genes and can express a maximum of two alleles for each locus (a locus is a single gene coding for a single product that can be genetically separated from all neighbouring genes). This reflects the *structural conservatism* of these ubiquitous FUELs. We shall encounter the same motif in other FUELs. This is a consequence of the energetic function of integral FUELs which is effected by soliton triplets. A chief objective of this chapter will be to elucidate this particular mechanism of the immune system.

The MHC genes that encode targets for CTL recognition are called *MHC class* I *genes*, typified by genes called H-2D and H-2K. MHC class I molecules are two-chain FUELs that consist of one polymorphic component and one constant chain, called β_2-*microglobulin*. These MHC proteins are part of the *immunoglobulin gene superfamily* (*Ig superfamily*). The self-MHC and the foreign peptide must be jointly presented to the T cell receptor to activate it. The T cell receptor of T helpers interacts with *MHC class* II. Class II molecules are found on most cells, especially in macrophages and B lymphocytes. MHC molecules are involved in interactions between immunocompetent cells which initiate the immune response. In particular, they are required for the activation of T helpers. Cells expressing MHC with foreign antigens are called *antigen-presenting cells* (APC).

The third group, *MHC class* III *genes*, codes the *complement proteins*. According to the dipole model, these humoral FUELs are strong *ionophores*. They operate as potent depolarizing agents that induce rapid cell stimulation. When the *complement cascade* (MAC) is activated, it can lyse both foreign and own body cells. This is an immediate and nonspecific reaction of the immune system to foreign antigens.

MHC class I and II bind peptides that are cleaved from foreign proteins; however, they cannot bind entire proteins. MHC class I binds peptides from *intracellular* proteins, MHC class II peptides from *extracellular* proteins. The foreign proteins are first assimilated by APCs and

cleaved in their lysosomes. Some of the resulting peptides are attached to MHC class I or II and are jointly transported to the plasma membrane. Only peptides having an appropriate sequence, called *aggretope*, can bind a particular MHC. Therefore, any body cell can be antigen-presenting.

B and T cell interactions: Let us now summarize the key interactions in the immune response, as far as they are known today. The primary interaction is considered to be between an antigen and B lymphocyte that bears a specific surface antibody. However, this interaction can be substituted by any other interaction, such as between an antigen and a macrophage, a dendritic cell, or other APC. The cells can digest the antigen and express it in an MHC molecule as a membrane-bound antigen-MHC complex.

This elaboration, which can be found in various comprehensive textbooks on immunology, does not consider the role of the *complement system*. It is a well established fact that the classical and the phylogenetically older alternative pathway of the complement system can be activated *independently* in the presence of antibodies. The complement cascade enhances the formation of MAC and activates various immunological processes which include B and T cells. These processes are usually excluded from the discussion, because they do not fit in with the current hypotheses on the mechanism of immune reaction. This is a typical example of selective determinism in immunology.

The different immunological processes are regarded as closed systems - their energy exchange with other body systems is usually ignored. In reality, the immune system is open and interacts with all somatic cells, as well as with all foreign organisms, and compounds that enter the organism. In our calculation of the energy balance of the human organism we pointed out that the survival of the organism depends on an unrestrained energy exchange with the surroundings. The immune system, which is responsible for the regeneration of the organism, must be an open system that responds not only to foreign organisms; it also includes interactions with other body systems such as the hormonal and nervous systems. The importance of these interactions is regularly ignored in immunology. Therefore, the interactions discussed in this chapter should be regarded as representative for the numerous other energy exchanges of the immune system. They are paradigmatic with respect to the Law when the axiom of reducibility is applied.

When a single B lymphocyte matures to a virgin B cell, it leaves the bone marrow and enters the circulation, where it lives for a couple of days. During this time it can interact with an antigen through its surface antibodies. This kind of reaction triggers further growth and maturation of the B cell. The activation of B cells requires T helpers. T cells have receptors which bind different antigens from those which B cell antibodies bind. T cells bind peptides which are expressed on MHC molecules in macrophages and B lymphocytes. B cells can degrade a protein to peptides and express them in association with MHC class II. The MHC-mediated antigen binding to T cell receptors is rather complex: it involves CD4 and some additional membrane FUELs (U-sets). This finding has led to the introduction of the "*two signal theory*". The deterministic character of the approach remains invariant, independently of whether a single cause or more causes (signals) are considered. We have pointed out on many occasions that the principle of causality is an erroneous epistemological concept and should be eliminated from science. Only the global approach as embodied in the new axiomatics renders the correct explanation of any energetic interaction in space-time (see the axiom of reducibility).

During this interaction B lymphocytes and T cells are simultaneously activated. They can proliferate under this *autocrine* stimulation, for instance by producing IL-2, and generate a pool of receptor-specific T helpers. This activation takes place in close collaboration with the B cell. For instance, a dinitrophenol-specific B cell binds a dinitrophenol-conjugated protein, internalizes it by endocytosis, cleaves it during cell metabolism, and expresses its active peptides bound to MHC class II. The T helper recognizes the peptide (antigen) and associates with the peptide-MHC complex expressed on the B cell surface. This interaction activates the common complex (propagation of solitons) and triggers a depolarisation of the T helper. The T cell is stimulated by this interaction and produces an excess of lymphokines (humoral FUELs) and eicosanoids. The majority of lymphokines excreted by immune cells are of the depolarizing type (see below). The most common lymphokines are Il-2, Il-4, Il-5, and Il-6. The same holds true for the various eicosanoids when the dipole model is applied. This mixture of humoral factors enhances the growth and differentiation of B cells. The B lymphocyte is transformed into a blast and divides every 8 to 24 hours. From this we conclude that, when B cells and T helpers interact with an antigen, a reciprocal activation is enhanced which is mediated by the

secreted humoral factors from the two interacting cells (axiom of CAP).

2.4.2 Soliton Triplets in Immune FUELs

In this section we shall discuss the amino acid sequences of various immune proteins and their genetic coding in the light of the Law. We shall pay special attention to the formation of solition triplets and their role in the biological function of immune FUELs. Selected examples will be presented. We begin with immunoglobulins because they are best investigated.

Immunoglobulins: The amino acid sequences of the H- and L-chains of various immunoglobulins reveal that the N-terminal domains have variable structures, while the C-terminal domains are fairly constant. The variable domains of L- and H-chains interact to form a single functional unit. An antigen which contains a reactive chemical group establishes a covalent bond to the variable domain of the H- or L-chain. This shows that the variable domain is responsible for the antigen-binding. Antibodies of the same specificity are likely to have similar variable region sequences. Antibodies of different specificity exhibit different sequences. This fact confirms that the binding specificity of immunoglobulins is mainly determined by the amino acid sequences of the variable region. Both the L- and H-chains are needed for a specific antigen-binding. The two chains join to form a supramolecular complex, in which the two variable regions of the chains form a binding site. Most of the variable regions of the chains do not have any direct contact with the antigen; they interact with each other and establish a stable energetic structure of β-*pleated sheets* around the binding site. This construction is known as the "*immunoglobulin fold*". The three amino acid segments of the variable region that bind antigens are *loops* that extend from the immunoglobulin fold. X-ray analyses have revealed a variable pocket, called the "cleft", on the surface of the antibody formed by three short polypeptide segments from each chain. These three segments are called *complementary-determining regions*, CDRs. The amino acid sequences of the CDRs are much more variable than those of the rest of the region. For this reason they are also called a "hypervariable region". Thus the variable regions consist of two types of sequences: highly variable CDRs which are embedded in less variable *framework regions* (FR) that form

the immunoglobulin fold. The variable region of the immunoglobulin has 4 FRs and 3 CDRs (CDR1, CDR2, and CDR3).

The immunoglobulin binding region for the hapten *phosphoryline* (PC) has been examined with great precision in x-ray analysis. It uses mainly H-chain residues for the PC binding[31]. Amino acids that are in contact with the hapten PC are numbered so as to indicate their position in the chains. Each of these amino acids is part of one of the 3 CDRs which belong either to the L- or H-chain. In the case of PC, mainly CDRs from the H-chain are involved. They form a cleft, into which the hapten PC accommodates. We shall now analyse the amino acid residues involved in the construction of the cleft.

Based on the soliton triplet concept, we expect to find the following soliton-specific amino acid residues: a) the positively charged Arg and Lys as electron acceptors; b) the negatively charged Asp and Glu as electron donors; c) the aromatic lipophilic amino acids Phe, Tyr, and Trp which carry π-electron systems and act as conductors between the charged residues. We showed that the transmembrane part of the integral FUELs contains at least one soliton triplet which is responsible for the propagation of solitons across the membrane and the function of the FUELs. We shall now prove that soliton triplets are also involved in the antigen (hapten)-binding of immunoglobulins. Thus we shall confirm the universal role of soliton triplets at the supramolecular level of proteins.

Indeed, in the immunoglobulin cleft which encloses the hapten PC we find two aromatic amino acids with π-electron systems, Tyr-33-H and Trp-104a-H. Two basic amino acid residues, Lys and Arg, are involved in the following positions: Arg-52-H and Lys-54-H. We also find two amino acid residues with negatively charged side chains: Glu-35-H and Glu-58-H. In addition, one Asp-90-H residue is found in the CDR region. The π-electron anions of the two aromatic residues, Trp and Tyr, seem to accommodate the hapten PC in the cleft. The positively charged amino acids Lys and Arg are situated at the negatively charged ending of the hapten, while the negatively charged Glu-35-H and Glu-58-H are located at the opposite, positively charged ending of PC. The hapten itself exhibits a pronounced dipole moment: it carries a negatively charged P group at one ending and a positively charged amino group at the other.

All peptides bound to immunoglobulins exhibit a pronounced dipole

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[31] See J. Darnell, H. Lodish & D. Baltimore, Molecular Biology, W.H. Freeman, New York, 1990, Fig. 25-17, p. 1019.

moment; otherwise they cannot interact with the CDRs of the antibody. For this reason foreign proteins first have to be cleaved in the cells before they can be expressed in the MHC molecule. As we see, the pieces of the immunological puzzle begin to fit together. The amino acid residues of the CDR region form the **soliton triplet** of the **immunoglobulin cleft,** which in turn interacts with the antigen. This interaction is a horizontal energy exchange between two systems of the supramolecular level; the latter is part of the electromagnetic level of organic matter. As any energy exchange is at once horizontal and vertical, it involves the energy exchange of the underlying quantum levels.

From this elaboration we gather that the soliton triplet represents a universal system of the supramolecular level of the FUELs. The soliton triplet is a pronounced dipole that operates as an **organic semiconductor**. The advantage of this quantum system is that it is capable of propagating solitons and inducing *motion* to the protein that carries it, while *inorganic semiconductors* are, more or less, rigid systems. However, when semiconductors are involved in the construction of robots or other electronically driven devices, they can also induce motion at the macroscopic material level by modulating the electric circuits of the device. This example illuminates the common pattern of energy exchange between the micro- and macroscopic levels. This view demythologizes the current approach to organic matter, which is incapable of explaining the **intentional motion** of cells and organisms.

We shall show below that the soliton triplet is the universal operational unit in MHC molecules and T cell receptors. This functional system of the supramolecular level always includes: a π-electron pathway, an electron donor, and an electron acceptor. In the immunoglobulin cleft, the negatively charged carboxyl groups of the glutamic acid residues donate electrons to Tyr-33-H and Trp-104a-H to form a delocalized π-electron anion. The adjacent positively charged amino groups of Lys-54-H and Arg-52-H accept the free spin electrons which are propagated along the π-electron system of the cleft. The specific dipole structure of the hapten participates in the soliton triplet of the immunoglobulin cleft (U-sets) too. The PC molecule represents a pronounced dipole with a negatively charged PO_4^{2}-group at one ending and a positively charged quaternary N^{+}-group at the other. The phosphate group exhibits a resonance - the electrons are delocalized and can be found on any of the oxygen atoms. This resonance energy may be substantial, as is the case with the phosphate groups in ATP.

The electric current that flows through this common soliton triplet represents the action potential of the supramolecular level. It induces a soliton, a standing wave, that propagates along the supramolecular structure of the immunoglobulin-antigen complex and causes a global conformational change of its spatial structure (motion is the universal manifestation of energy). The hapten itself may carry an incomplete soliton. For instance, PC represents a dipole without a π-electron system. Other haptens carry a complete soliton triplet (see below) which interacts with the soliton triplet(s) of the immunoglobulin cleft to form a common triplet. In this way an infinite number of different soliton triplets can be generated in organic matter; they operate as distinct semiconductors that transmit specific constant amounts of energy (quants) into the cell.

There can be many variations in this respect, but the energetic pattern remains invariant. We always find a restricted number of 7 soliton-specific amino acids that participate in the formation of soliton triplets in the active sites of immune FUELs. The remaining 13 amino acids of the amino acid alphabet of the human organism can be further subdivided into two groups when the dipole model is applied to their supramolecular electromagnetic structure: a group of *hydrophylic* amino acids with a weak dipole moment and a group of *hydrophobic* (*aliphatic*) amino acids with almost no dipole moment. These two groups participate in the construction of a pocket or rather "milieu" around the active site (cleft) of immunoglobulins and other proteins. The pocket represents a quaternary structure which is hydrophilic outside, towards the ionic solution of the cytosol or the extracellular compartment, and hydrophobic inside, towards the active site of the protein. Thus all the 20 amino acids found in the human organism have a specific function in the formation of the tertiary and quaternary supramolecular structure of proteins; the latter is energetically pre-determined and genetically stored as amino acid sequence in the DNA-code.

We can trace this pattern of construction in all FUELs. The rationale behind this finding is rather simple. The soliton triplets are *dipoles* that establish an electric gradient, a microscopic electric LRC, at the supramolecular level. This gradient must have a fixed orientation within the protein structure, so that a soliton can be adequately propagated. For instance, the electric gradient of a soliton triplet harboured in the transmembrane part of an integral FUEL is opposite to the membrane gradient of the cell (reciprocal behaviour of the LRCs of contiguous levels). This is a basic fact in electricity; it is also of central importance to chem-

istry. The *covalent bonding*, a basic concept of chemical reactions, considers the reciprocal behaviour of the LRCs of contiguous levels, the attraction of oppositely charged chemical groups. In terms of Schrödinger wave equation, the covalent bonding is explained as a superposition of two standing waves of electrons, e.g. two 1s atomic orbitals that give a new wave function. This wave function encompasses the two nuclei and counter-balances the internuclear repulsion. For this reason it is also called a *molecular orbital*. These terms are circumlocutions for a condition of constructive interference at the supramolecular quantum level.

In order to maintain the specific gradient of the soliton triplet, the protein structure must protect this functional unit from the ionic milieu of the cell, when the FUELs are intracellular enzymes, or from the ionic milieu of the extracellular compartment, when the FUELs are humoral factors or integral proteins. Otherwise the soliton triplet(s) will avidly interact with the ions of the surrounding solution and will be blocked by destructive interference. In particular, the "midgaps" of the π-electron system will be quenched; the positively charged electron donor and the negatively charged electron acceptor will be neutralized in this way (see the principle of electroneutrality) and the gradient of the soliton triplet(s) offset. In this state of energetic blockade they will no longer be in a position to propagate solitons.

This is the reason why we encounter soliton triplets only in the active sites of enzymes, receptors, and immunoglobulins, and in the transmembrane part of integral proteins. The active sites of the proteins are lipophilic and are protected by their quaternary structure, which is composed of *hydrophobic* (*aliphatic*) amino acids, located near the active sites, and of hydrophilic residues exposed towards the ionic solution. A typical example for this pattern of construction is *haeme* in haemoglobin, myoglobin, and cytochromes (chlorophyll)[32]. This group of proteins is the best investigated. Soliton triplets in the active sites of cytosolic enzymes are thus surrounded with hydrophobic residues. In addition, integral proteins use the lipophilic lipid bilayer to protect the soliton triplets of the transmembrane part from the ionic solution of the cytosol and the interstitial fluid. There is no exception to this pattern!

This "**energetic constraint**" determines the 3*d-structure* of proteins in the cell, including their amino acid sequence as a mirror image of the

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[32] For further details see L. Stryer, Biochemistry, W.H. Freeman, New York, last edition.

genetic code. The arrangement of amino acids in proteins is therefore not hazardous; it is not coincidental or a product of random mutations in the evolution of species, as is maintained in the present-day bio-sciences. In fact, the amino acid sequences of proteins strictly abide by the energetic constraint in the cell. The latter is an aspect of the Law. It is a manifestation of the electromagnetic LRC in the cell that determines the genetic code. We therefore say: "T**he genetic code is subjected to the energetic constraint of the Law**". This theoretical breakthrough in biology is a consequence of the discovery of the Law. It topples the present dogma postulating that the genetic code is the primary event in organic matter, while the amino acid sequences encoded by genes are purely random events (e.g. J.L. Monod).

The new axiomatics of the Law states that the basic term of Kolmogoroff's theory of probabilities, the probability set, is an equivalent concept of the primary term. Therefore, all the probabilities obtained from real samples are numerical space-, time-, or space-time relationships. This fundamental simplification of mathematics eliminates the numerous vague interpretations of the term "statistical probability". It repudiates all the metaphysical ideas which have evolved from the concept of "coincidence" or "randomness". Among these the concept of "information", being a synonym for energy/space-time, is often associated with the "randomness" of the genetic code. A chief objective of this survey is to prove that most variations in amino acid sequences follow the energetic constraint of the Law and are thus rather **conservative**.

Genetic mutations in proteins follow the construction rule of forming soliton triplets and protecting them from unwanted interactions (destructive interference) with external ions and charged groups. We shall show that when *functionally equivalent* amino acid residues are exchanged, for instance Lys for Arg, or Asp for Glu, the mutant proteins do not lose their function. However, when such residues are replaced by any other amino acid, this causes a loss of function. This fundamental conclusion of the General Theory can be empirically confirmed by the exponentially growing evidence of point mutations that impede the protein function. Cells carrying such deficient FUELs have an impaired metabolism and are less effective. Most of them succumb by lysis. Only cells that code effective FUELs can survive and proliferate - their natural selection is therefore energetically pre-determined. Thus, all mutations of the genetic code, leading to variations in the amino acid sequence of proteins,

abide by the energetic constraint of the Law and should not be characterized as "random" events. This conclusion revolutionizes our biological outlook. It is confirmed by all the facts[33].

The **conservative polymorphism** in the amino acid sequence of proteins can be illustrated by an analysis of the CDRs of various antibodies (see Table 1). A collection of amino acid sequences of the variable regions of human H-chain (Proteins I to IX) demonstrates the spectrum of variations found in CDRs on the one hand and the pronounced conservatism in the positioning of soliton-specific aromatic, basic, and acidic residues in the CDR sequences on the other. In the H-chain, CDR1 occupies the sequence segment 31-35, CDR2 the sequence segment 49-65, and CDR3 the sequence segment 99-111[34].

Table 1: Protein sequences in the CDR regions of immunoglobulins

Proteins	**Sequence CDR1**				
Position	**31**	**32**	**33**	**34**	**35**
I	Thr	–Ser	–Ala	–Val	***–Tyr***
II	Thr	***–Asp***	–Ala	–Met	***–Tyr***
III	Thr	–Ala	***–Trp***	–Met	***–Lys***
IV	Thr	–Thr	–Ser	***–Arg***	***–Phe***
V	***Arg***	–Val	–Leu	–Ser	–Ser
VI	Arg	***–Tyr***	–Thr	–Ile	–His
VII	B	–B	***–Phe***	–Met	–Thr
VIII	Ala	–Ser	–Ala	–Met	–Ser
IX	Ser	–Ser	–Ala	–Met	–Ser

[33] I have confirmed this pattern credibly for haemoglobin and myoglobin; these proteins are very similar to cytochromes, belonging to the respiratory chain in the mitochondrion. Since both protein groups involve proton-transport (proton-motive gradients), this is powerful evidence for the ubiquitous validity of the soliton concept. This aspect of great relevance cannot be discussed in this chapter because it involves further biochemical details which are beyond the scope of the present survey. Here, we can only present the general line of argumentation. However, the competent reader can analyse any specific biochemical detail on his own, by adhering to the principles of the General Theory as outlined in this volume. Its objective is not to solve each particular problem in bio-science, but to establish a universal epistemological approach to any specific phenomenon of biological regulation.

[34] Modified from J. Darnell, H. Lodish. & D. Baltimore, Molecular Cell Biology, W.F. Freeman, New York, p. 1021.

Table 1 (continues): Protein sequences in the CDR regions of immunoglobulins

Proteins	**Sequence CDR2**																
	49	**50**	**51**	**52**	**53**	**54**	**55**	**56**	**57**	**58**	**59**	**60**	**61**	**62**	**63**	**64**	**65**
I	Gly	–***Trp***	–***Arg***	–***Tyr***	–***Glu***	–Gly	–Ser	–Ser	–Leu	–Thr	–His	–***Tyr***	–Ala	–Val	–Ser	–Val	–Gln
II	Ala	–***Trp***	–***Lys***	–***Tyr***	–Gln	–***Glu***	–Ala	–Ser	–Asn	–Ser	–His	–***Phe***	–Ala	–***Asp***	–Thr	–Val	–Met
III	Val	–***Trp***	–***Arg***	–Val	–***Glu***	–Gln	–Val	–Val	–***Glu***	–Leu	–Ala	–***Phe***	–Ala	–Asn	–Ser	–Val	–Asn
IV	***Glu***	–***Phe***	–***Arg***	–Val	–Gln	–Gly	–Ser	–Ala	–Ile	–Ser	–His	–***Tyr***	–Ala	–***Asp***	–Ser	–Val	–Gln
V	Ser	–Gly	–***Arg***	–Leu	–Asn	–Ala	–Ser	–Ser	–Asn	–Leu	–His	–***Phe***	–Ala	–Val	–Ser	–Ala	–Gln
VI	Ala	–Val	–Met	–Ser	–***Tyr***	–B	–Gly	–B	–B	–***Lys***	–His	–***Tyr***	–Ala	–***Asp***	–Ser	–Val	–Asn
VII	Ala	–Asn	–Ile	–***Lys***	–Z	–B	–Gly	–Ser	–Z	–Z	–B	–***Tyr***	–Val	–***Asp***	–Ser	–Val	–*Lys*
VIII	Ala	–***Trp***	–***Lys***	–***Tyr***	–***Glu***	–Met	–Gly	–Met	–***Asp***	–Leu	–His	–***Tyr***	–Ala	–***Asp***	–Ser	–Val	–Asn
IX	Ala	–***Trp***	–***Lys***	–***Tyr***	–***Glu***	–B	–Gly	–Asn	–***Asp***	–***Lys***	–His	–***Tyr***	–Ala	–***Asp***	–Ser	–Val	–Asn

Proteins	**Sequence CDR3**												
	99	**100**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**	**109**	**110**	**111**
I	Val	–Thr	–Pro	–Ala	–Ala	–Ala	–Ser	–Leu	–Thr	–***Phe***	–Ser	–Ala	–Val
II	***Phe***	–***Arg***	–Gln	–Ala	–***Phe***	–Val	–Gln	–del	–del	–***Phe***	–***Phe***	–***Asp***	–Val
III	***Phe***	–Val	–Val	–Ser	–Thr	–del	–del	–del	–del	–Ser	–Met	–***Asp***	–Val
IV	Thr	–***Arg***	–Pro	–Gly	–Gly	–***Tyr***	–del	–del	–del	–***Asp***	–Ser	–Ala	–Val
V	Leu	–Ser	–Val	–Thr	–Ala	–Val	–del	–del	–del	–Ala	–***Phe***	–***Asp***	–Val
VI	Ile	–***Arg***	–***Asp***	–Thr	–Ala	–Met	–del	–del	–del	–***Phe***	–Ser	–Ala	–His
VII	Gly	–***Trp***	–Gly	–del	–del	–del	–del	–del	–del	–Gly	–Gly	–***Asp***	–***Tyr***
VIII	***Asp***	–Ala	–Gly	–Pro	–***Tyr***	–Val	–Ser	–Pro	–Thr	–***Phe***	–Ser	–Ala	–His
IX	***Asp***	–Ala	–Gly	–Pro	–***Tyr***	–Val	–Ser	–Pro	–Thr	–***Phe***	–Ser	–Ala	–His

del = deletion

Table 1 shows that even in the highly variable domains of immunoglobulins certain positions are preferentially occupied by aromatic residues and by positively, respectively, negatively charged amino acids that belong to soliton triplets. For instance, the aromatic amino acids Phe, Tyr, and Trp are predominantly found in the positions 50, 52, and 60 in CDR2, and in the position 108 in CDR3. The position 51 in CDR2 is mainly occupied by the basic amino acids, Lys and Arg, while the negatively charged amino acids Asp and Glu are most often found in the positions 53 and 62 in CDR2, and 110 in CDR3. The three groups of functional amino acids of the soliton triplet are located in several, well defined positions: 33, 35, 50, 51, 52, 53, 60, 62, 99, 100, 108, and 110, which establish the active binding region of CDRs in the cleft. This conservative pattern of mutations shows that, even in the highly variable domains of antibodies, the energetic constraint of the Law determines the polymorphism of amino acid sequences. From an energetic point of view, we define this polymorphism as "conservative".

At present any substitution of an amino acid residue with another is considered to be an equivalent permutation with respect to *Shannon's theory of information*. This theory says that any point mutation carries a new bit of information. As the term "information" has been found to be equivalent to the primary term, "energy = space-time", the tautological character of this statement should be cogent to the reader. Substitutions of aromatic residues, e.g. Phe for Tyr, or positively charged residues, e.g. Arg for Lys, are of a different quality than heterogenous substitutions such as Phe for Pro, or Arg for Leu. While the former kind of *functionally equivalent mutations* does not significantly alter protein function, the latter is usually associated with a loss of functional activity. However, spontaneous mutations causing cell deficiency do not seem to occur very often, most probably because such cells die by lysis. Mutations of residues which are *functionally equivalent* in the light of the dipole model occur preferentially in the variable CDR regions of immunoglobulins and determine the energetic variability of the active site. This pattern of mutation is observed in the immunoglobulins presented in Table 1.

This *conservative polymorphism* is also typical for the amino acid sequences of the constant transmembrane part of immunoglobulins, which is coded in the C_k region of the genetic code. Obviously, Nature has developed a "huge library" of α-helices that are variations on the same energetic theme. These α-helices operate as energetic *modules* that can

be attached to different proteins, for instance to proteins of the ubiquitous Ig superfamily. Such proteins participate in different physiological functions. The genetic mechanism that effects the translocation of these modules to various proteins is called "*splicing*"[35].

This observation casts considerable doubts on current estimations of the actual number of variable antibodies which an organism can produce when the variability of their amino acid sequences is interpreted in terms of soliton triplets. Although our information is still incomplete in this respect, we can nonetheless conclude that the actual number of functionally relevant permutations of amino acid sequences in immunoglobulins is much lower than that theoretically estimated at present. The conservative polymorphism as observed in CDRs repudiates the present deterministic view in immunology, which maintains that each particular antibody expresses a specific activity against a specific antigen. In fact, immunoglobulins exhibit an *overlapping* specificity for many antigens, as was elucidated by means of the soliton triplet concept and as confirmed in numerous experiments (see also Table 5).

The energetic differences between the various soliton triplets found in the variable regions are most probably finely tuned; they establish an energetic continuum of infinite, discrete (transcendental) action potentials of immunological response. This is a basic axiom of the new theory - space-time is continuous, but discrete. The actual number of relevant structural elements of energy exchange at the supramolecular level is however rather restricted. The permutations of these elements contribute to the infinite and discrete continuum of antibodies. This insight permits for the first time a rational analysis of genetic mutations with respect to protein function and cell regulation.

The antigen-antibody interactions essentially involve the three aforementioned amino acid groups consisting of seven residues; they build a small number of "energetic permutations", called soliton triplets. *Functionally equivalent residues* can be effectively substituted without causing any significant impairment of the soliton triplets and the corresponding FUEL. The energetic differences in the "binding specificity" of various antibodies are thus gradual and overlapping - they are U-sets that cannot be separated in real terms, but only in an abstract way in the

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[35] The General Theory suggests an elegant energetic model that explains this fundamental phenomenon of the genetic code. Its elaboration is beyond the scope of this survey.

mind. The remaining 13 amino acid residues, which constitute the pocket around the active site of the FUEL, may also contribute to the specificity of the variable domain, but their role in this respect is of secondary importance. The sequential polymorphism of the remaining 13 residues may gradually alter the hydrophobic (inside) and hydrophilic (outside) character of each particular immunoglobulin and thus induce discrete changes of its structure. This behaviour can be observed in haemoglobin during oxidation. The quaternary structure of this vital protein is finely tuned to the intrinsic pH-milieu - the transitory reshaping of haemoglobin regulates the affinity of oxygen to haeme. This energetic mechanism at the quantum level is basic to breathing.

Further examples: These observations can be substantiated by two further examples. 19 different antibodies were found to interact more or less specifically with the hapten PC. An amino acid sequence analysis of the H-chains of these immunoglobulins revealed that 10 antibodies on the H-chains had identical variable domains. The remaining nine antibodies differed in one to eight amino acids positions. Two particular H-chains residues, Tyr-33 and Arg-52, were present in all molecules. When the L-chain sequences were compared, they appeared to be markedly different. However, the residue Tyr-94 found to interact with the hapten was constant throughout all antibodies.

These results are confirmed by another example, given in Table 2. A monoclonal antibody specific to *sperm whale myoglobin* was prepared and the ability of myoglobins from different species to inhibit its binding to sperm whale myoglobin examined. From the 6 myoglobins tested, 2 myoglobins from different species inhibited the monoclonal antibody that was found to be specific to sperm whale myoglobin, while 4 myoglobins were inactive. An analysis of the amino acid sequences shows that the substitutions in the two competitive myoglobins from dwarf sperm whale and goosebeaked whale are functionally equivalent and involve soliton-specific residues. In the myoglobin from the goosebeaked whale, Glu, E (–) is substituted with Asp, D (–) in the position 109, and Tyr, Y (π) with Phe, F (π) in the position 151. The other substitutions affect non-soliton specific residues and are of secondary importance, for instance the substitutions in position 132. When we analyse the sequences of the four myoglobins that did not inhibit the monoclonal antibody, we find that they contain *functionally non-equivalent substitutions* of soliton-specific residues. This pattern is confirmed by numerous other experi-

ments in this field that cannot be discussed any further in this chapter.

These data support our sequence analysis of the variable CDRs and show that the putative "specificity" of antibodies, as propagated today, is in reality based on a few soliton triplets, which are functional variations on the same energetic principle. At this point it is important to observe that all qualitative differences which we observe in the physical world are caused by *discrete* energetic differences. For instance, the different colours of the visible light are caused by different frequencies $E = hf_{different}$, whereas the action potential h (Planck's constant) is the same for all colours. The same is true for the antigen specificity of antibodies. Their putative "specificity" is a product of discrete energetic variations of soliton triplets at the supramolecular level, which are caused by point mutations.

Table 2: Comparison of the amino acid sequences of myoglobin from different species with sperm whale myoglobin. For extra clarity, only the substitutions are given. Observe the conservative polymorphism in myoglobins obtained from six different species[36].

Myoglobin	**83**	**86**	**88**	**91**	**109**	**110**	**132**	**140**	**142**	**144**	**145**	**147**	**148**	**151**	**152**
Sperm whale	E	L	P	Q	E	A	N	K	I	A	K	K	E	**Y**	Q
Inhibition															
Dwarf sperm whale							S								
Goosebeaked whale					**D**		T							**F**	H
No Inhibition															
Sea lion	D						K	N				R		F	H
Human	I					C			M	S	N			F	
Ox		V	H	E	D		S	N	A	E			V	F	H
Sheep		V	H	E	D		S	N	M		Q		V	F	

[36] Modified from J.M. Austyn & K.J. Wood, Principles of Cellular and Molecular Immunology, Oxford University Press, Oxford, 1993, p. 357, Fig. 6.17.

The elements of the universal alphabet of organic matter - the 20 amino acids of (human) proteins - exhibit small energetic differences in their dipole moments that change discretely, depending on the pH-value (recall that pH is a measurement of an electric gradient) of the ionic solution. When these pH-differences (energy gradients) superimpose at the supramolecular level of proteins (U-sets), they can produce an infinite number of discrete energetic states (action potentials), which biologists interpret as "specific immunological qualities". This example illustrates a common semantic trap in science that is caused by imprecise terminology. In the case of immunoglobulins, one usually speaks of "antigen-specificity"; this property is considered a specific quality of immunoglobulins. However, this concept is of subjective anthropocentric origin - antigen-specificity is based on energetic differences (quantum leaps) at the supramolecular level of immunoglobulins. In the real world, there are no qualities, but only energetic differences. It is a privilege (and a flaw) of the human mind to define them as "qualities". This inherent deficiency is eliminated in the General Theory by a rigid axiomatisation of all scientific terms and concepts from the primary term.

2.4.3 The Genetic Coding of Immunoglobulins and Other Immune FUELs

The genetic coding of immunoglobulins is paradigmatic for all proteins and can be easily explained by the General Theory. In order to underline the cognitive leap of the new theory in this respect, we shall first discuss the present hypotheses dealing with this key process in the cell. These hypotheses focus on the interpretation of the genetic coding of antibodies in the B-lymphoid germ line in primary and secondary lymphoid organs because this aspect is best elucidated.

Two hypotheses have been suggested as to how an "antibody diversity" can be generated: the "*somatic mutation hypothesis*" and the "*somatic recombination hypothesis*". Both hypotheses appear to be intuitive perceptions of the dynamic regulation of the genetic code. The production of various antibodies is based on *DNA rearrangement* and *random mutations*. These processes involve vertical energy exchange between the various levels of organic matter. This aspect will be dis-

cussed for the *L-chain*, but it also holds for the H-chain. The basic facts are as follows[37].

The corresponding kmRNA of the L-chain is made from three exons. At the 5′ end we find the L_k exon. It encodes a leader or a signal peptide that directs the newly made protein into ER. The second exon builds the variable region V_k and the third the constant region C_k. In the germ line, the leader peptide and most of the variable region are encoded in one library consisting of several hundred units. Each unit consists of one L_k exon and one V_k region. The V_k makes for most, but not all, of the final variable region. The L_k and V_k are arranged in tandem along one long stretch of DNA. This region is followed by 5 joining regions J_k and the single-constant region. The DNA-string is energetically driven by the electromagnetic waves of the cellular action potentials. This electromagnetic interaction produces specific solitons (E_A) along the supramolecular nucleotide string of DNA that reshape its structure from the inactive into the active form. The exact mechanism involves several subsequent steps and will be outlined below (see also Davydov's solitons above). In the active state, the DNA-string is reorganized to make a functional k gene. One V_k region joins one J_k region with a deletion or inversion of the intervening sequence. Any V_k can join any J_k. This process is considered to be random, but in fact it is energetically controlled.

Once the regions are joined, the variable and the constant region are transcribed into a nuclear RNA and the intervening sequences are *spliced* to produce the mature mRNA for k protein. There are approximately 300 V_k regions and 5 J_k regions. These regions are bordered by recognition sequences that are organized as follows: at the 3′ end of V_k and at the 5′ end of J_k, there is a seven base sequence followed by 11 bases, respectively, 23 bases, and then by an AT-rich nine-base sequence. The 11 and 23 nucleotide sequences correspond exactly to 1, respectively, 2 turns of the DNA-helix. This enables their energetic joining that contributes to the diversity of immunoglobulin coding. During the joining of the two ends of the DNA, nucleotides can be lost and the code changed. However, the recognition sequence remains highly ordered.

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[37] For further reading we recommend the textbooks: Molecular Cell Biology, J. Darnell et al. Freeman, New York, 1990; Genes, B. Lewin, Oxford University Press, New York, 1994; Molecular Biology and Biochemistry, ed. R. A. Mayers, VCH, New York, 1995.

Delocalized regulation of the genetic code by action potentials: At present, these interactions cannot be explained from a kinetic point of view by conventional genetics, but are only depicted in a narrative and rather deterministic way. The active joining (interaction) of DNA-sequences producing variable immunoglobulins can be explained for the first time in the General Theory by employing the soliton concept. In this particular case, a soliton is an action potential of energy exchange at the supramolecular level of DNA, RNA, and their regulating proteins. At present, these interactions are circumscribed in traditional genetics as "joining", "transcription", "splicing", etc. This mechanistic terminology is proliferous and very imprecise, therefore we cannot introduce it at full length in this chapter. In this section, we shall present some dazzling solutions of key interactions that participate in the regulation of the genetic code. They are paradigmatic for further solutions which we shall leave to the competent reader. We shall begin with the *mechanism of delocalized coupling* (interaction at a distance) between the cellular action potentials and the DNA-solitons in the nucleus (axiom of CAP).

We have postulated that the genetic code is dynamically regulated by the energy exchange between the electric and metabolic levels of the cell. The action potentials of the plasma gradient produce coherent electromagnetic waves with a specific interference pattern that propagate in the cell and the nucleus with the speed of light (see quantum Hall effect in vol. I & II). The rigid *holes* in the nuclear membrane operate as a *diffraction grating* that establishes a specific *resonance pattern* in the nucleus. Energetic *maxima* and *minima* of exact magnitude occur on the fringes of this interference pattern. This is basic electromagnetism. In turn, they induce standing supramolecular waves (solitons) in the DNA-helix (axiom of CAP). These solitons propagate along specific segments of the DNA-string and activate the genes to encode. Thus the regulation of the DNA-code is effected in a *delocalized* manner through the electromagnetic LRC of the action potentials - it is a vertical energy exchange between the electromagnetic level (waves) and the biochemical systems (solitons in DNA, RNA, regulating proteins, etc.) of the metabolic level. Recall that matter, including organic matter, is of wave character (de Broglie). The final product of this electromagnetic interaction is the synthesis of proteins. This process takes place in ER and is driven in the same way as DNA-coding. The proteins are responsible for the structure and function of the cell by generating action potentials. This recurrent process merely reflects the closed character of space-time.

This interaction at a distance is carried out in a condition of constructive interference that determines the order in the cell. We also call it the "energetic constraint". It is an aspect of the Law. Below we shall present some new evidence that credibly confirms this conclusion.

We postulated that the nuclear membrane operates as a diffraction grating for the electromagnetic waves of the action potentials before they enter the nucleus and establish energetic maxima and minima. In this respect the nuclear membrane of eukaryotes is, indeed, unique - it is the only biological membrane that exhibits about 3000 rigid pores with an inner diameter of 15 nm (the outer diameter is about 70-80 nm)[38]. As it is permeable to ions, the nuclear membrane has no electric potential. Although this remarkable fact has been overlooked in biology, it is not coincidental. The holes in the nuclear membrane are formed by special integral FUELs. Spectral analysis has confirmed the precise geometry of these rigid transmembrane proteins. Their spatial form is determined by the specific space-time of the electromagnetic waves which the cellular action potentials create and propagate in the cell and the nucleus. This will now be proven in detail.

In chapter 1.2 we calculated that the average stored energy of the cellular action potential is in the order of $E_{c,total} = E_A f = \text{SP(A)}[2d\text{-}space\text{-}time] = 10^{-13}\ m^2s^{-2}$ (13). This amount of energy has been estimated for an average muscle cell, which takes an intermediary position among all body cells with respect to its metabolic rate. If we now assume a mean pulse frequency of about 60-70 heart strokes per minute, this means that the average muscle cell discharges this amount of energy about 60-70 times per minute, that is, if $f \cong 60$ strokes/60s = 1, then $E_{c,total} = E_{A,average} = \text{SP(A)}[2d\text{-}space]\ f = 10^{-13}\ m^2s^{-1}$. Within the new physical axiomatics, this cellular action potential can be expressed in terms of an electric current that is propagated in the cell (see vol. I & II). The actual definition of this quantity is: "charge/cross-sectional area per conventional time." From this we conclude that every second the average cross-sectional area of $10^{-13}\ m^2$ is propagated as an electromagnetic wave in the cell and reaches the nucleus:

$$E_A = K_s = \text{SP(A)}[2d\text{-}space] = 10^{-13}\ m^2, \text{ when } f = 1 \qquad (17)$$

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[38] Lexikon der Biochemie und Molekularbiologie, Herder, Spektrum Akademischer Verlag, Heidelberg, 1995.

The chief cognitive conclusion of the new physical axiomatics is that physics is applied mathematics or, in most cases, geometry applied to the real physical world. All physical quantities are of geometric, algebraic, or statistical character. For instance, *charge* is defined as the cross-sectional area that is moving in space-time (motion is the universal manifestation of space-time), while *electric current* is the amount of this cross-sectional area per conventional time. The human mind has no other access to space-time but to describe it in terms of geometry or algebra. This fundamental cognitive fact has been realized for the first time following the discovery of the Law. It abolishes numerous *embarrassing* misunderstandings in physics and other natural sciences.

The cross-sectional area that is moved within the cell during an action potential and drives cell metabolism is diffracted by the pores of the nuclear membrane to produce specific maxima and minima within the DNA-code. This interaction takes place under a condition of constructive interference. The aggregated cross-sectional area of all nuclear pores is in the same order as the cross-sectional area generated by an average action potential in the form of an electromagnetic wave:

$$S_{total} = 3000 \times \pi r^2 = 3000 \times 3.14 \times (7.5 \times 10^{-9})^2 \text{ m}^2 =$$

$$= 5.2 \times 10^{-13} \text{ m}^2 \cong E_A = 10^{-13} \text{ m}^2 \qquad (18)$$

This outstanding result of the General Theory illustrates cogently how the "prestabilized harmony" assumed by Leibniz is actually achieved in organic (and inorganic) matter. The order in the cell is not a random process of coincidence, as is believed today, but follows closely the exact space and time relationships of organic structures (systems of space-time) under a condition of constructive interference. In particular, this holds true for the electromagnetic waves of the action potential, standing quantum waves at the supramolecular level (solitons), protein structures (nuclear membrane holes), cell membranes (surface), etc. As space-time has only two dimensions, space and time, all we can do in science is to measure the space (e.g. charge), time (e.g. frequency, temperature), and space-time (e.g. mass) relationships of the systems. In volume II we have shown that the electromagnetic properties of photon space-time, as given by the electric and magnetic permettivity of "free space" $c^2 = 1/\varepsilon_o\mu_o$ (Maxwell's equation), are determined by the mean magnitudes of the space (diameter) and time (rotational frequency) of celestial bodies such

as pulsars and quasars (see chapter 7.9). The insight that the space-time of the systems is mutually determined (open U-subsets of a closed space-time) effects the greatest possible simplification in our scientific outlook on nature[39].

The above result also confirms the validity of our energy balance of cell metabolism. Exactly for this reason the vertical energy exchange between the electric and metabolic LRCs was selected for the calculation of the energy balance in the cell. By proving that the effective chemical energy of nutrition is completely transformed into the electromagnetic energy of cellular action potentials, and, from there, into structural proteins during DNA-coding (closed circle), we have confirmed that organic regulation can be reduced to an interaction between these two levels of organic matter (AR). In this sense, the DNA-coding is a particular system (energy exchange) of the biochemical level. Below we shall present another basic example that gives us a clue as to how the electromagnetic maxima and minima build a resonance pattern with the supramolecular structures of the DNA-string in the nucleus and trigger transcription by inducing specific solitons.

Before we finish our discussion of nuclear pores, we shall draw the reader's attention to another important energetic aspect associated with these structures that can be succintly explained with the Law. It has been established that DNA-regulatory proteins dissociate from the plasma membrane upon depolarisation and enter the nucleus through these pores. A prerequisite for their movement across the cytosol is the existence of a specific signal sequence, called "nuclear localization sequence", containing five consecutive positively charged residues:

–Pro-Lys–Lys (128)–Lys–Arg–Lys–Val–

This positively charged stretch drives the protein into the nucleus, where

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39 For instance, humans can only perceive visible light, which is a narrow spectrum (system) of photon space-time. Rhodopsin is activated by the photons of visible light. The evolution of human vision within this narrow frequency (or wavelength) range is not coincidental. When we apply Wien's displacement law as an application of the Universal Law ($f_{max} = K_{CBR}T$), we find that the frequency (time quantity) of the maximal radiation of the sun, which only depends on the surface temperature (6000 K), falls within the spectrum of visible light. We recommend the calculation as an exercise for the reader (see vol II, chapter 3.5).

it exerts its regulatory function. When the signal sequence is cleaved, the protein loses its ability to move in the cytosol and cannot enter the nucleus. The nuclear localization sequence is also rendered inactive when a single residue is exchanged in a functional non-equivalent substitution, e.g. Lys in position 128. This finding reflects again the central role of soliton-specific residues in the kinetic behaviour of proteins. How can we explain this fact within the General Theory? During depolarisation the charge of the cytosolic side of the plasma membrane becomes positive (e.g. during an overshoot). Proteins that carry a positively charged sequence are repelled from the plasma membrane and move towards the nucleus. This is a simple electromagnetic interaction that can be assessed with Coulomb's Law, which is an application of the Law. When the signal sequence is cleaved, the protein loses its ability to move because there is no electromagnetic interaction. We recommend that the reader uses the same principle to explain how proteins move away from the nucleus or ER during repolarisation.

The structure of the genetic code in the Light of the Law: We shall begin with an analysis of the structure of the DNA-regulatory *helix-loop-helix* proteins which participate in the coding of antibodies. As in all other genes (e.g. viral genes), each V region of the genes of these enzymes has a common sequence called a **TATA box**. The TATA box is a highly conserved sequence of adenine (A)-thymine (T) base pairs that is located in a fixed position about 25-35 bases (promoter) upstream of the RNA start site. The TATA box is found in all rapidly transcribed genes and is thus not specific for the helix-loop-helix proteins. The activation of RNA polymerase, which initiates the transcription, depends on the TATA box. Experiments with mutant and wild-type recombinant DNA constructs show that when a single base, e.g. T, is substituted for G (guanine) or A, the transcription of TATA-containing promoters is drastically reduced, while changes in the sequences between the TATA box and the start box do not significantly affect transcription. The repetitive motif of the TATA box clearly indicates that this nucleotide sequence builds a resonance pattern with the electromagnetic maxima and minima of the cellular action potentials obtained by means of diffraction at the rigid nuclear pores. Recall that all waves (rotations) are superimposed, as they are U-sets. Such a resonance pattern induces a specific soliton in the TATA box that drives the RNA polymerase kinetically along the DNA-helix. This energy interaction induces the actual gene transcription. The

interpretation of the TATA box, which is over-simplified in this presentation for didactic purposes, is paradigmatic for any DNA-interaction. We leave it to the reader to apply this approach to any other genetic structure, e.g. introns, OCTA, or process that has been determined in recent years.

We shall apply this approach to the *rearrangement* and regulation of DNA. In this process, certain genes preferentially join to construct a common protein. An inviolable rule is observed in this joining process: in all unions, a *one-turn recognition sequence combines with a two-turn recognition sequence*. Thus V_k segments have one-turn elements, and J_k segments have two-turn elements. The DNA is arranged in a highly ordered manner along the helix that constitutes its supramolecular level. What is the reason for this symmetrical rearrangement of the DNA? In the DNA-helix, the aromatic π-electron systems of the nucleotides are situated on the same side of the helix and are divided by a full number of helix turns. They form extended π-electron systems that are part of extended soliton triplets and can propagate solitons along the DNA-helix. The soliton triplets of the nucleotides are activated when the DNA is uncoiled. The regulating proteins can only interact with the DNA-string in this activated energetic state.

When the DNA is in the inactivated form, it winds around **histones** in chromatins. The role of histones for the energetic inactivation of DNA has not been elucidated yet. This will be done now. The amino acid sequences of major histones are highly conserved. For instance, the sequences of H3 and H4 are nearly the same in all plants and animals: "Thus the amino acid sequence of H4 has remained nearly constant in the 1.2×10^9 years since the divergence of plants and animals"[40]. The outstanding feature of these highly conservative proteins is that they harbour a large number of positively charged, soliton-specific amino acid residues, Arg and Lys. For this reason, histones are also referred to as *basic proteins*. The histones interact with the DNA-string and form *nucleosomes*, which are the repeating units of chromatin. Chromatin represents the inactive form of the genetic code. How can these two basic findings - the symmetrical rearrangement of the DNA-helix and the conservative Arg–Lys-rich amino acid sequences of histones - be explained in the light of the Law?

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[40] L. Stryer. Biochemistry, Freeman, New York, 1992, p. 825.

The histones build a common supramolecular complex with the DNA. In the chromatin, the midgaps of the extended π-electron systems of the nucleotides are melted by the numerous positively charged Arg and Lys of the histones and are thus completely inactivated by destructive interference. Subsequently, the DNA-helix is not in a position to propagate electrons and protons. For this reason Arg and Lys have preserved their position in the histone sequences of plants and animals during their long evolution. Obviously, this energetic process of inactivation presupposes a highly ordered protein structure, so that every DNA-helix turn fits in with the corresponding histone element. When this principle of organisation is infringed, the DNA-helix cannot be effectively inhibited in chromatin. In this context, the role of the *methylation* of nucleotides can also be explained. Methylation enables the occurrence of kinks only at certain positions of the DNA-string[41].

The genes are activated by **DNA-regulatory, helix-loop-helix proteins** of a highly ordered structure. Gene activation begins with the uncoiling of the DNA from the chromatin complex. This is effected by helix-loop-helix proteins. Each of the 9 fingers of a helix-loop-helix protein contains metal ions, e.g. zinc, which are powerful electron acceptors, cysteine residues (sulfide groups as electron donators) and histidine residues as sensory amino acids (their charge is variable at physiological pH). The finger of the helix-loop-helix protein binds about five pairs along the DNA helix. This stretch corresponds to half a turn of the double helix, so that this protein encompasses about five turns from the helix (45 nucleotides). The existence of 11- and 23-spacers in V_k and J_k, which are equivalent to 1 and 2 turns, represents a common motif in the DNA regulation; it reflects the rigid energetic arrangement of the DNA-helix. Obviously, the DNA-regulatory proteins carry pronounced electron acceptors and electron donors. When they interact with the DNA-string in the aforementioned way, they incorporate the extended π-electron systems of the nucleotides in the helix turns in an ordered manner and build common soliton triplets at the supramolecular level. The activation of these solitons promotes the detachment of the DNA-helix from the histones; it now acquires the active form, which is a prerequisite for the subsequent transcription. The attachment of RNA-polymerase and other

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[41] Indeed, the metabolic web of the cell and the genetic code is a fascinating, open-ended story when we start to uncoil every particular detail in the Light of the Law.

regulatory proteins to the transcription complex follows the same energetic pattern.

As we see, we can explain all the structures of the genetic code from an energetic point of view and thus establish a **new kinetic theory of genetic regulation**. This short survey only gives some glimpses into the universal character of the General Theory, which includes further breakthroughs in genetics and bio-science that are beyond the scope of this review. The advantage of the General Theory becomes evident when one compares the consistency of the new energetic approach to the disarray of scientific facts presented in conventional genetics. This virtue will be demonstrated for the following key process.

The **rearrangement of DNA** is the basic mechanism for producing various immunoglobulins. It takes place at high speed in the undifferentiated germ line in the bone marrow. After the immunoglobulin genes have been rearranged, the cell can differentiate and express various other receptors and FUELs on the membrane, which build the specific electric LRC of the immunocompetent cell (see below). In germ cells, the LRC is still not pre-determined and has the propensity of evolving in a multivariable energetic manner, thereby producing specialized immune cell lines. The rearrangement of DNA is regulated by modulations of the electric LRC of the germ cells and depends essentially on the kind of extracellular regulation, e.g. local lymphokines, membrane receptors of T cells, etc. As we see, the DNA rearrangement that produces variable immunoglobulins can be energetically modulated to meet the actual needs of the immune system. In this transition state of rearrangement, various immunoglobulin sequences can crystallize. However, the pattern of variations is determined by the energetic constraint of the cell as specified above and remains highly conservative. The amino acid sequences that contribute to the formation of soliton triplets are preserved in most proteins.

Immunoglobulin synthesis takes place in the ER that carries the **ribosomes**. Protein synthesis is regulated in a similar way to that of DNA transcription. The ER is a complex system of intracellular membranes which exhibits an electric gradient, similar to that of mitochondria, though less pronounced. In biochemistry it is referred to as a pH-gradient. This is another synonym for a proton-motive gradient. The antibodies are either secreted or expressed on the cell membrane of lymphocytes. This process is called "**targeting of proteins**" and is

extremely intricate; it is still very poorly investigated. The active secretion of immunoglobulins (or any other proteins) such as humoral factors or their expression as membrane FUELs is an extremely dynamic process - in fact, it is a cascade of kinetic processes - that cannot be explained in the bio-sciences in an interrelated manner. At present, the targeting of proteins is taken for granted and described incompletely from a static point of view. Although this aspect cannot be tackled in this chapter, we shall make several suggestions as to how the targeting of proteins can be explained within the General Theory.

In the ER lumen, the newly synthesized immunoglobulins acquire **carbohydrate units**, just like all the other proteins**.** The diversity and complexity of the carbohydrate units of *glycoproteins* are of great functional importance. This aspect has not been elucidated yet. In membrane glycoproteins, the sugar residues are either attached to the amide nitrogen atom in the side chain of Asn (defined as N-linkage) or to the oxygen atom in the side chain of serine or threonine (defined as O-linkage). The three acids have polar, but uncharged side chains. The sugars that are directly attached to one of these side chains are usually N-acetylglucosamine or N-acetylgalactosamine. N-linked oligosaccharides contain a common pentasaccharide core consisting of three mannose and two N-acetylglucosamine residues.

There are many variations of oligosaccharide-bindings, but it is a recurrent motif in all glucoproteins that **sialic acid** residues are attached on top of the oligosaccharides' terminal in the ER. Sialic acids are common in immunoglobulins, T cell receptors, peptide hormones, and other FUELs, all of which are glucoproteins. Sialic acids are *negatively* charged sugar residues that operate as a "cordon sanitaire" in immunoglobulins and other humoral proteins. Their physiological purpose is to prevent the active sites of circulating proteins from ionic interactions with the plasma or interstitial fluid. This explains their structural diversity.

Each protein, including immunoglobulins, carry one or more soliton triplets at the active site. They can be protected (inactivated) either by a surplus of positively charged adjacent groups, as seen in histone interaction with the DNA-helix in chromatin, or by a surplus of negatively charged groups as found in circulating glycoproteins. This specific protection is not coincidental. The cytosol is negatively charged, while the extracellular fluid, including plasma and lymph, is more positively charged - all cell potentials at rest are negatively charged inside and positively charged outside. The excess of positive charges in the extracellular com-

partment is counter-balanced by the negative charges of the sialic acid residues in the glucoproteins which form the glycocalix of the cell membrane. The excess of negative charges in the cytosol and in the nucleus is counter-balanced by the positively charged Arg and Lys in histones (see also anchoring of integral proteins below). This follows from the reciprocal behaviour of the LRCs of contiguous levels.

The histones inactivate the genetic code in the nucleosomes by means of their numerous basic residues Arg and Lys. Circulating proteins are shielded from the positively charged ionic solution by the negatively charged groups of the sialic acid residues of the glycocalix and thus remain inactive during transport. This is another recurrent motif in nature that confirms the universality of the soliton concept and the dipole model. The exact mechanisms by which oligosaccharides interfere with the soliton triplets of proteins have to be determined in the light of the Law. As every nucleotide carries a **deoxyribose** residue that builds the sugar core of the DNA stack, this will also shed light on the regulatory mechanisms of the genetic code; in RNA it is **ribose**. Obviously, sugar residues play, in conjunction with soliton triplets, a fundamental role in the energy exchange at the supramolecular level.

There are several basic facts in immunology that find an easy explanation in this context. Firstly, the most powerful polymeric antigens, also known as *superantigens*, are carbohydrates with repeating sugars as found in bacterial cell walls (LPS = lipid polysaccharides). These particles are multivalent, so that various antibody molecules carried on a single B cell can be bound together to form a tight patch. It is assumed that a competent antigen "*cross-links*" surface antibodies. This cross-linking is a key interaction in the activation of B cells. The correct energetic explanation is as follows: large carbohydrate particles neutralize the "cordon sanitaire" of the negatively charged sialic residues of the *glycocalix*, so that the soliton triplets in the active sites of cell-surface antibodies (variable regions) can be activated in a non-specific manner. LPS predominantly stimulate B cell proliferation. Concanavalin A activates immune cells in a similar way. This carbohydrate-binding protein has a high affinity to sugar residues; when it binds surface proteins, it deactivates their sialic shield. *Concanavalin A* mainly induces the polyclonal proliferation of T cells. Other mitogens act in the lipid membrane as direct cell-stimulating agents. These facts reveal the common energetic mechanism of cell stimulation and regulation.

This conclusion can be substantiated by the following basic immuno-

logical observation. Haptens such as dinitrophenol induce the production of specific antibodies only when they are conjugated to a protein, e.g. to MHC. Dinitrophenol itself does not stimulate an immune response. Otherwise, any drug or chemical compound circulating in the body would have the propensity to elicit an antibody response. This is unlikely, although many allergens that induce autoimmune responses are synthetic inorganic compounds. Evidently, dinitrophenol alone cannot activate an antibody. Any immunological activation requires the presence of a supramolecular structure as an antigen that associates with the variable region of the corresponding integral protein or as a superantigen (LPS) that neutralizes the sialic shield of the FUELs. We have already explained how small molecules, e.g. neurotransmitters, with a pronounced dipole moment, interact directly with the lipid bilayer and activate the cell. Foreign proteins and polysaccharides can interact with immunoglobulins because they activate the soliton triplet(s) in the cleft or other active sites harboured in the quaternary structure of these proteins. Below we shall show that the same kind of interaction also takes place between antigenic peptides and MHC molecules or T cell receptors.

Energetic structure of MHC molecules: We have specified that an antigen processing is required to produce peptides that can bind the MHC molecule and be recognized by the T cell receptor. The portion that interacts with the MHC molecule is called *aggregate*, while the part that interacts with the T cell receptor is called *epitope*. As all cells carry MHC, they can be antigen presenting cells (APC). For instance, dendritic cells are major APC in the human organism. The *self-MHC-peptide presentation* is thus a universal property of all cells. The exact mechanisms of protein degradation and presentation are still controversial: it is assumed that there may be several ways of degrading and presenting antigens. Proteins may enter the cell via *pinocytosis*, *endocytosis*, or *phagocytosis*. After being processed in cell metabolism, the cleaved peptides may be presented to MHC molecules in the ER lumen, where they interact to form an MHC-peptide complex (see targeting above). It is a fundamental property of the cell to express not only foreign, but also self-peptides.

As previously explained, *class* I *MHC binds peptides from intracellular proteins*, while *class* II *MHC* binds *peptides from extracellular proteins*. Most probably, this interaction takes place in the lysosomes during their transport to the cell surface. There is evidence that "empty" MHC molecules are also presented. They can bind extracellular peptides cleaved

from circulating proteins by proteases, nucleases, or other enzymes; the latter are secreted in the interstitial fluid by adjacent or distant cells. It is interesting to note that so far it has not been possible to visualize immunogenic peptides directly on the surface of APCs or target cells. Their presence is inferred from the ability of these antigens to stimulate T cell responses. The binding of peptides to isolated MHC molecules can be experimentally demonstrated. However, this binding is not specific, as usually presented in textbooks on immunology. It is effected by weak interactions (electromagnetism). The dissociation constant is estimated to be about 10^3 M^{-1}, which is less than that for the antigen-antibody binding. It has been postulated that, while some peptides may remain associated with an MHC molecule during their lifetime, other peptides may bind various MHC molecules with a wide range of affinities. Peptides that bind weak may be more readily displaced by peptides that bind strong. This interaction is called "competitive binding". Most of the experiments performed in this field are in vitro studies; however, we know virtually nothing about the actual physiological interactions in the organism. Therefore, this kind of biochemical research needs further development in the coming years.

Much more is known about the tertiary structure of MHC molecules. An analysis of their structure reveals that it fully complies with the soliton concept. This will be shown for **MHC class I,** which is the best investigated. This ubiquitous FUEL is a membrane glycoprotein, just like all immunoglobulins and T cell receptors. The class I α chain is polymorphic and encoded within the MHC genes, whereas polymorphism of β_2-microglobulin is limited. The fourth and fifth domains of the α chain comprise the transmembrane and the cytoplasmic domain. The transmembrane α-helix of MHC class I contains approximately 25 predominantly hydrophopic amino acids. The region is terminated by a stretch of 5 basic amino acids Arg and Lys, which are made responsible for the *anchoring* of this integral protein to the cytosolic side of the membrane. The *Arg–Lys-stretch* is a recurrent motif in most integral proteins. While the role of this sequence in the energetic attachment of integral proteins to the negatively charged cytoplasmic side of the lipid bilayer by means of electromagnetic forces (attraction of +/– charges) is beyond doubt, its participation in the soliton triplet is of no less importance. According to the Law, all systems of space-time are open U-sets and participate in infinite interactions at the same time.

The transmembrane α-helix of MHC (or any other FUEL) can be

regarded as a supramolecular dipole that is positively charged at the cytosolic side and negatively charged at the extracellular side of the membrane. Thus the orientation of the dipole gradient of any integral FUEL is inverse to that of the electric plasma gradient. This ubiquitous electric fact is covered by the axiom on the reciprocal behaviour of the LRCs of contiguous levels. The orientation of the FUEL dipole is effected by the π-electron anion(s) of the aromatic residues which are located in the transmembrane part of the integral protein. The aggregated dipole moment of this delocalized anion is opposite to the electric field of the electrochemical membrane potential. This is basic electricity. The Arg–Lys stretch of integral proteins is involved in the conformational perturbation that accompanies the activation of the soliton triplet(s) in the α-helix. The soliton propagates along the α-helix and induces further interactions between the cytoplasmic tail carrying the positively charged stretch and adjacent *effector systems* in the cytosol[42]. In addition, class I MHC are glycosylated near the binding domain and include up to 15 sugar residues at each carbohydrate moiety. Sialic acid residues are also present in the vicinity of the active site. The first 3D-structure of a human class I MHC antigen, HLA-A2, was reported in 1987. In the meantime, the structure of two further class I alleles has been determined (HLA-Aw68 and HLA-B27).

The α_1 and α_2 domains of MHC have similar tertiary structure and form one pair, while the α_3 domain and the β_2-microglobulin form another. This pair resembles the immunoglobulin constant domain. For this reason MHC class I is considered a member of the *immunoglobulin superfamily*. The α_1 and α_2 domains each consist of 4 β-strands spanned by a long α-helix, which are mirror images of each other. Thus the peptide-binding domain represents a platform of 8 β-strands topped by two parallel α-helices. The groove between them is about 2.5 nm long and about 1.0 nm wide. These space dimensions correspond to a peptide length of 8-9 amino acids. Such peptides are generated from a larger protein during its processing in the cell. In most cases, it should be assumed that such peptides form a short α-helix stretch consisting of 2 or 3 turns. X-rays have confirmed an extra electron density in the groove of MHC class I presenting a peptide, but until now its nature has not been directly

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[42] The idea that every element in organic life is at once moved and movable is basic to Aristoteles' concept of *entelechy*. Unfortunately, this popular idea has been ignored in modern bio-science and medicine.

demonstrated. Peptides that are present in the cleft of B27 molecules are composed of 9 amino acid residues and appear to be in an extended conformation that accommodates exactly in the α-helix stretch. Self-peptides bound to HLA-B27 were eluted and successfully analysed.

Evidence in support of the idea that the groove binds antigens in the form of peptides was provided by mapping the locations of the polymorphic amino acid residues. In the A2 α chain 17 amino acids were found to be polymorphic, out of which 15 were found to belong either to the α-helices or to the β-pleated sheets which formed the floor of the groove. All polymorphic residues interacted with the peptide (see Table 3 below).

Table 3: Comparison of the amino acid sequences of different HLA-alleles. Substituted amino acid residues which participate in the binding of the peptide to the groove (cleft) are indicated with (*), while the amino acid substitution postulated to affect the T cell receptor is indicated with (**). For extra clarity, only substituted amino acid residues are given with respect to Aw68.1[43].

Allele	**Amino acid sequences of the groove**													
	——— α_1 ———							——— α_2 ———						
	*		**	*	*	*	*	*	*			*	*	*
	9	12	62	63	66	70	74	95	97	105	107	114	116	156
Aw68.1	***Tyr***	Val	***Arg***	Asn	Asn	Gln	***Asp***	Ile	Met	Ser	Gly	*Arg*	***Asp***	***Trp***
Aw68.2		Met						***Arg***	Pro		His	Pyr		
AW69	Val	***Arg***	***Trp***	His	***Tyr***	Leu								
A2.1	***Phe***		Gly	***Glu***	***Lys***	His	His	Val	***Arg***		***Trp***	His	***Tyr***	Ala

The HLA-alleles presented in Table 3 carry all the components pertaining to a soliton triplet. While Aw68.1 and Aw68.2 are more or less iden-

[43] Modified from J.M. Austyn & K.J. Wood, Principles of Cellular and Molecular Immunology, Oxford University Press, Oxford, 1993, p. 78, Fig. 2.8.

tical in the sequences that include functional soliton-specific residues, their difference to A2.1 is substantial. Aw69 takes an intermediary position in this respect. When A2.1 is compared to Aw68.1, we find many *functionally non-equivalent substitutions* in this allele. For instance, in position 62 Arg (+) is substituted for Gly, in position 63 Asn for Glu (–), in position 66 Asn for Lys (+), in position 74 Asp (–) for His (+/–), in position 97 Met (because of the sulfide group this residue can be regarded as a weak electron donor) for Arg (+), in position 107 Gly for Trp (π), in position 116 Asp (–) for Tyr (π), and in position 156 Trp (π) for Ala. Therefore, we assume that the groove of this allele exhibits a different binding capacity for peptides. Indeed, this idea was strongly supported when the extra electron density in the two crystal structures was compared. They were found to be quite different. Positions 74, 97, and 116 form the so-called "74-*pocket*". While the majority of the polymorphic amino acid residues are located to the side and on the floor of the antigen binding groove, the amino acid residues that are conserved between the alleles are largely confined to the more external parts of the α_1 and α_2 chains. For this reason epitopes of HLA-A2 which are recognized by antibodies are found on the exposed surfaces of the protein structure and are not buried inside the molecule.

Thus the structure of MHC class I that emerges from this analysis indicates that the variability of MHC alleles involves mainly the groove and the binding of self-peptides, while the outer part that interacts with antibodies and T cell receptors is rather conservative. Epitopes that are unique to a particular MHC allele are called *polymorphic* or "private" determinants, while epitopes shared by more than one MHC allele are referred to as *monomorphic* or "public" determinants. This is a highly deterministic terminology which does not enlarge our knowledge of the energetic function of these integral proteins.

This evidence confirms the overlapping energetic character of MHC alleles - it is basic to an understanding of the mechanism of allo-reactivity and self-restriction, which we shall discuss in conjunction with the T cell receptor. The data presented above are collected from only 3 HLA-alleles. However, more than 80 class I alleles have been found in humans. It will be of great interest to know the exact amino acid sequences of these alleles in the population. This will permit the development of a complete map of the various soliton triplets which are located in the cleft of the various HLA-alleles. As many chronic diseases are associated with specific HLA-alleles, this will improve our

knowledge of their pathogenesis (see below).

This knowledge will be of paramount importance especially in transplantation medicine. Patients awaiting transplantation can be subjected to a specific systemic toleration with peptides which have been obtained from the HLA-allele of the donor. This chronic exposition of the patient's immune system to peptides from the donor will stimulate its adaptation to these antigens. This kind of artificial desensibilization will lower the risk of rejection in the early phase after transplantation.

MHC class I alleles have been identified in humans and mice which are very similar to a particular allele but contain some additional mutations. These alleles are known as *mutant* MHC molecules. For example, the sequences of MHC molecules in some mutant strains of mice differ from each other by only one or two residues. Such mutations are also observed in the HLA-locus and are held responsible for the pathogenesis of rheumatoid arthritis (see below) and other immunological diseases with *HLA association*. Some of the most carefully studied mutations in the mouse are those which occur in H-2K^b molecules, where 17 spontaneous mutations have been detected. Some of these mutations differ from K^b by a single amino acid residue (see Table 4):

Table 4: Mutant Class I molecules in humans and mice (x = unknown amino acid replacement)[44]

a) Location of amino acid changes in some HLA-A2 mutants in humans

Cell line	**Allele affected**	**Position in the polypeptide chain**	**Amino acid charges**	**Domain affected**
DK1	A2	149	Ala–Thr	α_2
	152	Val–**Glu**		
	156	Leu–X		
DR1	A2	43	Gln–**Arg**	α_2
M7	A2	43	Gln-**Arg**	α_1

[44] Modified from J.M. Austyn & K.J. Wood, Principles of Cellular and Molecular Immunology, Oxford University Press, Oxford, 1993, p. 83, Table 2.6.

b) Location of amino acid changes in mutant H-2K^b molecules in mice

Haplotype	Locus product affected	Position in the polypeptide chain	Amino acid charges	Domain affected
bm1	K	152	Glu–Ala	
		155	Arg–Tyr	α_2
		156	Leu–Tyr	
bm3	K	77	Asp–X	α_1
		89	Lys–Ala	
bm5	K	116	**Tyr–Phe**	α_2
bm6	K	116	**Tyr–Phe**	α_2
		121	Cys–Arg	
bm8	K	22	**Tyr–Phe**	α_1
		23	Met–Ile	
		24	Glu–Ser	
bm10	K	165	Val–Met	α_2
		173	Lys–X	

The amino acid replacements in each MHC molecule presented in Table 4 involve at least one soliton-specific amino acid residue. Except for the three replacements, Tyr for Phe in position 116 in bm5 and bm6, and in position 22 in bm8, all the other substitutions are *functionally non-equivalent*. The association of certain immunological diseases with mutant MHC-alleles indicates that the energetic function of these central immunological FUELs - their ability to establish and propagate solitons - is profoundly impaired. This finding is a major breakthrough in the pathology of diseases. It explains the origin of many chronic immunogenic diseases which are HLA-associated. Their aetiology is unknown at present (see chapter 2.6).

This pathogenic mechanism can be observed in HLA-A2 mutants. The expression and appropriate function of MHC class I molecules is essential for the differentiation of CD8 T cells. Therefore, HLA-alleles leading to an impaired function of these FUELs may result in a deficient cytotoxic response. Indeed, many autoimmune reactions are associated with particular HLA-alleles and exhibit abnormal T cell reactions. Typical examples are *rheumatoid arthritis* and *multiple sclerosis* which are

HLA-associated (see chapter 2.6). The impairment of energy exchange of immunocompetent cells due to mutant MHC-alleles depreciates the *self-tolerance* of the T cells.

As observed in cancer, any impairment of energy exchange at the supramolecular quantum level causes a reduced efficiency at the cellular level. This deficiency is further propagated to the whole immune system (U-sets). If we define the total set of all immunocompetent cells in the organism as an organ, then we can also speak of an *organ deficiency*, e.g. immune deficiency in AIDS. The reason for this global impairment is that deficient HLA-alleles are expressed in all the immune and body cells. The new theory of the pathogenesis of diseases departs from the basic axiom stating that all systems of space-time are U-sets and contain themselves as an element. Whenever a particular energy exchange is impaired at the quantum level, this defect is propagated through all the levels of organic matter and can be manifested as clinical symptoms at the level of the organism. It is a tradition in medicine to attribute an arbitrary name to a recurrent set of clinical symptoms and define this constellation as a "disease". In this case, the symptoms are usually manifestations of the impaired energetic function of different organs. On the other hand, the same symptoms may appear in different diseases (U-sets)[45]. As with the laws in physics, many names of diseases carry physicians' names. Unfortunately, this kind of voluntary taxonomy does not enlarge our knowledge of the energetic pathomechanism of diseases.

Another fundamental aspect of the dynamic development of diseases is the *time of occurrence*, which is a particular quantity of time. Unless the disease is immediately manifested as *congenital*, the time of its exacerbation (specific Ljapunov time) is usually unpredictable and depends essentially on the particular energetic condition of the patient's organism. We shall show in chapter 2.8 that the occurrence of HLA-associated chronic immunological diseases can be postponed or even offset by early chronic treatment with cell-stimulating drugs. This holds true for most diseases which are caused by genetic mutations affecting the function of soliton triplets.

Typical chronic diseases which exhibit a strong association with a

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[45] This aspect is clearly documented in a standard textbook on internal medicine: R. Hegglin & W. Siegenthaler, Differentialdiagnose innerer Krankheiten, Georg Thieme Verlag, Stuttgart.

particular HLA-allele are *narcolepsy* (HLA-DR2) and *ankylosing spondylitis* (class I HLA-B27). Many autoimmune diseases, such as insulin-dependent *diabetes mellitus*, IDDM type I, *celiac disease*, *Graves' disease*, *systemic lupus erythematodis*, show an increased frequency with particular class II alleles (HLA-DR). When individuals with a type I IDDM are tissue-typed, 95% of patients possess either HLA-DR3 or DR4 alleles compared to 45-54% in the normal population. When the sequences of 4 polymorphic gene products of MHC isolated from IDDM patients were compared with MHC alleles from normal controls, it was found that a single position (in HLA-BQB1 gene) in the polypeptide chain correlated with the disease. Individuals with Asp (–) at position 57 in the β_1 domain of the DQB1 chain were resistant to the disease, while patients in whom this position was substituted with a neutral amino acid, for instance with Ser, Ala or Val, were susceptible to diabetis mellitus. This substitution is functionally non-equivalent and impairs the soliton triplet(s) in the MHC molecule. These results are substantiated by further clinical evidence.

The selective autoimmune destruction of the islets of Langerhans in pancreas in Type I IDDM patients is T cell mediated. This histological finding is held responsible for the development of diabetes mellitus, type I. Evidently, an impairment in the function of MHC molecules infringes upon the self-tolerance mechanism of the immune system - the T cells become autoreactive and destroy the body's own cells. The existence of an energetic defect in the antigen-binding of MHC molecules which participate in the T cell-mediated autoimmune reaction is a recurrent motif of pathogenesis in most chronic autoimmune diseases. We shall show below that self-tolerance and allo-reactivity are closely associated with such genetic failures[46].

The structure of MHC class II will not be discussed here. We shall only point out that this protein shares many similarities with the class I molecules. In general, the class II β chain exhibits a higher degree of polymorphism. Nevertheless, the amino acid residues of the soliton trip-

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[46] Indeed, it can be shown that the polymorphism of MHC alleles determines the type of peptides that bind MHC class I. The first direct evidence for this relationship was that a sequence polymorphism in the rat TAP2 gene correlated with a change in the spectrum of the peptides eluted from MHC molecules (Powis et al., Nature, 1992, p. 159). The authors correctly assumed that this phenomenon might be very important in human autoimmune diseases.

lets found in the allelic hypervariable regions of MHC class II molecules share the typical conservative variability as that observed in the CDRs of immunoglobulins.

As previously mentioned, *superantigens* bind to MHC molecules by cross-linking their glycocalix. They can activate about 5 to 25% of the responding T cells. The superantigens do not bind class II peptides in the peptide binding groove, but rather attach to the side of the molecule, in association with the β chain. The binding of superantigens is therefore not specific. The expression of MHC class I depends on the binding of peptides in the cleft. Mutant cell lines which cannot express MHC class I can do this only after they have been previously incubated with peptides. From this evidence the following conclusion has been drawn: an association of antigenic peptides with the peptide-binding groove of the MHC is required for the correct folding of the α chain, its association with β_2-microglobulin, and its transport to the surface. This interaction activates the soliton triplet(s) in the binding domain of MHC and triggers a soliton. This soliton induces the folding of the α chain, its association with β_2-microglobulin, and its transport to the surface in the same energetic manner as described for DNA solitons which drive transcription. Evidently, the binding of a peptide in the groove is essential for the activation of soliton triplets in the MHC. The binding of T cell receptors to external epitopes of MHC molecules activates the latter and contributes to the propagation of solitons in these FUELs. A mutant strain of mouse with a defective β_2-microglobulin gene and a loss of the ability to propagate solitons leads to a virtual absence of CD8+ T cell population in peripheral lymphoid tissue.

Energetic structure of T cell receptors: We showed that all FUELs operate according to the same energetic principle. This will be substantiated for T cell receptors which are central to all immunological interactions. It can be demonstrated in experiments that T cells respond in culture to antigenic peptides with a sequence length between 8 to 9 amino acids which may be part of a longer peptide sequence. These peptides are surprisingly homogeneous in length and very similar to those isolated from MHC class I molecules. In both cases, peptides with heterogeneous amino acid residues were found to bind preferentially to T cell receptors. A minimal length of the epitope is required for a recognition by the T cell receptor. A peptide that includes two or three residues which are known to be critical for the T cell recognition may not actually trig-

ger the response, unless the peptide is lengthened by the addition of one or more amino acids. Sometimes, when a single amino acid position is changed in the peptide, this may completely abolish the T cell response to this antigen. It has been correctly assumed that such residues are essential to the binding. We shall show below that the amino acid sequences of such peptides contain *soliton-specific* residues. Some peptides may carry a complete soliton triplet, while others carry an incomplete soliton triplet which has to be complemented with soliton residues from the binding domain of the T cell receptor. This aspect determines the specific energetic affinity of antigens to T cell receptors.

T cell receptors bind the *exposed* side of the MHC-groove-peptide complex. This energy exchange at the supramolecular level effects the interaction between B cells and T cells. From this we conclude that the MHC-groove-peptide binding is a prerequisite for the establishment of a common soliton that encompasses the MHC-peptide complex and the T cell receptor. This will be discussed in detail below.

Great efforts have been made to predict which sequences in proteins are T cell epitopes. It is believed that, by knowing this, it will be possible to prepare immunogenic peptides for vaccination. Based on theoretical considerations it has been predicted that the T cell epitopes consist of amphipathic α-helices, similar to the transmembrane α-helices observed in integral proteins. This prediction is not far fetched when one considers the fact that each α-helix turn consists of 3.6 amino acids. Peptides with 8 or 9 residues will fold to approximately 2.5 turns. We showed that the components of the soliton triplet are normally situated on one side of the α-helix. Usually, we find an integer number of turns separating two aromatic residues which form an extended π-electron system. The electron donors Glu and Asp (but also the weak donors Met and Cys) and the electron acceptors Lys and Arg are normally found at a distance of $3 \times n$ or $4 \times n$ residues away from an aromatic amino acid, where n is often 1. Therefore, selected peptides with 8 or 9 amino acid residues are likely to carry a complete or an incomplete soliton triplet. Evidently, both the MHC molecules and T cell receptors bind preferentially such peptide sequences.

Some authors have analysed the sequences of peptides which bind avidly epitopes of T cell receptors and discovered that an extraordinarily large number of peptides contain a particular sequence motif. Initially, it was proposed that this motif carried two hydrophobic residues flanked by a charged residue on the N-terminal ending and a polar residue on the

opposite ending. A surprisingly high proportion of these peptides turned out to be recognized by T cells in experiments. Other empirical models were also proposed. These models take into consideration the polymorphism of MHC molecules.

In one particular experiment, the epitope of the moth cytochrome *c* recognized by a mouse T helper cell clone was defined. The T cell clone A.E7, which was originally defined to be "specific" for pigeon cytochrome c and IE^k, was found to also recognize moth cytochrome *c*; the epitope was mapped to the region shown in Table 5. The size of the epitope necessary for T cell recognition, as determined by the T cell proliferative response in the presence of antigen and H-2k APC, was examined by using synthetic peptides of different length. The first response was elicited by peptide 97-103, the shortest molecule to stimulate the clone; this response was dramatically increased when the peptide was lengthened by two amino acids (95-103) or more.

When we analyse the sequence of the 97-103 peptide, we find Tyr (Y) at position 97 and further down two positively charged Lys (K)-residues at positions 99 and 103. In this minimal sequence, we find a π-electron system (Tyr-97) and two electron acceptors (Lys-99 and Lys-103). The negatively charged Asp (D) at position 93 completes the soliton triplet. The existence of an incomplete soliton triplet in this peptide explains why the response is dramatically increased when the epitope is enlarged to include Asp at position 93. When a shorter peptide is chosen, 98-103, from which the functional aromatic residue Tyr is cleaved, the epitope loses entirely its binding activity. This proves the central role of the π-electron system in the soliton triplet. The effect of the substitution of Ile (I) at position 95 was also examined. The binding specificity of the epitope was not substantially altered when different functional amino acids were replaced. However, there was a dramatic reduction in the binding affinity when a Lys residue was exchanged for Ile at position 95 (last peptide). In this substitution, a positively charged amino group is situated very near to Tyr and melts the "midgaps" of its π-electron system. This particular example confirms again the ubiquitous presence of soliton triplets. They are the functional units that produce standing waves (solitons) at the supramolecular level and mediate interactions. The example illustrates the common mechanism of inhibition by means of adjacent positively charged moieties.

Table 5: Analysis of the epitope sequences of moth cytochrome *c* recognized by a mouse helper T cell clone. The (+) signs correspond to the logarithmic binding affinity of the peptides to the T cell receptors[47].

90						**95**								**100**				**103**	
E	**R**	**A**	**D**	**L**		**I**	**A**	**Y**		**L**	**K**			**Q**		**A**	**T**	**K**	
90	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	103	++++
			93	—	—	—	—	—	—	—	—	—	—	—	—	—	—	103	+++(+)
				94	—	—	—	—	—	—	—	—	—	—	—	—	—	103	++++
						95	—	—	—	—	—	—	—	—	—	—	—	103	+++(+)
							96	—	—	—	—	—	—	—	—	—	—	103	++
									97	—	—	—	—	—	—	—	—	103	+
											98	—	—	—	—	—	—	103	–
					Val–	95	—	—	—	—	—	—	—	—	—	—	—	103	++++
					Phe–	95	—	—	—	—	—	—	—	—	—	—	—	103	+++(+)
					Met–	95	—	—	—	—	—	—	—	—	—	—	—	103	++(+)
					Gln–	95	—	—	—	—	—	—	—	—	—	—	—	103	+++
					Glu–	95	—	—	—	—	—	—	—	—	—	—	—	103	++
					Lys–	95	—	—	—	—	—	—	—	—	—	—	—	103	+

Generally, two types of T cell receptors are distinguished: the αβ T cell receptor to which we have referred above and the less well-understood γδ T cell receptor. The variable domain of the α and β chains form together the antigen-binding site of the T cell receptor. Sequence data suggest that the variable domains are folded into β-pleated sheets, closely resembling the immunoglobulin variable domains. Hypervariable or complementary determinants have been identified within these variable domains in at least three regions equivalent to those of immunoglobulins. No structural data are available for the γδ T cell receptor. The αβ T cell receptor recognizes antigens in the form of MHC-bound peptides which are expressed by APC. This process usually occurs in the *thymus* and *lymph nodes*. The γδ T receptor cell may not need the thymus to differentiate. It is assumed that this T cell type may also be selected in the gut epithelium where nests of numerous T cells are found. At present, their role is very poorly understood.

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[47] J.M. Austin & K.J. Wood. Principles of Cellular and Molecular Immunology, Oxford University Press, Oxford, 1993. p. 159. Fig. 3.33.

In addition, there are many other FUELs designated with a CD number (standing for *cluster differentiation*) on the T cell surface which also participate in the immune response. CD4 is the most prominent among them because of its ability to bind HI-virus. Some anti-CD4 antibodies precipitate the gp120 envelope glycoprotein of HIV, which mediates the attachment of the virus to the cell membrane (chapter 2.5). Evidently, both CD4 and gp120 exhibit homologous amino acid sequences. Since CD4 binds HIV, it can be assumed that they establish a common soliton, which effects the entry of the virus into the cell. It is important to observe that the bio-sciences are incapable of forwarding a stringent explanation of what force drives the penetration of the virus in the cell. From a theoretical point of view, this should be a key question in viral pathology. Only after this question has been properly answered can we develop new therapeutic strategies against AIDS and other viral infections (see chapter 2.8).

When gp120 is expressed on HIV-infected cells, this integral protein stimulates the cell as a proviral FUEL that induces the transcription of the viral code. The coupling mechanism is effected by the electromagnetic waves of the cellular action potential, which can be modulated by any membrane FUEL. Thus the expression of virus glycoproteins on the membrane of infected cells determines the cell metabolism in a specific delocalized manner. This circumstance enables the virus replication in the cell genome. The mechanism of virus replication can be explained in the utmost detail within the General Theory. Until now the viral-specific regulation of infected cells was an enigma for virologists. The role of virus glycoproteins which infected cells express for the transcription of proviral DNA (or RNA) is not realized because the regulation of the genetic code is still considered a “free lunch” in terms of energy consumption. This cellular process is currently regarded as completely uncoupled from extracellular regulation.

Not only T cells, but also all the immunocompetent cells express numerous other FUELs (receptors, channels, cytochromes for oxydative burst, etc.) with more or less specific effects. Many more FUELs are being continuously discovered. It is not possible to refer to all of them. This review of immunological regulation is limited to *immunoglobulins*, *MHC molecules*, and *T cell receptors* because they are considered central to the immune response. In this respect we should bear in mind that all immune FUELs operate according to the Law - when they are acti-

vated, they interact with the electric LRC and participate in the energy exchange[48] of the immune cell.

Within the General Theory, the presence of soliton triplets was confirmed in a large collection of membrane and humoral FUELs, such as IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, G-CSF receptors, C5a receptor, PAF receptor, etc. These proteins are involved in the stimulation of the immune system. Lymphokines and other humoral factors operate as mediators between the immune cells. According to the dipole model, they are cell-stimulating compounds. It is important to observe that all the immune cells interact with all other immune and body cells because they are open systems of space-time. In this context, we should warn the reader not to take too literally the specific cell interactions presented in standard immunological textbooks. These interactions represent a small sample of the infinite set of immunogenic interactions in the organism voluntarily selected for didactic purposes. Such examples illustrate the infinite vertical and horizontal energy exchange between the various systems and levels of the immune system.

2.4.4. The Energetic Mechanism of Self-Tolerance and Allo-Reactivity

The development of **self-tolerance** and **allo-reactivity** by the immune system is a central cognitive problem of modern immunology that can be explained for the first time in the light of the Law. This is of great practical value, as impaired self-tolerance and allo-reactivity are held responsible for the immunopathogenesis of various diseases. Before we proceed with the explanation of these phenomena, we shall present some fundamental facts that have so far evaded any logical interpretation.

Most relevant evidence in this field comes from experiments on mice tolerance. The immune system of the mouse becomes responsive to foreign antigens soon after birth. All antigens, present in the body while the immune system matures, are recognized as *self-compounds* and are tolerated by the organism. Thus, if foreign antigens are incorporated into a new-born mouse, it will not be able to enhance an immune response against these antigens when the immune system is developed.

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[48] Conventionally, this process is referred to as “signal transduction”. However, there is no valid and clear-cut definition of this term.

Such tolerance to a specific antigen can also be induced in mature animals. Inoculations with large amounts of foreign protein can make a mouse non-responsive to a later challenge with a dose and application form thereof that would otherwise have stimulated a high production of antibodies. For instance, cartilage collagen type II is considered autoimmunogenic in rheumatoid arthritis (RA). In animal models, epitopes of native cartilage collagen type II induce an inflammation (adjuvant arthritis) similar to that observed in RA patients. At the same time, when patients with RA are treated with type II collagen, the symptoms improve. This is termed "*oral toleration*". Oral toleration is an established method of inducing antigen-specific tolerance that suppresses artificially induced multiple sclerosis (MS), uveitis, and diabetes in animal models. Recent clinical trials confirm the beneficial effects of oral toleration in patients with MS and other diseases.

These results seem to be paradoxical at first glance. On the one hand, animal models do show that antigens can induce an immunological inflammation when they are topically applied. On the other, such antigens enhance tolerance and improve the clinical state when they are administered chronically at low doses. The inability to explain this paradox has led to the simultaneous advocacy of antithetical therapeutic approaches: *immunosuppressive* and *immunostimulating* treatments for one and the same disease (for details see Harrison's Principles of Internal Medicine). The proponents of immunosuppressive treatments claim that autoimmune diseases result from an immunological "over-reaction" caused by a deregulation of a specific effector system. This enhanced reaction of the immune system should be suppressed by a "specific" blockade. They recommend the administration of various cell-inhibiting drugs to which a specific blocking effect for only one effector system is ascribed.

This is a principal flaw in modern pharmacology. As all chemical agents that come in contact with a cell exert their effects through modulating its electric LRC according to their dielectric properties, all chemical compounds administered as drugs have a global effect on the cell. If they exhibit no dipole moment and carry one or more positively charged groups, they inhibit the body cells in a global manner. The magnitude of this cell-inhibiting effect depends only on the drug concentration at the site of reaction. Vice versa, any drug with a pronounced dipole moment stimulates all body cells in a dose-dependent manner. Therefore, cell-stimulating drugs are not specific in their therapeutic effect either. We shall prove this in detail when we discuss the group of polyenes in chap-

ter 2.7. This conclusion follows consistently from the dipole model and the principles of cell regulation as elaborated in the General Theory.

The minority of specialists who propagate immunostimulating treatments have no obvious explanation for this recommendation but the empirical evidence that oral toleration is beneficial to some chronic autoimmune diseases. Immunosuppressive therapies have so far failed to cure any chronic autoimmune disease, while immunostimulating therapies which have recently been developed show a systemic improvement of many diseases during chronic application (see chapter 2.8). The solution to this problem of great clinical relevance lies in explaining the immunological mechanism of self-tolerance and allo-reactivity. Both are aspects of one and the same thing - the Universal Law in respect of the self-organisation of organic matter.

In the absence of a general theory of biological regulation, the concepts and terminology which have been developed for these fundamental immunological phenomena are rather confusing. For this reason we shall first present the major concepts in this area; thereafter, we shall deal with the energetic explanation of self-tolerance and allo-reactivity. We shall only consider T cells because they are best investigated. The underlying energetic mechanism is paradigmatic for any other immunological process, for instance it is also valid for B cells which carry surface antibodies. Before we begin with our discussion, we must point out that the verbs “bind, recognize, respond, interact, etc.”, which are very often used in immunological textbooks, are imprecise circumscriptions of energy interactions at the supramolecular or cellular level. They abide by the axiom of CAP.

We indicated above that the three major groups of FUELs involved in the immunological response are B cell surface immunoglobulins, T cell receptors, and MHC molecules. They exhibit similar structural and functional properties. The active sites (binding regions) of these FUELs contain soliton triplets. The activation of these integral proteins upon antigen-binding or mutual binding (e.g. a T cell receptor binds a MHC-peptide complex) is in fact an activation of their soliton triplets. The soliton triplet is the fundamental functional unit of biological regulation at the supramolecular level - it includes a π-electron system, an electron donor and an electron acceptor. In proteins which constist of α-helices and β-pleated sheets aromatic, basic, and acidic amino acids are involved in the formation of soliton triplets. Further variations of soliton triplets at the supramolecular level are ATP, GTP, and the nucleotides of the DNA stack.

The soliton is a standing quantum wave that represents an action potential at the supramolecular level of organic matter. The discovery of the suprachemical structures of soliton triplets permits for the first time an understanding of the functional syntax of the amino acid sequences of proteins which are a mirror image of the genetic code.

The role of solitons cannot be properly understood unless the existence of the electric LRC of the cell is considered. The vertical energy exchange between the action potentials of the cellular level and the quantum solitons of the supramolecular level is responsible for the kinetic behaviour of cells and organisms. The intentional motion of organic life makes it seem entirely different from inanimate matter. The principal energetic difference between organic and inanimate matter is that organic matter exhibits a powerful electric gradient at the cellular level. This is the "driving force" behind its intentional motion. When a similar gradient is established in inanimate matter, e.g. in electronic circuits, inorganic matter can also be set in motion (e.g. robots). Both organic and inorganic matter are levels of space-time and abide by the Law.

The metabolic web as presented today is held responsible for the production of biochemical structures. However, their role in the motion of cells and multicellular organisms cannot be explained. Even the kinetic behaviour of individual biochemical moieties which is a prerequisite for any kind of cell metabolism poses insurmountable difficulties for the present biological outlook. For instance, what drives the intermediate compounds of the cytosolic metabolism into the mitochondrion, where they are further degraded in the OP to produce a proton-motive gradient and ATP? The same holds true for any energy interaction that is associated with the first and second messengers considered to be specific "signal transducers of cell information". Neither classical biochemistry, nor Mitchell's chemiosmotic theory gives us any answer to this crucial problem of cell metabolism. For this reason it is entirely omitted as a scientific problem in biochemical research and is not discussed in textbooks.

As the scientific presentation of organic matter is exclusively based on biochemistry, which is a pure description of structures, the bio-sciences have failed to grasp the "miraculous force" behind the "intentional motion" of organic matter. In the absence of an adequate theory, the motion of organic matter is attributed to God or his "invisible hand". However, according to the principle of last equivalence, God is a synonym for the primary term which is **energy exchange**. Insofar, this religious inter-

pretation is an intuitive notion of the Law. Unfortunately, bio-scientists have overlooked the fact that motion is the universal manifestation of energy exchange, so that organic matter is by no means an exceptional phenomenon in the universe, as some authors erroneously believe.

Every physical system is in permanent motion. This is also the basis of the theory of relativity. The term "intentional motion" is a subjective anthropocentric idea; for instance, it can also be applied to the rotation of the earth around the sun - we may as well claim that its intention is not to fall on the sun or leave the solar system. We have proved that gravitation is closely related to electromagnetism (U-sets) by deriving the gravitational constant *G* in Newton's law of gravity from the two basic electromagnetic constants ε_o and μ_o ($c^2 = 1/\varepsilon_o\mu_o$), which participate in Maxwell's four equations of electromagnetism and their predecessors - the conventional laws of electricity and magnetism. In fact, the two levels, conventionally defined as forces, are abstract U-sets of space-time defined within mathematics and cannot be separated in real terms - for instance all material charges through which electromagnetism is observed have a mass. At the same time we have proved that electromagnetism is the driving force behind intentional motion at the cellular level. The electromagnetic waves of the cellular action potentials superimpose at the organic level (e.g. ECG, EEG, EMG) and drive the body kinetically in a co-ordinated manner. Therefore, the emergence of organic life on earth is not a coincidental and unique fact, but an inevitable energetic outcome.

We can now proceed with this disquisition and apply the cosmological principle which is an application of the principle of last equivalence to the distribution of organic matter in the universe. In this case, we must inevitably come to the conclusion that organic life and intelligence are evenly distributed in the universe. In the absence of a reference system, we are unable to determine whether human intelligence tends more to the mean or to the underdeveloped species of transgalactic consciousness. It would, however, be arrogant to consider the human species the crowning of universal consciousness, given the fact that mankind has not realized the existence of the Universal Law of Nature yet. In cosmic scales, one million years, being the estimated period of evolution of human consciousness, is no more than an instant - a mere breath in the infinitude of space-time; human scientific consciousness itself only has a history of several thousand years.

Although this theoretical and philosophical introduction to the foun-

dations of the General Theory may seem far-fetched at first glance, it is indispensable for a better understanding of self-tolerance and allo-reactivity, which are much older events than consciousness. It also gives us an idea as to why these phenomena have been totally misapprehended in biology. Both phenomena are intricately linked to the new concept of evolution (see Evolution Law). We begin with the selection (evolution) of self-tolerance and allo-reactivity in the T cell population. The same principles also hold in B cells and any other histological type of tissue cell.

The T cell activation and selection in the thymus and lymph nodes renders immunocompetent T cells; they are said to be **MHC-restricted**. This means that T cells are activated only when they come into contact with peptides presented on MHC molecules of APCs (e.g. B cells). Therefore, from now on we shall speak of interactions between a T cell receptor (in fact some other T cell integral proteins of the CD type are also involved, but they are excluded for the sake of didactic clarity) and an MHC-peptide-complex. In fact, this energy exchange at the supramolecular level involves all T and B cells which are immunological systems of the cellular level. We begin with the conventional view.

CTLs interact predominantly with MHC class I, T helper cells with MHC class II. The interactions between T cells and B lymphocytes to antigen-antibody responses is MHC class II restricted. *Allo-reactivity* is defined as the ability of a large portion of the T cell pool to react with foreign (= **allogenic**) MHC molecules. About 1 to 10% of the T cell repertoire has been found to be reactive against <u>any</u> complete MHC disparity. It is an established fact that the T cell receptor responds to antigens defined as *allo-peptides* only when they are bound to MHC molecules. Essentially, there are two modes of interaction: the peptides are either presented on self-MHC or allo-MHC molecules. There is strong evidence that most self-MHC molecules are presented on the cell surface as *self-MHC-self-peptide complexes*. Thus, when a T cell receptor binds an allo-MHC, it actually binds an *allo-MHC-allo-peptide-complex*. Although the possibility that a T cell receptor reacts with a self-MHC-allo-peptide complex cannot be wholly excluded, the density of such complexes in the organism is estimated to be negligible.

The recognition of an antigen bound to allo-MHC is called **allo-restriction** which is a synonym for **allo-reactivity**; the recognition of self-MHC is called **self-restriction.** Self-restriction describes the *absence of*

reactivity (the absence of visible energy interactions) between T cells and self-MHC-self-peptide complexes expressed on body cells. This definition of *allo-reactivity* and *self-restriction* is based on present experimental data, and was performed for the first time in a clear-cut manner within the General Theory. Let us summarize these results for the sake of clarity:

Immunological Manifestation	Energetic Interaction
Allo-reactivity	T receptor binds an allo-MHC-allo-peptide complex or a self-MHC-allo-peptide complex and exerts an immune reaction
Self-restriction	T receptor binds a self-MHC-self-peptide complex, but exerts no reaction

Tolerance is the opposite term to *reactivity*. Normally, the organism, that is, the T cell (the T cell receptor) is non-responsive to *self-MHC-self-peptide*(*s*)*-complexes*. This self-restriction is also called **self-tolerance**. Sometimes, the T cell receptor may not recognize allo-MHC-allo-peptide complexes. This is called **allo-tolerance**, or **anergy**. The third possibility is when T cell receptors interact with self-MHC-self-peptide complexes. This **auto-intolerance** is observed in autoimmune reactions. Let us summarize these definitions too:

Immunological Manifestation	Energetic Interaction
Self-tolerance	T receptor binds a self-MHC-self-peptide, but exerts no immune reaction
Allo-tolerance	T receptor binds an allo-MHC-allo-peptide, but exerts no immune reaction
Auto-intolerance	T receptor binds avidly a self-MHC-self-peptide and exerts an auto-immunological reaction

The verb “bind” will be used in the following as a neutral term: it will not say anything about the outcome of an interaction between an MHC molecule and a T cell receptor. “Bind” means simply that the T cell receptor has a certain affinity to the MHC-peptide complex and associates (interacts) with it. The outcome of a binding may be, depending on the affinity between the two components, an *apoptosis* or *stimulation* of the interacting cells.

At present, apoptosis is considered the mechanism of “clonal deletion”. Cell stimulation is defined as *positive selection* in the case of allo-reactivity and as *negative selection* in the case of self-tolerance. The outcome of non-binding (no stimulation) is *anergy*, *functional inactivation*, and *cell lysis*. Clonal deletion, anergy, or functional inactivation are basic to the hypotheses which are currently forwarded to explain tolerance and reactivity in the immune system. The third hypothesis that assumes immune suppression is a variation of the functional inactivation hypothesis.

We showed that the immune regulation is based on cell stimulation, which can be depolarisation (increased cell metabolism, growth, and proliferation) or repolarisation (maturation and differentiation). Both types of stimulation occur simultaneously. Sometimes, one stimulatory process may suppress another. Maturation due to repolarisation may suppress proliferation due to depolarisation or vice versa. In this case, one often speaks of “refractory cells”. These terms are introduced at this point, so that they are not confused in the following discussion. Human language is intrinsically imprecise. This is especially true for immunological terminology.

Cells survive as long as they are in a position to maintain their electric LRC, that is, their electrochemical potentials across the plasma membrane and other intracellular membranes. The electric LRC undergoes incessant cyclic modulations, called action potentials. They are indispensable for the maintenance of the electric (and metabolic) LRC because they provide a continuous flow of energy into the cell - the import of substrates and the export of humoral factors that constitute the supracellular regulation. Depolarisation of the plasma gradient induces cell stimulation because of the transformation of electric energy into metabolic energy in the cell (axiom of CAP). When cell depolarisation occurs within the physiological range, it is automatically compensated by the simultaneous entry of substrates into the cell through Na^+-coupled amino acid and sugar symports (depolarisation results

mainly from Na^+-influx in the cell). This leads to the production of ATP in the OP and the repolarisation of the membrane potential by ATP-pumps (see above).

Under normal conditions, body cells die incessantly in the organism and are substituted by new ones. This is especially true for the immune system, where the turn-over rate of cells is very high. All systems of space-time have a finite lifetime. The natural death of cells is called **apoptosis**. Apoptosis is physiologically indispensable for the *regeneration of tissues* in the organism (see chapter 2.6). It is a universal property of the organism. The longevity of organisms is intrinsically linked to the capacity of the cells to die through apoptosis. In terms of wave theory, apoptosis fulfils a condition of *destructive interference*: physiologically, it is achieved by excessive depolarisation or repolarisation; therapeutically, unphysiological apoptosis, called *cell lysis*, is caused by cell-inhibiting drugs. The actual processes leading to apoptosis may vary, but they inevitably involve interactions between membrane FUELs. A prolonged depolarisation causes a dissipation of the electric LRC and cell metabolism. The same holds true for excessive repolarisation. Over-stimulation inhibits the import of substrates into the cell and reduces the metabolic rate.

The propensity of the cell to endure a certain degree of depolarisation or repolarisation without succumbing through apoptosis may differ from one histological type to another; its resistivity also depends on the initial conditions of the cell. For instance, all polyenes stimulate cell cultures by depolarisation. At higher concentrations (> 100 µg/ml), some cells may be lysed after a given period of incubation. However, most cells can recover when the time of incubation is not too long. There is an inverse correlation between the basic level of cell stimulation and metabolism and the propensity of the cells to survive during prolonged depolarisation. Renal tubulus cells operate at maximal rate under physiological conditions and can be easily impaired if they are additionally depolarized. Such cells quickly reach the threshold of dissipation, beyond which they can no longer compensate the additional stimulation. For this reason cell-stimulating polyenes become rather toxic in the kidney when they are applied intravenously. The same holds true for any other cell-stimulating drug of the depolarizing type (e.g. interleukins). Immune cells are quiescent cells and are thus much more resistant to excessive depolarisation. They can be stimulated many-fold as reflected by the extremely high concentrations of lymphokines and other humoral factors (ca. 10^4

higher than normal) which are released during the acute reaction. We can therefore conclude:

> **Apoptosis** is the only physiological mechanism leading to *self-tolerance* and *allo-reactivity* in the immune system.

This energetic mechanism will be explained for the interactions between MHC molecules and T cell receptors. T cell receptors bind to the exposed side of the MHC groove, predominantly with MHC-carriers of peptides. The binding of various peptides to the MHC groove activates the soliton triplet of the MHC-peptide complex. The MHC groove operates as a universal binding domain. It possesses a repertoire of soliton-specific amino acids, which are responsible for the non-specific binding of peptides with a sequence of 8-9 residues. The MHC cleft is energetically reshaped to accommodate the various peptide sequences. This interaction involves weak electromagnetic forces at the supramolecular level. The peptides may carry a full or an incomplete soliton triplet, which is complemented during interaction with soliton-specific amino acids from the MHC groove. The binding domains of the T cell receptor and immunoglobulins operate according to the same principle. These are the basic immunological interactions at the supramolecular level. What kind of interactions induce the development of self-tolerance and allo-reactivity at the cellular level and the level of the immune system?

Undifferentiated T cells in the thymus and other secondary immune organs meet APCs presenting self-MHC-self-peptide complexes. Since the MHC molecule may bind a variety of self-peptides, the pool of APCs represents all possible combinations of self-peptides. Although their number can be very high, the set of distinct functional permutations at the amino acid sequence level is rather restricted (see above). A peptide with 8 to 9 residues contains at least 2 soliton-specific amino acids, preferably, positively and negatively charged residues that bind the MHC-groove. This horizontal energy exchange involves electromagnetic forces (weak forces). This kind of interaction is competitive and non-specific. The total number of *functionally equivalent substitutions* of soliton-specific amino acids is rather restricted. The peptides that emerge from such substitutions exhibit an overlapping binding affinity. In the case of *functionally non-equivalent substitutions*, a significant drop in the binding affinity is observed when soliton-specific residues are substituted by non-soliton residues.

The actual arrangement of amino acid residues in common proteins shows that the sequences are rather conservative. This was proven for many representatives of the Ig superfamily. Usually, soliton-specific residues are separated by at least 2 or 3 residues that belong to the group of the thirteen non-soliton amino acids. This arrangement is typical for transmembrane α-helices. The cytosolic and extracellular sequences of integral proteins contain predominantly hydrophilic amino acid residues. From this we conclude that the MHC molecules do not randomly bind every amino acid sequence cleaved from a protein during cell metabolism, but "select" energetically active sequences with soliton-specific amino acids. Such peptides are in a position to activate a soliton in the groove. They cannot circulate in a free form in the body, because they will be deleterious to the organism - they will avidly associate with any kind of membrane FUEL. In this way they will infringe upon the coordinated energy exchange of the electric LRC in the cell. This kind of interaction is not compatible with organic life. Therefore, Nature (the Law) has provided energetic mechanisms of prevention. MHC-restriction is such a universal mechanism.

Peptides carrying complete soliton triplets are powerful dipoles; they interact with the cell membrane and make it permeable for ions. This kind of interaction is observed in the presence of *heat shock proteins*, which are powerful ionophores; they induce a rapid depolarisation and stimulation of the cells after heat injury. This stimulatory effect protects the cells in the acute burning phase; however, this effect may be deleterious when a prolonged and excessive depolarisation takes place, for instance, during a higher degree of burning. For this reason physiological proteins are secreted by the cell in the form of precursors. Most of the circulating proteins of the supracellular regulation are precursors. Both *precursor sequences* and *sugar residues* (sialic acids of the glycocalix) protect the active sequences of circulating proteins which contain soliton triplets from an unwanted contact (interaction) with the active sites of adjacent membrane FUELs. When the precursor sequences and their sugar residues are cleaved by various serum enzymes, the circulating proteins are transformed in the active form; they immediately interact with the cell membrane and exert a modulating (dielectric) effect on the plasma potential. When we consider the extensive body of biochemical evidence, which we cannot discuss in detail in this chapter, we can draw two basic conclusions with regard to immunology:

1. The physiological purpose of binding self-peptides to self-MHC is to neutralize the active amino acid sequences of cleaved oligopeptides that carry soliton triplets, so that they cannot interfere with the supracellular regulation of the body cells.

2. The *self-MHC-self-peptide complexes* are presented to immunocompetent cells for their *selection*. The purpose of this interaction is to induce and maintain **self-tolerance** and **allo-reactivity**.

The mechanism of selection involves the binding of T cell receptors to self-MHC-self-peptide complexes. Because of their energetic structure at the supramolecular level, the two FUELs avidly interact. Therefore, it is unlikely that large quantities of empty MHC and unbound peptides would circulate in the organism. This aspect should be further investigated. When a T cell receptor binds a self-MHC-self-peptide complex, a soliton occurs (axiom of CAP). Other T receptors of the CD type also participate in this supramolecular process by *cross-linking* (open systems). Undifferentiated T cells bound for selection encounter in the thymus a pool of self-MHC-self-peptide complexes expressed on APCs. Each complex represents a slightly different soliton pattern because of the different peptides carried in the MHC-groove. They establish a discrete continuum of solitons that covers the spectrum of all antigens (soliton-specific permutations) which an organism will encounter during its life. Recall that all qualitative differences are energetic differences between the systems (quantum energetic leaps). As the T cell receptor binds the conservative outer part of the MHC molecule, it can bind any self-MHC-self-peptide complex. Thus the energetic diversity of the solitons in the cleft does not affect the interactions between the T cells and APCs, but only modulates the degree of stimulation in a specific discrete manner.

In addition, this interaction is influenced by all other humoral factors present at the site. And last, but not least, the initial energetic conditions of the T cells determine significantly the kind of cellular response. Undifferentiated T cells may express different types of T cell receptors generated by DNA rearrangement in the germ line. This affects the degree of cellular affinity. Some T cells may bind self-MHC-self-peptide complexes of APCs very tightly, so that the cells are subjected to a prolonged depolarisation. Such cells are more likely to dissipate; they die by apoptosis in the thymus and do not enter the circulation. The binding affinity of

another portion of T cells to self-MHC-self-peptide complexes may be less pronounced. This kind of interaction provides an optimal depolarisation and stimulation of the T cells. In this case an average degree of depolarisation can be regarded as optimal for the cells (see Pareto criterion). As this kind of depolarisation is below the threshold of apoptosis and cell lysis, the T cells subjected to it are the actual survivors of this energetic selection in the thymus. They enter the circulation as immunocompetent cells. The same holds true for interactions that involve an optimal repolarisation. Cells involved in such Pareto-optimal interactions will grow, proliferate, differentiate, and maturate. The rest of the T cells in the pool bind very weakly or may not even bind the self-MHC-self-peptide complexes of APCs in the thymus. The activation of such cells is not sufficient, or as we say, it is suboptimal. These cells become anergic and die by cell lysis.

The T cell selection is thus determined by discrete energetic differences and is a highly dynamic process. Like any energy exchange, it can nonetheless be precisely assessed by means of mathematics - by the universal equation or a derivation thereof - which is the only adequate reflection of space-time. The phenomenon of T cell selection can be subsumed under the broader concept of "evolution". Alternatively, it can be described in terms of destructive and constructive interference. However, although mathematically and epistemologically correct, the wave theory approach is less feasible to the human mind, when it is applied to complex systems of organic matter. It requires a very high degree of abstraction, which is not taught in present-day natural sciences. Therefore, our approach in this volume is essentially descriptive - nevertheless, it is fully subjected to the inner mathematical and logical consistency of the new axiomatics of the Law.

As we see, T cells which are stimulated in the average are best adapted to survive. They represent the so-called "**wild type**" in the population. This term is of historical value and is rather confusing. In terms of statistics, the selected T cell population represents a normal distribution of various T cell lines around the mean value, which can also be defined as the value of optimal stimulation. Such distribution curves can be observed in any energy exchange. For example, the energy distribution curve of emitted photons follows this pattern when it is expressed as a function of the wavelength in Wien's displacement law for maximal radiation (see thermodynamics in vol. I & II).

In the General Theory, the *selection of T cells* in the thymus is called

the "**first selection**". The same pattern of selection can also be observed in the lymph nodes or any other secondary immunological organ (for instance, in the poorly investigated intestinal wall). This selection involves B cells too. There is no principal difference between the selection of T cells and that of B cells, as all body cells obey the Law of energy exchange. The "first selection" generates immune cells which can optimally interact with APCs carrying self-MHC-self-peptide complexes. These energetically selected cells enter the blood circulation and exert their actual immunological effects in the periphery.

What is the teleological purpose of this initial energetic selection? T cells selected in this way are tolerant to all body cells, because any body cell can be an APC. Immune cells of the first selection can interact with any body cell in the periphery and both cell types will be optimally stimulated. This is usually described as *self-tolerance*. At present, the term "self-tolerance" reflects only one side of the phenomenon. Selected immune cells are not merely self-tolerant, which implicates a notion of energetic indifference; in fact, they optimally stimulate all body cells and contribute to their supracellular regulation. We recall that all tissues regenerate, so that a certain percentage of cells dies every day by apoptosis and has to be replaced. The growth, proliferation, differentiation, and maturation of the body cells is thus regulated by immunocompetent cells generated from the first selection.

This is a well established fact and can be observed in any injury - for instance, *healing* is effected by the active migration and participation of various immunocompetent cells at the site of lesion. This ubiquitous histological fact is beyond doubt. In chapter 2.6 we shall show that the regeneration of bone tissue (about 20% per year) is effected by osteoclasts and osteoblasts which are transformed leukocytes. This pattern is without exception. Although these facts are well known, the central role of the immune system in the regeneration of body cells is usually neglected, while the interactions of immune cells with foreign bodies (antigens), which are probably much more seldom, is over-emphasized. It is very important to point out this epistemological aberration in medicine because it vitiates most current therapeutic strategies. Let us now summarize the chief conclusion from this discussion:

> The **first selection** in the *thymus* and *lymph nodes* produces immune cells that are *self-tolerant* to body cells. Immune cells from this selection can optimally stimulate the growth,

proliferation, and differentiation of body cells and thus regulate the *regeneration of the organism*.

The second equally important function of the immune cells is to establish *self-defence* against foreign antigens, also called **allo-reactivity**. The first selection engenders self-tolerance, but it does not determine the optimal T cell population against allo-MHC-allo-peptide complexes and self-MHC-allo-peptide complexes which can be encountered in the periphery. During the first selection, a random T cell repertoire is selected. Each cell from the pool is in a position to interact with a small portion of foreign antigens. Thus the first selection produces cell lines that exhibit an overall immunocompetence against any set of foreign antigens; their antigenic spectrum overlaps and builds a discrete immunogenic continuum. The explanation of this *a priori* property of the selected T cell pool will be given below.

When T cells from the first selection encounter antigens, a **second selection**, also called "**allo-selection**", takes place in the periphery. The allo-selection follows the same pattern as that of the first selection, which can also be called "**self-selection**". Some T cells are excessively stimulated by the antigen-MHC complexes and die by apoptosis. The majority of the T cells is, however, optimally stimulated. This group corresponds to the wild type; it is essentially responsible for the immune response. These cells will grow, proliferate, and produce new immunocompetent cells, such as *T killers* and *memory cells*. The rest of the T cell repertoire is poorly activated by the antigen-MHC complexes. These cells become anergic and die by cell lysis. It is generally acknowledged that the lifetime of circulating T cells is comparatively short. The two selections of T cells correspond to the *antigen-dependent* and *antigen-independent phases* of B cell selection as described in traditional immunology.

The *first* and *second selection* reveal a fundamental aspect that has not been realized yet. What mechanism is responsible for the fact that the repertoire of T or B cells generated during the first selection contains a broad spectrum of various immune cells that can cope with all the potential allo-antigens which may enter the organism? It is important to observe that the concept of the first and second selection repudiates the current idea that the immune system contains pre-determined responses for all possible antigens in advance.

Although the notion of the "*a priori* antigen-antibody specificity" of the immune system is in contradiction with the overwhelming evidence

in immunology, it is still the underlying explanatory principle in all therapeutic concepts in clinical medicine. The assumption that immune cells display primary antigen-antibody specificity has created the greatest cognitive dilemma facing modern immunology. The hypothetical number of cells with specific antibodies or T cell receptors which should circulate in the body so as to meet all possible antigen challenges must be virtually infinite. How could such a diversity be acquired in the body? And how could the immune system know in advance the existence of the new antigens which have been synthetically produced in the last few years? The paradoxical nature of this traditional view should thus be cogent to everybody.

This paradox is eliminated in the General Theory by the introduction of the soliton triplet concept. It restricts the number of possible permutations and energetic interactions at the supramolecular level and explains the "*a priori* antigen-antibody specificity" of the immune system after the first selection. We showed that the evolution of species has produced a pronounced conservatism in the variations of amino acid sequences of different proteins, which comprise the actual spectrum of antigens. The reason for this polymorphic conservatism is the energetic constraint under which organic matter has evolved. Only proteins with intact functions are selected and survive (constructive interference). Such FUELs must preserve their soliton triplets, which are the basic functional units at the supramolecular level. As these units consist of only seven soliton-specific residues, the number of combinations is rather restricted. Histones are a typical example in this respect. The remaining thirteen amino acids participate in the protection of soliton triplets. Therefore their position is also conserved, though to a lesser extent. This conservatism holds true in all proteins and genes throughout the various species, including viruses, bacteria, protozoa, and multicellular organisms. The number of peptides which are cleaved from such proteins and presented as antigens by MHC molecules is thus rather restricted. This polymorphic conservatism in the evolution of organic matter explains why the restricted repertoire of self-peptides presented in the first selection covers the whole spectrum of all possible foreign antigens which can be encountered during the second selection in the periphery.

The first and second selection, as presented above, are abstract simplifications done for didactic purposes. In science, we should be aware of the fact that space-time is a unity, so that all systems contain themselves as an element. It is a privilege of the human mind to discriminate

space-time in subsets in an arbitrary manner. This propensity of the mind is the origin of all categorical systems in science and daily life. As all natural sciences are categorical systems of mathematical origin, they have emerged from the mind, just as in Greek mythology Athene, the goddess of science, emerged from Zeus' head.

Below we shall present some examples for the "degenerated specificity" of antigens. For instance, the existence of superantigens confirms that the soliton triplets of MHC molecules and T cell receptors may be activated by molecules that cross-link membrane FUELs in a random way. Cell-stimulating drugs such as polyenes carry a complete soliton triplet (see below) and can activate all immune and body cells. The polyene molecule interacts directly with cholesterol in the lipid bilayer and depolarizes the membrane through its ionophoric property. The kind of energy interactions that polyenes exert on membranes is quite different from that of superantigens, but the final result is the same - both groups of compounds cause cell stimulation through modulation of the electric LRC. Let us now summarize the basic conclusions from this elaboration of the immune system:

1. **Apoptosis** is caused by excessive depolarisation or repolarisation of the electrochemical potential of the cells (condition of destructive interference).

2. **Soliton triplets** are functional units of the *supramolecular level*. The *action potential* of this level is called **soliton**. The soliton is a *standing wave* that induces the motion and function of proteins. According to the axiom of CAP, solitons are vertically exchanged with other action potentials, e.g. with the electric action potentials of the cell. The soliton triplets can be activated by energetic interactions at the supramolecular level (horizontal energy exchange). The binding of peptides that carry complete or incomplete soliton triplets to MHC molecules is such an interaction.

3. Interactions between soliton triplets of *self-MHC-self-peptide complexes* and those of the *T cell receptor* are responsible for the **first selection** that generates **self-tolerance**.

4. Interactions between soliton triplets of *self-MHC-allo-peptide complexes* or *allo-MHC-allo-peptide complexes* and soliton triplets of the

T cell receptor are responsible for the **second selection** that generates **allo-reactivity**. Both self-tolerance and allo-reactivity are dialectical aspects of the immune system, which is an open system of energy exchange.

Self-tolerance and allo-reactivity in the pathogenesis of diseases: Self-tolerance and allo-reactivity are two dialectic aspects of the immune system. When energy exchange during the first and second selection of immunocompetent cells is impaired, we observe **auto-intolerance** and/or **allo-tolerance**. For instance, when the T cell receptor binds a deficient allo-MHC-allo peptide complex carrying functionally inequivalent soliton-specific mutations, this interaction may not trigger an immune response. When observed at the level of the organism, this phenomenon is circumscribed as *immunodeficiency*. Allo-tolerance against self-MHC-allo-peptide complexes may be beneficial in some clinical conditions. This type of tolerance is of great importance in *oral toleration*. If an individual receives foreign proteins (but not bound to MHC-carriers), these proteins are processed and expressed in the MHC-grooves of self-APCs. If they are available in sufficient concentrations in the organism, they are also presented in the thymus and participate in the first selection (self-selection) of the T cell repertoire. After a given period of time, T cells will be selected which are tolerant to these allo-antigens.

This phenomenon can be employed in transplantations. Prior to transplantation, the recipient should be treated with proteins from the donor, including MHC-peptides. Alternatively, special immunisations can be developed. Such immunisations will represent mixtures of peptides that carry specific soliton triplets of the donor's HLA-allele. They should be chronically administered before transplantation. In this way the immune system of the recipient is "educated" to tolerate the transplant before transplantation. Such a therapeutic approach will render the use of immunosuppressive drugs which are highly toxic obsolete or reduce their dose significantly.

Immunosuppressive drugs are potent cell-inhibitors. As immune cells proliferate at a high rate, such drugs tend to inhibit the immune system in the first place. The first and second selections are energetic processes based on optimal stimulation - they involve all immune cells and FUELs. Immunosuppressive drugs impair the function of both processes. While immunosuppression is deliberately induced in the acute post-transplantation phase, its long-term adverse effects may outweigh the initial ben-

efit, as the results of many recent transplantation studies (some of them carried out by myself) indicate. Many patients die in the acute post-transplantation phase because of opportunistic infections due to immunodeficiency; in the late phase, they develop cancer and chronic disorders of vital organs, which are responsible for most subsequent premature deaths (see chapter 2.9).

Selected examples will confirm below that the pathogenesis of all viral infections (e.g. HIV) and autoimmune diseases can be logically and consistently explained on the basis of the energetic mechanism of the immune system as outlined above. Before we switch to medicine, we shall shed some light on a highly confused area in immunology which deals with humoral factors.

2.4.5 The Energetic Structure of Common Humoral FUELs of the Immune System

In this section, we shall discuss some common cell-stimulating proteins that are excreted as humoral FUELs by the immune cells and play a major role in their supracellular regulation. In particular, we shall focus on cytokines, such as IL-1, IL-8, and TNF (tumour necrosing factor), and interferons, such as IFN-γ, IFN-α, and IFN-β. These cytokines are most commonly quoted when the function of the immune system is discussed. They are paradigmatic for the overwhelming variety of humoral factors produced by the cells of the immune system. It is important to observe that these factors are also produced by other body cells.

Interleukin, IL-1, and *tumor necrosing factor*, TNF, are considered proinflammatory kinines. Like all other lymphokines, they have pluripotent effects. Present immunology has great difficulty in systematizing these factors because it tackles the kinines from a deterministic point of view and searches in vain for monocausal relationships between individual kinines and their effects. The two factors IL-1 and TNF are produced by a variety of cells. Lymphotoxin, a TNF homologous protein, is mainly secreted by CD4 and CD8 cells. Mature TNF is trimerous. Each subunit contains a single disulfide bond. The three subunits are most probably non-covalently bound. Each subunit consists of 2 β-pleated sheets and five antiparallel β-strands. The outside β-sheet is rich in hydrophilic residues which protect the active sites; the inner sheet is also largely hydrophilic and contains the C-terminal segment, which is lo-

cated close to the central axis of the trimer. Up to 71% of the TNF residues are structurally equivalent to residues in satellite tobacco necrosis virus capsid protein. Sequence homologies between human and viral proteins are quite common. We shall show below that there is a close homology between gp120 of HIV and human MHC class II. Such structural and energetic homologies play a major role in the pathogenesis of viral diseases. This functional conservatism of proteins of different species results from the energetic constraint of the Law.

Based on the soliton triplet concept and the dipole model, an analysis of the amino acid sequences of several hundred physiological proteins was performed. The analysis is ongoing, as almost every day the structure of a new protein is elucidated. It includes many common cytokines with depolarizing or repolarizing properties. The chief result of this evaluation is that such proteins exhibit at least one α-helix, which normally corresponds to the transmembrane part when these proteins are membrane-bound, e.g. as receptors. Many membrane-bound proteins form only one α-helix of the C_cN_e-type. The depolarizing properties of these cytokines can be adequately analysed when they are compared to proteins of the repolarizing type. Repolarizing proteins are found less frequently in the organism than depolarizing proteins. This indicates that the supracellular regulation is predominantly of the depolarizing type. However, this quantitative estimate needs further confirmation. For a repolarizing protein of reference we shall now choose *somatostatin*, because the effects of this hormone are extensively evaluated. This ubiquitous protein is a *cyclic* protein that consists of two 14-amino acid chains (see Table 6.):

Table 6: Amino acid sequence of somatostatin

COOH	14	13	12	11	10	9	8	7	6	5	4	3	2	1	(COOH)
	Lys	**Arg**	**Glu**	**Arg**	Pro	Ala	Met	Ala	Pro	Asn	Ser	Asn	Ala	Ser	
	°														
	°														
NH_2	15	16	17	18	19	20	21	22	23	24	25	26	27	28	(NH_2)
	Ala	Gly	Cys	**Lys**	Asn	**Phe**	**Phe**	**Trp**	**Lys**	Thr	**Phe**	Thr	Ser	Cys	

Somatostatin has a sequence of 3 π-amino acid residues (Phe-Phe-Trp) at positions 20, 21, and 22, and another π-amino acid (Phe) at position 25. The sequence of the three aromatic π-residues is flanked on each side by one basic amino acid Lys (+) at positions 18 and 23 which act as electron acceptors. At position 12 we encounter Glu (–) as electron donor flanked by two Arg-residues at position 11 and 13, and Lys at position 14. Thus somatostatin carries all the components of a soliton triplet. The three positively charged residues build the anchor of somatostatin on the negatively charged cytosolic side of the membrane. As already mentioned, this is a recurrent motif in all membrane FUELs.

Somatostatin is a humoral factor, a hormone that exerts its action on the cell membrane, that is, it interacts with the lipid bilayer and the FUELs embedded in it. It has been experimentally demonstrated that the activity of somatostatin resides in the four π-amino acid residues belonging to the soliton triplet. The exact orientation of somatostatin in the membrane is not known. From its cyclic structure we can conclude that its possible orientation is of the C_eN_e-type (recall: the index "c" indicates (c)ytoplasmic (intracellular) ending and "e" - (e)xtracellular ending; COOH = C and NH_2 = N). The COOH-ending of Ser at position 1 and the NH_2-ending of Cys at position 28 must be exposed to the extracellular side. In this case somatostatin consists of two α-helices of 14 residues, each spanning the lipid bilayer. Experimental data shows that the peptide is also active when it is not cyclated. The 15-28 peptide of somatostastin carries an incomplete soliton triplet and can exhibit a rest activity. These data also comply with the new theory.

The antagonism between depolarizing proteins of the C_cN_e-type and repolarizing proteins of the C_eN_e-type is quite pronounced in most primitive species, where both FUEL types are found to be involved in *chemotaxis*. This antagonism causes the *tumbling* of primitive species. Depolarizing agents usually act as *chemoattractants*, repolarizing agents as *chemorepellants*. However, under certain conditions these effects can be reversed. Immune cells also respond to various humoral factors that act as chemoattractants. While depolarizing cytokines, set free as proinflammatory agents, induce chemotaxis of immune cells towards the site of infection, repolarizing agents may inhibit chemotaxis (refractory cells) or migration of immune cells away from the site of infection.

The supracellular regulation contains both types of proteins, which interact simultaneously with the body cells. For instance, the GABA-receptor in CNS belongs, like somatostatin, to the repolarizing C_eN_e-

type. GABA is an inhibitory neurotransmitter in the synapses. When this compound with a pronounced dipole moment[49] interacts with the GABA-receptor, which is in fact a Cl^--channel, the Cl^--inward conductance that is responsible for the repolarisation of the cell is increased. It is a well established fact that neuronal inhibition at the synapses is achieved by repolarisation. This also indicates that the C_eN_e-type of membrane proteins have repolarizing properties.

Somatostatin has been found to induce K^+-inward current into the cell (against the potassium gradient). K^+-inward current is coupled to Cl^--conductance. It is assumed that somatostatin also modulates intracellular calcium levels by inhibiting either calcium influx or intracellular mobilisation. These repolarizing effects of somatostatin can be reversed by the *calcium ionophore* A23187, which is a potent depolarizing agent. The effects of this compound on the cells are very similar to those of polyenes. The repolarizing effects of somatostatin can also be blocked by potent cell-inhibiting drugs such as *tetraethylammonium* (TEA), which is known to inhibit potassium channels in the CNS.

The "nicotine paralysing action" of TEA has been known since the beginning of this century. TEA is a small, positively charged molecule which carries a quaternary amino group that "melts" the midgaps of the π-systems of soliton triplet(s) of integral FUELs and inhibits their function in an unspecific manner. The effects are most pronounced in the nervous and cardiovascular system. Similar, though less pronounced, inhibitory effects are attributed to the repolarisation of neuronal synapses

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[49] GABA is a ubiquitous central neurotransmitter, just like Glu and Asp. These compounds have a pronounced dipole moment. The idea that amino acids like Glu and Asp may also play a major role as neurotransmitters has posed great problems for neurophysiologists, who are still attracted to the deterministic view that amino acids are structural elements of proteins and cannot have a regulatory function at the same time: "The CNS contains uniquely high concentrations of certain amino acids, notably glutamate and gamma-aminobutyrate (GABA); these amino acids are extremely potent in their ability to alter neuronal discharge. However, many physiologists were extremely reluctant to accept these simple substances as central neurotransmitters. This reluctance was based in part on conceptual problems of how to discriminate amino acids acting as transmitters from the same compounds acting as precursors for protein synthesis." from Goodman & Gilman's The Pharmacological Basis of Therapeutics, p. 256. These conceptual problems are eliminated in the General Theory based on the Law by introducing the concept of U-sets.

and have been reported in hippocampal slices, rat cortex, cerebellum, and hypothalamus in the presence of somatostatin.

Because of its repolarizing effect, somatostatin is conventionally defined as a "weak cell-inhibitor". However, we should distinguish between the cell-inhibiting effects of the TEA-type and the physiological inhibition due to repolarisation. The latter is opposite to depolarisation (reciprocity of the LRCs of contiguous levels) - repolarized cells are less responsive (refractory) to cell stimulation by depolarisation. Initially, somatostatin was found to inhibit the secretion of the pituitary growth hormone and other hormones, such as TSH, prolactin, etc. Subsequently, it was established that somatostatin affects all body cells. This is in agreement with the fact that all cells are open systems - their electric LRC can be modulated by all the supracellular regulation's agents.

We have introduced the effects of somatostatin by assuming that it acts as an integral protein. Although the existence of somatostatin receptors has been postulated, they have not been found yet. In the General Theory, all FUELs are U-sets. Therefore, we repudiate the present deterministic view of causality and substitute it with the global approach of the Law. From an energetic point of view, it does not make any difference whether somatostatin needs a receptor to exert its action on the cell or acts as an integral FUEL, because the final effect on the electric LRC is the same.

Present ligand-binding research on the other hand cultivates the idea that a hormone binds specifically a corresponding integral receptor. This monocausal approach does not consider other interactions that may occur simultaneously. In fact, the hormonal effects observed in the organism are the integrated product of all cells and tissues - cells respond to hormones globally and never specifically. This scientific purism introduces insurmountable difficulties in explaining the kinetic curves of ligand-binding studies performed in cell cultures, as they do not comply with the results predicted by this theory. Indeed, there is substantial evidence that many hormones such as somatostatin react with the cell membrane without having a specific membrane FUEL, called "receptor". Their mechanism of action is, nonetheless, invariant. All FUELs that interact with the electric LRC affect cell metabolism in a global manner.

Somatostatin is a typical example of a physiological agent of the repolarizing type. One should be cautious when analyzing the effects of repolarisation. Repolarisation does not necessarily mean inhibition of cell activity. This is the actual effect of unphysiological cell-inhibiting

drugs, some of which we shall present below. Repolarisation merely raises the setting point (the threshold) of cellular activation. It is a physiological switch from one metabolic state to another without impairing the efficacy of the cell. During repolarisation a different set of proteins can be encoded because of the altered pattern of electromagnetic wave interference, which drives transcription and replication in the nucleus in a delocalized manner.

Exactly this kind of effect can be observed in the presence of repolarizing cytokines. Different set points of the ground electrochemical potential affect the whole metabolism of the cell in a coherent manner. For instance, there is evidence that proliferating immune cells are transformed into mature cells by increasing the set point of their electrochemical potential through repolarisation. While there is no doubt that depolarisation enhances cell growth and proliferation, e.g. by mitogens, ionophores, antigens, etc., the experimental evidence for repolarisation is less clearly worked out in bio-research, probably because of the difficulties in interpreting this phenomenon in a coherent manner. A basic example in this respect is *embryogenesis*, which is regulated by a finely tuned depolarisation and repolarisation caused by sexual hormones and cytokines which are produced by the mother and the foetus during pregnancy. This fact confirms that the development of the foetus abides by the Law[50].

TNF (tumour necrosing factor) is a typical example of a repolarizing cytokine when its effects are properly analysed. This protein has 157 residues in the active form. When its amino acid sequence is compared to that of the homologous *lymphotoxin*, it becomes evident that most of the aromatic π-residues are preserved. This homology is also observed when TNFs from various mammalians are compared. The tertiary structure of TNF is no less important than its amino acid sequence. While the role of α-helices is well established in biology, the energetic function of

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[50] According to the principle of last equivalence, we can use any word for the primary term. For instance, we can replace the physical term "space-time" with the religious concept of "God" without affecting anything in the new axiomatics. In this sense, the religious statement that pregnancy is "God's affair" is an intuitively correct perception of the Law in embryogenesis. The ethical implications that are derived from this statement in Christian religion are, however, in breach of the Law.

β-*pleated sheets* has been very poorly investigated. The fact that β-pleated sheets form the outer coat of proteins and thus protect the soliton triplets in the active site(s) from unwanted interactions with the ionic solution indicates that these tertiary structures have an important stabilizing effect on the membrane potential. This aspect needs further elucidation.

There is an important observation associated with TNF that cogently confirms the delocalized coupling between the OP in mitochondria and the plasma potential. Mitochondria of TNF-treated cells look swollen and have a few cristae. This is the result of a prolonged repolarisation with this cytokine. Anaerobic respiration is increased in such cells so as to compensate for the reduced oxydative respiration in the mitochondria. In this case, we have the classical opposite effect to depolarisation as previously described. Repolarisation of the plasma potential leads to a corresponding depolarisation of the mitochondrial potential. The magnitude of the mitochondrial potential is proportional to the rate of OP and ATP-production, as proven in the chemiosmotic theory. This delocalized coupling is at the heart of the energy balance of the cell and the organism, as proven for the first time within the General Theory. A repolarisation of the plasma potential causes a depolarisation of the mitochondrial potential because the two potentials are serially coupled by the cytoplasm, which is conductive and electroneutral. The mitochondria of TNF-treated cells will drive down OP and less ATP will be produced. Thus, cell metabolism is decreased during repolarisation.

The observation that mitochondria have a few cristae under TNF-repolarisation is of special interest with respect to the Law. The energy stored in the electrochemical gradient is proportional to the surface of the membrane, which operates as a capacitor. The disappearance of cristae corresponds to a reduction in the electric energy produced by the mitochondria and stored as a mitochondrial potential across the outer membrane. Recall that the action potential is defined as the cross-sectional area per time E_A = SP(A)[2*d-space*]*f*. Cristae, invaginations, large membrane surfaces (Golgi), etc. indicate that more energy is stored in such membranes and organelles when $f = cons$. This is another recurrent motif of nature that can be histologically observed - it is powerful morphological evidence in biology that confirms the validity of the Law.

As the supracellular regulation is a mixture of depolarizing and repolarizing agents, the effects of repolarizing cytokines can only be assessed in conjunction with the effects of depolarizing cytokines, as both groups simultaneously affect the immune cells. A higher level of

repolarisation means a higher threshold for the depolarizing agents. TNF-repolarisation increases the expression of MHC class I molecules and decreases the endocytosis of membrane FUELs during cell activation. The net effect depends on the initial energetic conditions of the cells, which hitherto could not be assessed under physiological conditions. The supracellular regulation is finely tuned and exhibits an optimal ratio of depolarizing and repolarizing factors at any time (Pareto-optimal). This is a recurrent, self-perpetuating energy exchange based on constructive interference. In extreme situations, e.g. in acute peritonitis, the self-regulation of the immune system may fail. In this case it should be supported by medical measures. For instance, in the largest multicentral controlled trial ever performed in acute trauma patients in intensive care units (ICU), which I headed, we found that the additional application of cell-stimulating drugs (Amp) decreased early mortality. ICU patients with severe trauma normally die of sepsis and not from the injury itself. In sepsis, the depolarisation limb of the humoral cascade is weakened and therefore should be therapeutically supported by immunostimulating agents.

IL-1 exhibits similar properties to those of TNF. Two types are known: IL-1β and IL-1α. Like all cytokines, the two proteins are glycosilated. The three-dimensional structure of IL-1β reveals 12 β-pleated sheets held together by hydrogen bonds. Extended β-pleated sheets are a recurrent motif in repolarizing cytokines. IL-1β and IL-1α produce fever, sleepiness, anorexia, generalized myalgia (impaired depolarisation of muscle cells), arthralgia, etc.; at higher doses, they induce hypotension (impaired adrenergic depolarisation) and suppress the expression of other genes, e.g. albumin, cytochrome p450. IL-1 reduces the surface expression of its own type I receptor (self-regulation) by accelerating mRNA degradation (energetic coupling between genetic regulation and membrane gradient). IL-1 inhibits gene expression of thyroglobulin and thyroid peroxidase. A subpeptide of IL-1β consisting of residues 208-240 possesses sleep-inducing and pyrogenic properties, whereas a subpeptide 237-269 antagonizes the effects of mature IL-1. The latter phenomenon indicates that single sequences may act in a depolarizing way and thus reverse the effect of the whole protein. The spectrum of cellular effects of IL-1 covers most common phenomena observed during repolarisation and thus fully complies with the General Theory. In order to underline the validity of the new theory, we shall present a key example of repolarisation which at first glance may seem to be unrelated to cytokines, yet cogently demonstrates the role of *protein orientation* in cell membranes.

Why do retinal rods repolarize upon photon interaction? Although vision is one of the most thoroughly evaluated phenomena in physiology, this central phenomenon cannot be adequately explained. Based on this example, we shall show that organic matter has developed a vast repertoire of reciprocal energetic effects which reflect the basic axiom of the reciprocity of contiguous LRCs. *Rhodopsin*, like bacteriorhodopsin, is an integral photosensitive FUEL of the depolarizing type that is found in retinal rods. However, photon interactions with rhodopsin lead to repolarisation of the rods. How can we explain this apparent paradox in the light of the General Theory?

The discs in the outer segment of retina cells (rods) that harbour rhodopsin are invaginations of the cellular membrane of these cells, so that the lumen inside the discs represents the extracellular compartment. Rhodopsin in disc membranes is thus turned upside down. When a photon falls on rhodopsin, there is a profound depolarisation of the disc membranes with respect to their lumen. As the discs are invaginated in the outer segments of the rods, they operate as intracellular organelles, such as mitochondria. The electric LRC of the disc membrane is serially coupled to the electric LRC of the plasma membrane. When the intracellular potential of the discs is depolarized in the course of a photon interaction with retinal in rhodopsin, this automatically triggers a corresponding repolarisation of the plasma membrane of the rods. This is effected by the delocalized coupling of the two LRCs of contiguous levels that behave reciprocally. This interaction is inverse to that observed in normal cells subjected to external depolarisation by chemical moieties. This indirect, photon-induced repolarisation closes the cation-specific channels (voltage-gated channels) in the plasma membrane of the rods.

At present, this effect is erroneously attributed to cGMP; it also involves another integral protein, called *transducin*. Transducin belongs to the *G-protein* family and is a ubiquitous cell-stimulatory protein. It can be shown that stimulatory G-proteins are always involved in cell depolarisation. Why should transducin make an exception in retinal cells by acting as a repolarizing agent? This is the weak point in the traditional interpretation of this phenomenon[51].

There are four basic arguments on behalf of the new energetic interpretation: 1) The light-harvesting membrane protein, rhodopsin, is very

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[51] Stryer, L. Ann Rev Neurosc, 1986, 9: 87-119; Fesenko et al. Nature, 1985, 313: 310-313, etc.

similar to bacteriorhodopsin, which is also of the C_cN_e-type and is a classical depolarizing FUEL. 2) Rhodopsin should be regarded as an irreversible proton-pump, while bacteriorhodopsin is a reversible proton-pump. 3) The existence of more than a thousand discs in each outer segment of a rod clearly indicates that this enlarged aggregated membrane surface augments the photon-rhodopsin interaction, from which vision emerges. 4) In this particular case, rhodopsin is a photoreceptor inserted into the cell; it reacts with photons from the visible light which can reach the photoreceptor directly by passing through the cytoplasm of the rods. This solution is not applicable to somatic receptors that interact directly with the chemical compounds of the supracellular (extracellular) regulation, because the latter must first enter the cell through the membrane without exerting any effect on it, and this is virtually impossible.

Obviously, intracellular rhodopsin is activated by photons from the visible light in a delocalized manner. These photons are electromagnetic waves with the energy $E = hf = E_A f$; they are of the same origin as the electromagnetic waves produced during repeated depolarisation and repolarisation of the plasma membrane. According to the General Theory, the electromagnetic waves of the cellular action potentials drive the DNA code in a delocalized manner. This mechanism is identical to that observed in vision. Thus, the activation of rhodopsin through photons, being responsible for the visual perception, is paradigmatic for the delocalized regulation of the genetic code by external modulations of the electric LRC. We shall discuss this aspect in detail in conjunction with the pathogenesis of AIDS (chapter 2.7).

Preliminary experimental data on TNF confirms the existence of specific soliton triplets in this protein. Histidine at position 146 or a single Trp (π) in IL-1β is required for its biological activity. N-terminal mutations suggest that a single point substitution of Arg-127 (+) to glycine (functionally non-equivalent substitution) results in a 100-fold loss of activity of T cells without affecting the magnitude of the receptor-ligand binding. This fact alone is sufficient warning not to over-estimate the validity of ligand-binding studies. Substitution of Arg (+) to Gly at position 120 in IL-1β results in an absence of pyrogenic activity, but the kinine retains its ability to stimulate ACTH release. Changing Asp-151 (–) to Tyr (π) results in a loss of PGE_2 induction and fibroblast growth, but retains T cell responses. This mutein also antagonizes IL-1β and IL-

1β induction of PGE_2. Changes involving soliton-specific amino acid residues of this mutein can reverse the aforementioned effects.

IL-1 induces two nuclear factors: NF-kB and AP-1. It is remarkable that proteins of the family NF-kB/Rel also act as "signal enhancers" of the proviral DNA of HIV. These signal proteins are also stimulated by other repolarizing cytokines, such as TNF and IFN-γ. This fact confirms that repolarizing kinines stimulate HIV-replication, while depolarizing kinines, such as IFN-α and IFN-β, suppress HIV-replication. The last two IFNs were found to be effective in the treatment of many chronic immunologic diseases, while the therapeutic results with IFN-γ were less reassuring. Most of the effects presented above are derived from in-vitro studies under unphysiological conditions. When administered to subjects, the effects of cytokines should be evaluated in the context of the humoral cascade of the immune system. Such global evaluations under real conditions have not been performed in immunology yet.

Let us now briefly discuss IL-8, before we turn to interferons. IL-8 is a depolarizing kinine. It is a small non-glycosidated protein produced as a precursor of 99 amino acids and secreted after cleavage of a signal sequence of 20 residues. The active form consists of 72 residues. The IL-8 constitutes three antiparallel β-strands connected with loops and one helical stretch comprising the carboxy-terminal residues 57-72. Obviously, the existence of at least one α-helix is a necessary prerequisite that determines the depolarizing character of a hormone. Its orientation in the membrane indicates that IL-8 is of the depolarizing C_cN_e-type. IL-8 is found in nature as a dimer, but tetrameric and monomeric forms are also reported. The α-helix of IL-8 begins with Trp-57 (π), further down two other soliton-specific amino acids are found, Arg-60 (+) and Glu-63 (–), each at a distance of 3 residues ($3 \times n$; $n = 1$). The α-helix contains a second π-residue Phe-75 that is positioned between two Lys (+) residues. Lys-77 and Arg-78 build the anchor of the α-helix to the cytosolic side of the membrane. As pointed out, this is a common motif of depolarizing FUELs of the C_cN_e-type. Trp can also be found in the α-helices in a variety of other humoral factors, as predicted from their typical cysteine bridges. These are: MCP-1, RANTES, LF78, ACT-2, I-309. RANTES, LD78, and ACT-2 have an additional Phe four positions down the α-helix.

All the α-helices exhibit at least one complete soliton triplet. Many cytokine receptors carry a typical cluster of Trp-Ser-X-Trp-Ser sequences at the beginning of the transmembrane domain (receptors for β-subunit

of IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, prolactin, erythropoetin, granulocyte colony stimulating factor (GSF), and granulocyte/macrophage CSF). It has been established that some receptors are shared by more than one kinine. One can assume that both repolarizing and depolarizing kinines establish specific solitons with the same receptor, thus causing opposite effects. Alternatively, we can postulate that each kinine is in a position to affect many different receptors at the same time, for instance, through cross-linking. These are didactic finesses. In this case we should always bear in mind that space-time is continuous and that all systems are open U-sets.

Depolarizing kinines lead to a deeper insertion of the transmembrane domain that carries the Trp cluster, while repolarizing kinines pull the cluster towards the extracellular side. Such modulations of the insertion position of transmembrane α-helices may be very discrete, but they appear to be highly effective from an energetic point of view. This motion of the integral FUELs in the cell membrane is driven by the solitons of the transmembrane soliton triplets, which induce transitory (intermediary) conformational changes in the protein structure. As the actual kinetics of membrane FUELs has not been investigated, we can only take a cursory glance at the kinetic behaviour of integral proteins, as reported in the literature.

A further analysis of the amino acid sequences of the human receptors, formylpeptide receptor, C5a receptor, PAF receptor, and IL-8 receptor, reveals that the seven-helix-loops of these integral proteins are also of the depolarizing C_cN_e-type. They carry at least one soliton triplet per α-helix. Trp is a common aromatic amino acid residue in these proteins. Altogether, Trp seems to play an important role in the formation of soliton triplets in the transmembrane part of most immunological FUELs. This observation is of relevance when we discuss the effects of IFN-γ below. The special effects of IL-8 will not be discussed in detail, as they fully correspond to those of a depolarizing cytokine.

Interferons, IFNs are of special interest because they are used as drugs in the treatment of various clinical conditions. Nevertheless, their mode of action is poorly understood. The difference between IFN-γ on the one hand and IFN-α and IFN-β on the other has not been worked out. IFNs are said to be secreted in response to virus infections. This effect may be a defence mechanism of the cells, or may result from the subordination of cell metabolism to the needs of the virus (proviral regulation). There-

fore, it is not possible to decide in an *a priori* manner whether IFNs are beneficial or deleterious in each particular situation.

Chronic treatment of immunological diseases with the repolarizing IFN-γ has yielded poor results. This cytokine did not fulfil the initial expectations. IFN-α and IFN-β were subsequently registered; they were found to be effective in various clinical conditions, such as multiple sclerosis, chronic myeloid leukemia, rheumatoid arthritis, etc. This will be substantiated by quoting some clinical results with these cytokines (see also chapter 2.8).

In a randomized controlled trial, IFN-α was compared to conventional chemotherapy in the treatment of chronic myeloid leukemia (CML). 322 patients with previously untreated or minimally treated Philadelphia chromosome-positive CML were treated for 5 and more years. The 6-year survival (median > 72 vs. 45 months) was significantly better in the IFN-α group than in the conventional treatment group (50% vs. 29%, $p = 0.002$). However, treatment was discontinued because of side effects in 35 patients (16%) in the IFN-α group and the cost of interferon treatment was 200 times higher than that of conventional treatment.

The most important result of this study was that during the first 2-3 years there was no difference in the clinical response (progression of disease or survival) when IFN-α treatment was compared with chemotherapy, but the difference in both parameters increased continuously after the third year[52]. Similar results were obtained in other long-term trials. For instance, the large Helsinki Heart Study in atherosclerosis (4081 patients, 1987) reached significant therapeutic effects only after 2 years of chronic treatment.

These results reveal an important aspect that is not considered in clinical research. The absolute time $f = 1/t$ is a specific constant of each system of space-time. For instance, many natural constants in physics are time quantities (see vol. I & II). Any energy exchange has a specific constant space-time, that is, space and time. Treatment with cell-stimulating drugs is a specific energy exchange between these chemical compounds and the organism which alters the energetic state of the latter. Some effects may be observed after a short period of time, while others become manifest only after a long treatment period. Although space and time are the only two constituents of space-time, time is completely neglected in clini-

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[52] N Engl J Med, March 24, 1994, p. 820.

cal trials. This is a key fallacy in the current designing of clinical trials with grievous consequences for the life of the patients (see chapter 2.9). In fact, time is a hidden constituent of any clinical parameter or endpoint in clinical research (e.g. mortality), because space-time has only two dimensions.

For instance, a pronounced positive change in the clinical state of a chronic disease is observed not earlier than after 6 months, and usually after one to two years of chronic treatment with cell-stimulating drugs. In physics one speaks of *Ljapunov time*, which is conventional time in the exponent and is thus a reciprocal quantity of time (see exponential laws). The Ljapunov time is long in patients with chronic diseases in whom beneficial effects are induced, e.g. by treating them with cell-stimulating drugs. The Ljapunov time after which deleterious effects become manifest in humans is, however, very short when cell-inhibiting drugs are used. The registration of most cell-inhibiting drugs is based on short-term studies using surrogate endpoints that have not been validated with respect to the constituent time, e.g. by selecting primary quantities of time, such as survival, mortality, or cure, in clinical research.

Plainly speaking, the organism needs a lot of time to respond to a positive treatment, but it reacts immediately to a negative therapy. The irony and tragedy of modern pharmacology and clinical research is that they have misinterpreted such negative effects by declaring them beneficial for the patient. This subjective anthropocentric interpretation has prompted the registration of numerous cell-inhibiting drugs. More than 90% of the drugs now available on the market are cell-inhibiting and thus detrimental to the patient (see chapter 2.9). When the dipole model is applied to these compounds, it becomes evident that they carry at least one or more positively charged groups and have no or very weak dipole moment. Such drugs interact with the soliton triplets of integral and cytosolic FUELs as described above. They melt the midgaps of the π-electron systems in the protein structure and thus inhibit the occurrence of solitons. These drugs cause a global inhibition of the energy exchange in the cell and the body. This inhibition is immediately sensed and manifested through a variety of adverse events which can affect any organ or system. These effects are well documented in the literature and in official drug information sheets. However, in the absence of any theory of biological regulation (and an independent critical reassessment), some of these effects have been declared positive and this unproven erroneous

argumentation has permitted their registration.

This crucial fallacy on the part of the pharamaceutical industry and the national and international drug registration authorities was possible for one single reason. Almost none of drugs registered before 1985 have been evaluated in double-blind, placebo-controlled trials testing **primary endpoints,** such as *cure*, *mortality*, or *life expectancy*[53]. These primary endpoints are direct quantities of time - they are the only appropriate parameters for providing us with adequate information on the actual treatment outcome. Most of the registration trials are based on *surrogate* endpoints, which have been totally misinterpreted and have no correlation with the expected beneficial outcome. In fact, most of these surrogate endpoints are inverse to an improved energy exchange, circumscribed as "health" (Pareto-optimal condition). In addition, most of the trials used for registration are not placebo-controlled. This is the greatest embarrassment of modern medicine and bio-research - morally speaking, it is the greatest scientific evil perpetrated on mankind since the development and explosion of the atomic bomb (see also chapter 2.9).

2.5 TREATMENT OF AIDS IN THE LIGHT OF THE LAW

AIDS is probably the best investigated viral disease. The facts are well known and shall not be discussed at length in this chapter. We shall rather focus on the relevant biochemical data, using them to explain the pathogenesis of AIDS in the light of the Law.

HI-virus is enveloped by a lipid bilayer membrane containing two glycoproteins: gp41 spans the membrane and is bonded to the extracellular gp120. In addition, the lipid bilayer of the virus may carry MHC class I and II molecules, and some more FUELs from the human cells with which it fuses. The virus fuses with the cell when the extracellular gp120 binds the variable region V1 of the CD4 molecule near the N-terminal. HIV-infected cells express the viral gp120-gp41 on their surface as a transmembrane FUEL. Nonpolymorphic determinants of MHC class II molecules, particularly HLA-DR and HLA-DQ, share striking structural homology with the gp120-gp41 complex of HIV type I. Antibodies to these HIV proteins can cross-react with MHC class II molecules. Anti-

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[53] Although substantial efforts have been made in the last few years to reverse this situation, it is still deplorable.

bodies against MHC class II are often found in the serum of HIV-patients. These antibodies can prevent interactions between CD4 and MHC II on APCs and inhibit antigen-specific functions mediated by helper T cells.

It is assumed that the **gp120-gp41 complex** is an *alloepitope* that binds CD4 molecules on T cells and triggers a long-term allogenic response in the patient. In the General Theory, the gp120-gp41 complex is a "*proviral allo-MHC*" that mimics the MHC class II molecule of the patient. This is confirmed by the following results. When complexes of gp120-antigen and antibody bind CD4, the helper T cells become refractory. Anti-gp120 antibodies were detected on CD4 T lymphocytes in HIV-patients. Perturbations of T cell subgroups bearing specific variable-β regions have also been observed. Many infected and non-infected T lymphocytes from HIV-patients die by apoptosis when they bind foreign antigens (proteins). These findings indicate that the gp120-gp41 complex, because of its homology with the MHC molecule, enters into a competitive binding with this integral protein in the MHC-restricted first and second selection of the T cells as described in the previous chapter. This integral protein of viral origin biases the physiological selection of immunocompetent cells and renders peripheral lymphocytes that are functionally deficient. The mechanism of interference is energetic. Mainly, the CD4 T cell subpopulation is affected.

Apoptosis represents the energetic mechanism of CD4 T cell depletion during the first selection. Apoptosis can be induced in mature murine CD4 T cells after cross-linking CD4 molecules and activating the T cell receptor. It has been suggested that cross-linking of CD4 molecules by gp120 or gp120-anti-gp120 immune complexes also induces apoptosis. Thus, apoptosis may occur in cells with or without direct infection by HIV when solitary gp120 or gp120-gp41 complexes are linked to CD4 at the T cell surface. The apoptosis hypothesis was put forward to explain the observed depletion of CD4 T cells in HIV-patients. It fits in with the mechanism of the first and second selection as outlined in the General Theory. Only individual cells are affected by this kind of apoptosis. It has been established that only 1 in 10,000 to 1 in 1000 CD4 in circulating T cells in HIV-patients are actively expressing the virus at any time. This indicates that only a few cells die through HIV-induced apoptosis. These findings explain the slow progression of CD4 depletion in HIV-patients; the process may last for years.

Although HIV can infect both resting and activated CD4 T cells equally

well, its ability to replicate is a highly complicated process that depends on the state of activation of the infected cells. Efficient replication of HIV and other viruses in monocytes and macrophages depends to a large extent on the activation and differentiation state of the infected cells. Many viruses, such as cytomegalovirus, HSV, hepatitis B virus, human-herpes virus 6, HTLV, type I, etc. can up-regulate the expression of HIV. Cytokines of the repolarizing type, such as IL-1, TNF-β, IFN-γ, etc. stimulate HIV replication in cell lines of monocyte-macrophage lineage with chronic infection and in primary culture of cells of the same lineage by inducing the expression of membrane HIV-FUELs in infected cells. Cytokines of the depolarizing type, such as IFN-α, IFN-β, IL-4, TGF-β, etc. suppress the effects of HIV infection by inducing the endocytosis of proviral proteins in infected cells.

This is key experimental evidence in the field of AIDS research that gives a clue to the energetic, that is, dynamic pathogenesis of this disease. According to the General Theory, repolarisaton upgrades the expression of integral FUELs, while depolarisation enhances their endocytosis. This kinetic behaviour of integral FUELs is without exception. It is fundamental to the development of adequate treatments of AIDS and other viral diseases (see below).

The clinical approach to AIDS focuses on the peripheral blood counts of CD4 and CD8 T cells, despite the fact that the two subpopulations represent only 2% of the total T cell pool. The disease begins to evolve in secondary lymphoid organs, such as thymus, lymph nodes, adenoids and tonsils. In the early and intermediate phase, HIV particles, predominantly gp120 associated with antibodies and complement, accumulate in the lymph nodes of the patient. These antigen-antibody complexes are trapped in follicular dendritic cells, which are the most active APCs in the germinal centres. In this stage, only a few cells - predominantly CD4 T cells and dendritic cells - are infected with HIV. In the advanced stage of the disease, free viral particles are no longer detectable in blood circulation and in the extracellular compartments. The HI-virus can only be detected in infected cells. The progression of the disease is associated with the histological degeneration of the dendritic network and the loss of ability of the lymphoid organs to trap HIV particles. This process determines the clinical progression and final outcome of the disease.

The primary infection with HIV results in intense viremia soon after seroconversion, which leads to the seeding of multiple lymph nodes with

the virus. This causes a detectable lymphadenopathy and initiates a HIV-specific immune response. Associated with this process, there is a nodal accumulation of CD4 T cells, either by in situ proliferation or migration (chemotaxis) to the lymph nodes. Infected CD4 T cells induce HIV-specific B cell response in the germinal centres (see interactions between B and T cells above). In addition, HIV-patients exhibit polyclonally activated B lymphocytes, which result in hypergammaglobulinemia and produce high quantities of circulating immune complexes. The antigen-driven migration of CD4 T cells from the periphery in the lymphoid organs contributes to the abrupt decline in the peripheral counts of circulating CD4 T cells, which is characteristic in the acute HIV syndrome. The dichotomy between the absence of HIV in the peripheral blood and the invisible progressive destruction of the dendritic network in secondary lymphoid organs is interrupted in the late phase of AIDS when the trapping mechanisms of the dendritic cells are completely destroyed and high levels of viremia are observed again. The last clinical phase, called *AIDS-related complex*, manifests the total destruction of the immune system at the level of the organism and soon leads to death.

These are the visible signs of AIDS pathology as observed by the clinician and the pathologist. Until now, there has been no coherent theory capable of explaining the clinical course of AIDS so as to include all virological and clinical facts. This is the privilege of the General Theory. For this reason no effective treatment of AIDS could be developed yet. Let us now summarize the major aspects of the *immunopathogenesis* of AIDS, before we proceed with its elaboration from an energetic point of view:

1. HIV-infected cells, such as CD4 T cells, but also macrophages, monocytes, and dendritic cells (APCs) express the viral gp120 glycoprotein. Non-infected cells can also express this protein on their surface.

2. gp120 and the transmembrane gp41 are homologous to the patient's MHC class II and can be regarded as "proviral allo-MHC"; the two viral proteins can mimic the function of the MHC class II molecule. Therefore, gp120 and gp120-gp41 participate in all energy interactions of the immune system at the supramolecular level that involve MHC molecules.

3. Infected CD4 T cells can proliferate, die by apoptosis, or become anergic in the lymphoid organs, where the first selection generating self-tolerance takes place. Circulating T cells from the reservoir of HIV-patients can die by apoptosis when they bind to foreign proteins, or exhibit immunodeficiency (impaired second selection, or allo-reactivity). Therefore, the first and second selection of the T cells is impaired by the HI-virus. This immunodeficiency also involves B lymphocytes. Evidently, there are many different mechanisms by which CD4 T cell depletion can be induced. These energetic interactions at the quantum level involve the natural mechanism of self-tolerance and allo-reactivity and abide by the Law.

4. The primary cause for the pathogenesis of AIDS is the established homology between gp120-gp41 and MHC class II. The two viral FUELs interfere with the specific energy interactions of the immune system and cause its ultimate dissipation. This viral interaction with physiological energetic mechanisms of the first and second selection fulfils the condition of destructive interference. Although this interference occurs at the quantum level, it is propagated to the level of the organism and, in particular, in the distribution pattern of CD4 counts during the course of the disease (U-sets)[54]. It should be assumed that other viral proteins may also contribute to this dissipation, which is energetically determined. In this sense, gp120-gp41 is paradigmatic for the energetic immunopathogenesis of AIDS, but most probably it is not the only reason for the disease.

AIDS patients exhibit typical immunological symptoms that can be observed in a state of deficient self-tolerance and allo-reactivity. The HI-

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[54] Some preliminary statistical evaluations stress the "chaotic behaviour" of CD4 counts in the HIV-patient during the course of the disease. The long-term curves of CD4 counts exhibit a striking similarity to the charts of future and stock markets. One of the most valuable applications of the Law is the possibility of predicting the behaviour of such charts in the future. This achievement is closely associated with the new General Theory of micro- and macroeconomics, which will appear as a separate book. The mathematical method employed in the evaluation of equities can also be applied to CD4 counts and other parameters of HIV-patients and is a valuable indicator for the progression of the disease. This is a new dazzling perspective of applied mathematics in medicine.

virus inserts the gp120-gp41 complex in CD4 T helper cells as a proviral integral FUEL that is very similar to human MHC class II, so to say, as a kind of "Trojan Horse" that ultimately destroys the infected cell. This FUEL is then transformed to other cells, such as monocytes, macrophages, follicular dendridic cells, and other human cells. This foreign FUEL impairs the MHC-restricted first and second selection as presented in the General Theory. Although the initial defect is at the supramolecular level, the clinical results of this *biasing* soon become manifest at the level of the organism. This confirms again that all systems are open U-sets and are involved in a vertical and horizontal energy exchange.

The pathogenic potential of the integral glycoproteins of the virus envelope has not been realized by virologists, because virus replication in the cell is still considered a "free lunch" - the energetic forces that drive this process are totally neglected in virology and genetics. The replication of HIV and other viruses is in fact a complex energy-driven process that abides by the Law. The virus uses the genetic mechanisms of the host cell to replicate. In particular, it employs the delocalized electromagnetic coupling between the electric LRC of the cell and gene expression in the nucleus. The electric LRC of the infected cell is specifically modulated by the viral membrane FUEL gp120-gp41 to serve the metabolism of the virus. The genetic replication of the virus follows essentially the same pattern as already described for the cell and can be explained by the General Theory in a consistent way. Its detailed description is beyond the scope of this survey on AIDS. Here we can only point at the weak points of modern virology that have hindered an understanding of the pathogenesis of this viral disease.

The genetic mechanisms, including the reverse transcriptase, gag, pol, and env genes of the virus, are relatively well known. However, their regulation has still remained a mystery. For instance, it is an established fact that the env-gene that codes for the amino acid sequence of gp120 undergoes rapid mutations so that particles obtained from different patients or even from the same patient at different times exhibit a high degree of sequential variability. The rate of mutation correlates with the outcome of the disease. The high variability of gp120 renders the development of specific immunisations a futile task. The propensity of this gene to mutate is also responsible for the high rate of resistance to treatments with inhibitors of the reverse transcriptase. The sequential variability of gp120 results from the biased selection of the immune system, which is caused by the same viral FUEL.

We have shown that immune cells are selected by means of energetic interactions between their membrane FUELs, which trigger the proliferation and differentiation of various subpopulations. The production of immunoglubulins or T cell receptors with variable domains is based on this mechanism. The immune system is in a position to maintain its own evolution with respect to the surroundings. When a foreign FUEL such as gp120 participates in interactions between the immune cells, it is inevitably subjected to this evolution and mutates under the energetic constraint. The link between its function as a membrane FUEL and its genetic evolution as a system of space-time is effected by the electromagnetic waves of the action potentials of the infected cell. As immune cells have a high proliferating rate (short lifetime), the evolution of gp120 is fairly rapid. This is a self-perpetuating process that enhances the vicious circle of AIDS pathogenesis. From this we conclude that the dynamics of this viral disease cannot be explained in the bio-sciences, because the role of the electric LRC of the cell has not been appreciated.

The HI-virus can replicate in CD4 T cells only when they are adequately activated. The gp120-gp41 complex modifies the electric LRC of the infected cell in a specific way and enables the replication of the viral genome. However, the presence of this integral proviral protein is not sufficient for the viral replication. The axiom of reducibility of the new axiomatics says that any energy exchange is an interaction between two entities. The same holds true for this viral FUEL. It can be activated only when it interacts with the host FUELs expressed on other immune cells. Thus, the replication of the HI-virus makes use of the physiological energetic mechanisms of the immunological regulation of the host.

CD4, CD8 T cells, and B lymphocytes are selected in secondary lymphoid organs after leaving the bone marrow. The development of self-tolerance is based on interactions between MHC molecules and T cell receptors, or any other receptors, and integral FUELs. The gp120-gp41 is an integral protein that is homologous to MHC II class molecules, with which the CD4 receptor of the helper cells normally interacts. Antibodies against MHC class II can also bind gp120 and these complexes can interact with CD4.

The gp120-gp41 complex is a classical integral protein; its structure is comparable to that of immunoglobulins and T cell receptors. The transmembrane gp41 protein consists of α-helices and is rather conservative, while the variable gp120, which corresponds to the variable domains of MHC molecules or the T cell receptor, is subjected to continuous muta-

tion under the energetic constraint.

It has been established that the proviral DNA of HIV is coded dynamically through splicing similar to that observed in the DNA rearrangement of immunoglobulins. The high mutation rate of gp120 is based on this mechanism. The gp120-gp41 complex is stimulated either by direct binding and activation with the CD4 of the same cell (autocrine activation) or with CD4 of other T cells. This interaction permits several outcomes with respect to the virus. When gp120-expressing cells are optimally stimulated, the virus can replicate and the cells will ultimately burst. New viruses are disseminated in the organism. When gp120-expressing cells are excessively stimulated, they die by apoptosis. When they are poorly stimulated, they die in a state of anergy. In the last two cases, there is a strong energy constraint in the infected cells to mutate in order to survive. This mutation affects in the first place the gp120-gene. The proviral DNA is dynamically rearranged and new "alleles" of gp120 are coded. This explains why different types of gp120-antibodies are found in one and the same patient during the course of the disease.

Another major factor that supports this kind of selection is the immune response of the host. The polyclonally activated B lymphocytes produce hypergammaglobulinemia in most HIV-patients. This clinical finding reflects the continuous adaptation of the virus (gp120) to the immune challenge and the response of B lymphocytes to the changing antigen challenge (space-time is closed). The virus-host interaction is thus a recurrent input-output process. The tragedy about this perpetuating, interactive adaptation is that the host, precisely, the CD4 T cells and other immune cells, such as dendritic cells, are ultimately destroyed. With the death of the patient, the HI-virus destroys its environment and also dies. This is a classical example of a destructive interference that causes the annihilation of both interacting systems (CAP).

However, the destruction of the host is not an inevitable fate. There is growing evidence that the immune system of many HIV-infected individuals can cope with the challenge. Long-term seropositive persons may live more than 25 years without any clinical symptoms and feel healthy, although they are carriers of the virus (in fact, each organism carries thousands of viruses during its life span without becoming ill). Such individuals exhibit a strong immune system. New-born children who, having been infected by the mother, are seropositive during the first year may convert in the second year and remain seronegative. Seropositive homosexuals who are exposed to a high risk of reinfection for more than

11 years may exhibit an intact immune system for a long period of time. Prostitutes in HIV endemic regions in Africa with extremely high risk of infection may not be infected at all. Evidently, not every HIV challenge leads to a disease and not every HIV-infection causes an early death.

What are the possible approaches to the treatment of HIV in the light of the General Theory? At present, the only major pharmacological approach to AIDS is treatment with *inhibitors of the reverse transcriptase* or other enzymes. However, we have proved that there is no such thing as a "specific" inhibitor. This assertion is one of the most grievous mistakes of modern pharmacology. **Cell-inhibiting drugs always inhibit the whole cell**! Inhibitors of the reverse transcriptase are potent non-specific cell-inhibitors with numerous adverse events. For this reason they are usually administered in the AIDS-related complex or in the late phase of the disease (see CONCORDE trial below). Recently, combinations of these drugs have been suggested to reduce the severity of the adverse events by lowering the dose of the individual compound. Although inhibitors of reverse transcriptase and other enzymes evoked great expectations, it was soon established that such combinations enhance the mutation rate of gp120 and ultimately contribute to the progression of the disease which correlates with the mutation rate of this FUEL. From this it becomes evident that the use of cell-inhibiting drugs constitutes deadlock in the treatment of AIDS.

This theoretical analysis of the negative impact of cell-inhibiting drugs in the treatment of AIDS was credibly confirmed by the famous **CONCORDE trial**[55]. In this double-blind, placebo-controlled, randomized trial early treatment with AZT (immediately after randomization) was compared to late AZT treatment at the onset of ARC (AIDS-related complex), AIDS (CDC IV), or at the development of persistently low CD4 cell counts.

According to the dipole model, AZT is a strong cell-inhibiting drug that induces various adverse events (see also the discussion on phenytoin below) and increases morbidity and mortality when administered chronically. The CONCORDE trial is the biggest double-blind, placebo-controlled, randomized trial ever performed in AIDS. It offsets the results of all other trials in this indication, most of which were not controlled (this also holds true for the registration trial of AZT performed in many European countries in 1985-86).

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[55] Lancet, 1994, 343: 871-81.

Between Oct 1988 and Oct 1991, 877 HIV-patients in the UK, Ireland, and France were randomly allocated to receive 1 g daily dose of AZT (4 times 250 mg) in the early group and 872 patients to receive matching placebo in the late group. The follow-up was to death or Dec 31, 1992 (total 5419 person-years, median 3.3 years). Only 7% of the patients did not have a full clinical assessment by July 1, 1992. Thus, the CONCORDE trial was the largest single clinical trial in HIV-patients; it included more deaths (primary endpoint) than all other previous HIV-trials put together. It also had the longest period of follow-up.

In this trial, no difference could be found between the early and the late groups, despite the significant difference in the amount of AZT administered. This clearly showed that AZT had no beneficial effect in delaying the outcome of AIDS. A close analysis of the results of this trial reveals some remarkable facts that cannot be explained by the authors, but find a coherent interpretation within the General Theory. This analysis confirms the expected negative effect of AZT as a potent cell-inhibiting drug in HIV-patients. The results of the CONCORDE trial can be summarized as follows.

The 3-year estimated survival probabilities in the CONCORDE trial were 92% in the early group and 94% in the late group. However, 99 patients in the early group stopped the trial medication prematurely as a result of adverse events (AE) on AZT compared to only 38 patients in the late group. These data reveal two important facts.

Firstly, the expected adverse effects of AZT resulting from its ubiquitous suppression of the energy exchange in the body cells really did occur when HIV-patients were treated over a long period of time. There were three times more AEs in the early group than in the late group. The total trial time spent on AZT was 80% in the early group and 23% in the late group. This indicates that the number of AEs that led to withdrawal was nearly proportional to the duration of the treatment. The same ratio was also observed for serious AEs. Of the 6 patients who had life-threatening AEs, only one event occurred under placebo treatment. In this case, the event was a fatal hepatic failure during treatment with tricyclic antidepressants. Contrary to some atypical stimulant-like antidepressants, which carry an extended π-electron system in their chemical structure and have a pronounced dipole moment, tricyclic antidepressants appear to be potent cell-inhibiting drugs when the dipole model is applied. They carry one or more amino groups, which are positioned either on the aliphatic side chain and/or in the middle ring; in this way they separate

the two aromatic rings and disrupt the energetic continuum of the π-electron structure. Thus, all serious AEs in this trial can be either attributed to AZT or to other potent cell-inhibitors.

Secondly, if the patients with serious AEs had not been prematurely withdrawn from treatment, the outcome of the trial might have been even worse in the early group. This assumption is substantiated by the following data. 96 patients died in the early group compared to only 76 deaths in the late group. Therefore, **more AZT led to more deaths**. 15 deaths in the early group and 7 deaths in the late group were judged unlikely to be HIV- or drug-related. All deaths (except 2) occurred before a prior diagnosis of AIDS (CDC IV), or ARC was made, but during AZT treatment. Seven deaths were due to malignant tumours, which can be considered as evidence for our basic conclusion that all cell-inhibiting drugs increase the incidence of malignant mutation (see chapters 2.3 & 2.9). This circumstance is also reflected in the 3-year probabilities of death, which were 8% in the early group and 6% in the late group. An early treatment with AZT led to a relative increase in the probability of death of 29% in the early group vs. the late group. Thus, **significantly more patients died in the early group compared to the late group** ($p = 0.02$) without developing ARC or AIDS (CDC IV) from causes which were considered not HIV-related. The authors defined these deaths as "drug-unrelated" in addition to their non-relatedness to AIDS, but, according to the General Theory, this assumption is not correct - all systems are U-sets and contain themselves as an element.

While the mean CD4 count in the early group was higher than in the late group, this difference had absolutely no impact on the outcome of the disease. For this reason the authors considered CD4 counts to be an inappropriate "surrogate endpoint" for the outcome of AIDS. In this respect, it is important to observe that the putative efficacy of the numerous inhibitors of reverse transcriptase and other enzymes has been concluded on the basis of peripheral CD4 counts in most AIDS trials performed so far.

The progress of the CD4 counts during treatment in the CONCORDE trial are very instructive in the light of the General Theory. After the first 3 months, there was an initial median increase in the CD4 count in the early group and a decline in the late group. This trend continued during the first 6 months of treatment. In the second 6 months there was, however, a decrease in both groups, which was *greater* in the early group than in the late group. The difference in the median change from base-

line between the two groups, as established in the first 6 months, persisted for at least 3 years. The authors suspected that early AZT shifted a larger portion of poorly functioning CD4 cells into the circulating pool. This conclusion is fully compatible with the energetic mechanisms of the first and second selection of T cells and with the postulated decrease in cell efficiency during the administration of cell-inhibiting drugs. The lower the efficiency of each individual cell, the higher the cell number (recalls the higher PMN counts in sepsis). This finding reflects the reciprocity of space and time.

The results of the CONCORDE trial disclose the inherent bias observed in most short-term trials with cell-inhibiting drugs, in which surrogate endpoints are usually selected for the treatment outcome. Such trials implicate putative therapeutic effects with cell-inhibiting drugs in the short run, while in reality they are profoundly deleterious to the patient in the long run. While these negative effects can be concealed in a short-term follow-up, they become manifest during a long-term observation which takes into consideration the specific Ljapunov time of the disease. This is a chief advantage of the CONCORDE trial over the other AIDS trials, which are characterized by a much smaller number of patients and a shorter follow-up period. As most of these trials do not evaluate mortality as a primary endpoint, they have rendered highly inconclusive results that merely manifest the cognitive misery in AIDS research.

The General Theory clearly says that the only adequate treatment of AIDS is the **chronic administration of depolarizing agents**. The rationale behind this strategy is fairly simple and can be deduced from our previous discussion:

1. AIDS destroys the immune system. Patients with an intact immune system are less likely to develop the AIDS-related complex and die earlier. A large portion of these patients may even have a normal life-expectancy. Depolarizing agents *stimulate* the immune system.

2. Depolarizing agents induce endocytosis and reduce the expression of gp120 in infected cells. They inhibit the virus replication by employing the delocalized electromagnetic coupling between the electric LRC and the genetic code. HI-viruses which are not replicated are metabolized in the cell and disappear. Thus, therapy with depolarizing agents diminishes the infection potential of the HI-virus in the organism and prolongs life.

3) As the disease progresses immediately after seroconversion by destroying the dendritic network in secondary lymphoid organs, it is mandatory to begin an early treatment with depolarizing agents in order to support the immune system.

I discovered that nystatin (Nys), amphotericin B (Amp), and the group of polyenes are the most potent oral immunostimulating agents of the depolarizing type. Nys and Amp are available on the market. The exact mode of action of these drugs is given in chapter 2.7. This discovery is patented. In addition, I have found that, contrary to current prejudices, these drugs are almost *completely* resorbed from the gastrointestinal tract after oral application. Due to their lipophilic character, they are stored and metabolized in deep compartments, such as liver, thymus, lymph nodes, and pancreas. In these organs, they enhance a pronounced immunostimulating effect. This pharmacodynamic behaviour is quite advantageous, as it permits a specific systemic immune response in HIV-patients without affecting other vital organs, such as kidney, to which i.v. polyenes may be rather toxic.

Oral Nys and Amp are the *most* safe drugs now available on the market. Probably for this reason, it is generally believed that they are not resorbed from the gut. A search in the literature, including more than 3000 publications, has revealed that there was not a single report of a seriously adverse effect associated with these drugs. This is unprecedented, considering the fact that these drugs have been used orally in millions of patients for half a century. This exceptional tolerability has also been confirmed by my own experience in several hundred patients with different indications.

The excellent tolerability of oral polyenes is in apparent contradiction with their high toxicity after i.v. application. This has given rise to the general belief that polyenes are not resorbed from the gastrointestinal tract. This erroneous conclusion is based on the fact that serum concentrations of oral Nys and Amp are very low. However, polyenes are lipophilic compounds and do not appear in a free, soluble state in ionic solutions, such as serum. Instead, they immediately interact with the lipid membranes of the body cells. In vitro experiments show that when cell cultures are incubated with Nys or Amp, almost 100% of the drug is membrane-bound, so that there is virtually no free soluble Nys or Amp. These properties make out of polyenes ideal drugs for the early chronic treatment of AIDS and many other diseases (see chapter 2.7).

In vitro and clinical results confirm the antiviral effects of polyenes. Nys inhibited in vitro the expression of gp120 and gp41, and p24 in H9 lymphocytes, and suppressed almost completely the reverse transcriptase. Nys inhibits HSV I and HSV II in cell cultures at concentrations between 3 and 25 µg/ml. We observed a rapid improvement of labial HSV infections after topical application of Nys ointments (40 to 200 mg, preferably about 50 to 100 mg polyene macrolide/g ointment). Depending on the concentrations of the active ingredient, the ointment can be applied 3 to 10, preferably 5 to 8 times a day. A chronic administration of oral nystatin may prevent the recurrence of herpes. The daily dose for chronic oral administration is 1 to 1.5 g Nys daily. The drug inhibits HZV in cell cultures in concentrations between 3 and 25 µg/ml. After topical administration of high-dose ointments (about 40 to 200 mg nystatin, preferably, 50 to 100 mg/g ointment) the efflorescence of shingles remits more rapidly than without therapy. The ointment may be applied several times a day, e.g. 3 to 6 times a day. Nys inhibits the production of hepatitis B surface antigen (HbsAg) in human hepatoma cell line PLC/PRF/5; it also inhibits in vitro Sindbis virus and vaccinia virus.

The antiviral effect of Nys has been confirmed for all the viruses examined in vitro. From this we conclude that HIV patients should be treated with Nys immediately after seroconversion so as to suppress the virus replication from the very beginning and to impede CD4 depletion, which begins immediately after seroconversion and proceeds to exitus. The outcome of the disease depends on the speed of CD4 depletion in the secondary lymphoid organs and not so much on the depletion of peripheral CD4 counts, which are not reliable tools for the outcome of AIDS. It has been established that long-term survivors (20 and more years after seroconversion) have a much stronger immune response than drug-addicted HIV-patients with a repressed immune system, who normally die after 4 to 7 years. For this reason Nys and Amp therapy must be chronic for the duration of the disease. Double-blind placebo-controlled mortality trials should be performed with Nys and other polyenes to confirm statistically their superiority over conventional treatment, e.g. over inhibitors of the reverse transcriptase. These cheap drugs will undoubtedly revolutionize AIDS treatment in the next years. Based on the General Theory, further effective and cheap treatments can also be developed. It is important to observe that more than 90% of all HIV-patients live in poor countries and cannot afford present expensive therapies.

2.6 TISSUE REGENERATION IN THE AETIOLOGY OF DISEASES

Tissues are constantly remodelled throughout life. This is a common feature of all tissues involved in immunological diseases. For instance, osteoblasts and osteoclasts are immunogenic cells that remodel bone tissue. Demyelination and remyelination of oligodendrocytes is an incessant process in the CNS. *Rheumatoid arthritis* (RA) and *multiple sclerose*s (MS) are common chronic diseases associated with the regeneration of these two tissues. They are representative of many other chronic immunogenic diseases that involve tissues subjected to rapid regeneration. This knowledge is important for a proper evaluation of the pathogenesis of *autoimmune* diseases. In this chapter we shall focus on the regulation and regeneration of bone tissue. The new approach can be applied to any other tissue or body system.

2.6.1 Supracellular Regulation of Bone Tissue Regeneration

The properties of the bone are essentially determined by its extracellular components. Bone tissue consists of a solid mineral phase and an organic matrix, 90 to 95% of which is type I collagen and the rest is type II collagen, and other collagens. The organic matrix also contains various proteins, such as bone GLA protein, osteocalcin, osteonectin, etc., which regulate bone formation as cell-stimulating agents. Bone is formed by *osteoblasts*, which are transformed immune cells of mesenchymal origin. They synthesize and secrete an organic matrix that is mineralized in osteons. Osteoblasts express a specific *alkaline phosphatase* (AP), receptors for *parathyroid hormone* (PTH), and 1,25-*dihydroxivitamin D* ($1,25(OH)_2D$), and can synthesize type I collagen, osteocalcin, and osteopontin. AP is a marker for osteoblasts - the cellular level of this enzyme correlates with the mineralization potential of these cells.

Resorption of bone is carried out by *osteoclasts*, which are multinucleated cells derived from a haematopoietic stem cell that is related to the mononuclear phagocyte series. Bone resorption by *nucleoclasts* takes place in the Howship's lacunae. The nucleoclasts use various proteins, including two membrane FUELs, a membrane proton-pump, and a carbonic anhydrase, to maintain an acidic pH. These cells also express receptors for calcitonin and integrin. Osteoblasts and osteoclasts differ-

entiate and perform their specific osteogenic activities under the influence of various growth factors and cytokines, such as IL-1, TNF, IFN-γ, and CSF. These immunological factors also pertain to the supracellular regulation of bone metabolism.

The effects of these agents on bone cells can be direct or indirect. For instance, some of the effects on osteoclasts are mediated by osteoblasts and adjacent fibroblasts. PTH receptors are not expressed on osteoclasts, so that PTH acts on these cells through osteoblasts. Thus the different FUELs expressed on osteoblasts and osteoclasts determine the functional antagonism of the two cell types that regulate bone metabolism. In fact, all cells of bone metabolism and agents of supracellular regulation are interrelated, as they are U-sets. Generally speaking, bone resorption precedes bone formation and is more intense, but it does not persist as long as formation (specific constant time of the systems of bone metabolism). About 18% of the total skeletal calcium may be deposited and removed each year. This shows that bone is an active metabolizing tissue.

Calcium metabolism is essential to bone formation. It is regulated by *vitamin D* and *PTH*. Vitamin D is a hormone that is derived from cholesterol, as are all steroid hormones. As postulated in the General Theory, all physiological hormones which are derivatives of cholesterol have a more pronounced dipole moment than their precursor. Therefore, they augment the dielectric properties of the lipid bilayer when they substitute cholesterol molecules in the membrane. This is the actual energetic mechanism of action of sexual steroid hormones as revealed for the first time in the General Theory. The same holds true for vitamin D; it interacts with the membranes of various cells and increases their dielectric permeability. This modulation in turn enhances the activity of integral FUELs in a global manner. Vitamin D is synthesized by successive hydroxylations in the liver and kidney and is considered to exert its effects chiefly on the two target tissues, small intestines and bone, while maintaining calcium homeostasis. However, its effects are much broader, as can be concluded from the biosynthesis of its chemical structure and mode of action.

Vitamin D_3 is a derivative of 7-dehydrocholesterol (provitamin D_3), the immediate precursor of cholesterol. It is synthesized in the skin under the photobiochemical effect of ultraviolet radiation (vertical energy exchange between photon space-time and organic matter). Wavelengths between 290 and 315 nm are absorbed by the conjugated double bonds at C_5 and C_7 of 7-dehydrocholesterol that results in an opening of the B

ring between C_9 and C_{10} to yield a 9,10-secosterol, called previtamin D_3. The latter is unstable and undergoes a spontaneous rearrangement of its conjugated triene bonds in *cis*-position to form the stable vitamin D_3. This vital vitamin again illustrates the close functional relationship between the biosynthesis of molecules with conjugated double bonds in the body and their energy exchange with photons from the visible light (systems of photon space-time); the latter are the driving force of chemical biosynthesis. Therefore, it is no coincidence that photosynthesis is also based on similar supramolecular compounds which carry multiple conjugated double bonds. We can observe the same motif in vitamin D. Vitamin D_3 is a *polyene* and for this reason exhibits a more pronounced dipole moment than cholesterol, although it still preserves the aliphatic tail at C_{15}. This analysis is based on the dipole model.

Ageing decreases the capacity of the skin to produce vitamin D_3. The reduction is more than 50% after the age of 70. To a large extent this reduction is caused by the accumulation of *melanin* in the skin, a black pigment rich in hydroxylated tyrosine, which absorbs the light and thus prevents the dermal photosynthesis of vitamin D_3. As we see, the aromatic residue Tyr is also involved in this process. This again confirms the ubiquitous role of the three soliton-specific aromatic amino acids in organic energy exchange. The role of light in vitamin D_3 metabolism is substantiated by the following example: in northern countries (e.g. UK and Scandinavian countries), the absorption of photons by ozone layers may be complete, so that no vitamin D_3 is synthesized in the winter months. Not surprisingly, RA and osteoarthritis are much more common diseases in these countries than in the Mediterranean countries[56].

Ageing is also associated with a decrease of other sexual steroid hormones, e.g. oestrogens in females and testosteron in males. These sexual hormones enhance energy exchange in the cell, because they have a greater dipole moment than cholesterol when they are inserted in the lipid bilayer and subjected to the electric LRC. As the relative cholesterol-phospholipid ratio in cell membranes also increases with ageing, the two processes lead to a *cumulative increase in the insulating properties of biological membranes in the elderly organism*. Conventionally, one speaks of an increase in the "rigidity" of membranes, but this view ignores the

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[56] For this reason most of the trials on osteoarthritis and RA are performed in Scandinavia and UK and not in Mediterranean countries, where the incidence of these diseases is very low.

energy exchange between the electric and metabolic LRCs, as presented for the first time in the General Theory. Altogether, we can say that the dielectric properties of physiological cell membranes continuously decline with ageing, and subsequently their propensity to exchange (modulate) the electric LRC into cell metabolism. Hence the global decline of cell metabolism observed in the elderly organism - this is the outstanding energetic characteristic of ageing. This decline is the pathophysiological basis of many chronic diseases, some of which we shall present below. *Osteoporosis* in ageing is a typical example of this process.

Evidently, ageing is closely associated with a diminishing propensity of the organism to maintain an adequate energy exchange between the electric and metabolic LRCs in the body cells. An impaired energy exchange in the cell is always associated with increased risk of pathogenesis. This was proven for cancer, but is also true for the occurrence of any disease. The clinical manifestations of this reduced energy exchange may vary. The most common are: hypercholesterolemia, hyperlipidemia (see also cholesterol-phospholipid ratio above), postmenopausal syndrome, reduced libido and impotence due to a decline in the production of sexual hormones, osteoporosis, etc. These clinical manifestations are associated with a variety of chronic diseases, the incidence of which grows exponentially with ageing. These diseases are responsible for most deaths. In this sense, biological death is an energetic state of the organism that fulfils a condition of destructive interference caused by a gradual decline of energy exchange in the body cells.

All systems of space-time have a finite lifetime: for instance, all cells and organisms are mortal. The full realization that death is caused by destructive interference at the level of organic matter opens bright new perspectives of interfering in an active way in the cell regulation so as to postpone or offset the occurrence of this condition. This is the chief objective of the General Theory in medicine and geriatrics. To put it bluntly, we can prolong life-expectancy significantly if we abide by the Law. Below we shall suggest some effective treatment strategies that can be immediately implemented in elderly patients. These strategies can significantly prolong human life.

Typical diseases that occur in the elderly, such as atherosclerosis, hypertonia, cancer, type II diabetes, osteoporosis, and a variety of immunological diseases, are associated with an age-dependent multifactorial reduction of cholesterol-derived hormones. Although the diminishing production of sexual hormones is genetically pre-determined (all sys-

tems have a finite lifetime), there is no objection in principle as to why this decline should not be energetically counter-balanced to improve life-quality and longevity. For instance, oestrogen substitution in post-menopausal women decreases mortality from cardiovascular diseases, as shown in the Framingham study. Chronic treatment with cell-stimulating drugs in the elderly can improve the energy exchange and thus decrease the risks of many chronic geriatric diseases, which are responsible for the bulk of morbidity and mortality statistics in industrialized countries (see chapter 2.7 & 2.8). Back to bone metabolism[57].

Dietary vitamin D is necessary only when solar radiation is insufficient to produce the required quantities of vitamin D_3 in the skin. Once vitamin D enters the circulation, either by absorption or through the skin, it is transported to the liver bound to a specific $alpha_1$ globulin (vitamin D-binding protein). In the liver, vitamin D is metabolized to 25-hydroxyvitamin D, 25(OH)D, by hepatic mitochondrial and microsomal enzymes. From the liver, 25(OH)D is transported to the kidney, where it is transformed into the active metabolite, $1,25(OH)_2D$. In this form the aliphatic tail is hydrolyzed - this reaction increases the dipole moment of this cholesterol derivative. The production of $1,25(OH)_2D$ in the kidney is stimulated by PTH, which in turn is excreted in dependence on the calcium concentration in plasma. The exact mechanism of PTH stimulation is not known at present. It can be explained by the General Theory as follows.

The intracellular concentrations of calcium are extremely low, while the extracellular concentrations of this ion are fairly constant (between 2.2 to 2.6 mmol/L). Calcium participates in the establishment of the electrochemical plasma gradient, though to a lesser extent than Na^+ and K^+- ions (see Nernst's equation). During cell activation, the intracellular concentration of calcium rapidly augments, while the calcium gradient across the cell membrane is virtually abolished. For this reason this ion is conventionally regarded as a second messenger in the cell. This concept is rejected in the General Theory as causative and deterministic. In fact, calcium participates in the building and modulation of the electric

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[57] Indeed, as the organism is an open system, it is possible to depart from one particular system such as bone metabolism and end up with another. While this may be a challenge to traditional didactics, this branch of knowledge itself may be an obstacle to true understanding when its rules are comprehended too literally.

LRC. It is a system of the electric level of the cell. While calcium does not seem to be involved in the rapid depolarisation of the cell, it does play a key role in the maintenance of cell depolarisation.

When the extracellular concentration of calcium decreases for whatever reasons, the calcium gradient across the cell membranes also decreases. This situation is equivalent to a depolarisation phase of the action potential which is associated with an increased release of intracellular Ca^{2+}. A decreased level of extracellular calcium stimulates the body cells by a relative depolarisation. This triggers, among others, the release of PTH in a direct manner. PTH is a depolarizing hormone that stimulates the production of vitamin D in renal cells; the latter regulates calcium metabolism. Therefore, the regulation of PTH, vitamin D, and calcium, being central to bone metabolism, are interrelated through the electric LRC, which is the common effector level of cell regulation. As we see, any particular aspect of bone metabolism can be consistently explained within the General Theory. This can be done for any other specific cell metabolism and consequently for the whole metabolism of the organism. We shall present some more facts in support of this conclusion.

As already stated, PTH stimulates the metabolism of $1,25(OH)_2D$ in the kidney. The actual mechanism by which PTH exerts its influence on vitamin D is not established because the endocrinologic effects of this hormone are multiple and contradictory. According to the dipole model, PTH is a depolarizing hormone that stimulates all body cells, including renal metabolism. This conclusion follows from the sequence structure of PTH and its seven-helix-loop receptor, as well as from its effects on other integral proteins and cellular cascades, such as G-proteins, IP_3, and DAG. In addition, 25(OH)D is metabolized to $24,25(OH)_2D$ in the kidney, chondrocytes, skin keratocytes, fibroblasts, intestinal, and melanoma cells. This metabolite is less potent than $1,25(OH)_2D$. In the intestine, $1,25(OH)_2D$ is bound to a cytoplasmic receptor, similar to those for steroid hormones. The $1,25(OH)_2D$-receptor belongs to the superfamily of steroid receptors that are related to the oncogene v-erbA. They are DNA-regulatory proteins. For instance, v-erbA may contribute to tumorigenity, such as the inducement of carcinoma in association with other oncogenes, notably, v-src, v-fps, and v-ras (see also the discussion of proto-ongenes in chapter 2.9). Given the ubiquitous effect of vitamin D on cell membranes, any impairment of its effector systems affects the energy exchange in the cell in a global manner. We showed that an impaired

energy exchange is a prerequisite for a carcinogenic transformation (see also chapter 2.9).

The effect of $1,25(OH)_2D$ on the enhancement of bone resorption is believed to be synergistic to PTH, although mature osteoclasts do not possess receptors for $1,25(OH)_2D$ or PTH. We explained that vitamin D and other steroid derivatives affect the dielectric properties of the cell membrane directly by replacing the insulating molecules of cholesterol in the lipid bilayer and therefore do not need special receptors. Some evidence suggests that PTH and vitamin D increase resorption activity by stimulating immature osteoclastic precursors that possess receptors for both hormones; this is achieved by increasing the dielectric properties of the membrane. Receptors for $1,25(OH)_2D$ are present in intestine, bone, and kidney, and in cells which have not been recognized as classical target organs for this hormone, including skin, breast, pituitary gland, parathyroid glands, beta cells of the pancreatic islets, gonads, brain, skeletal muscle, circulating monocytes, activated B and T lymphocytes. $1,25(OH)_2D$ inhibits in vitro human keratinocytes and fibroblasts, stimulates terminal differentiation of human keratinocytes, induces monocytes to produce interleukin 1 and to mature to macrophages and osteoclast-like cells, inhibits interleukin 2 and immunoglobulin production by activated T and B lymphocytes. These selected effects of $1,25(OH)_2D$ can be found in any comprehensive textbook on endocrinology, but they do not enlarge our knowledge of the energetic principle of cell regulation - they merely illustrate that the organism is an open unity of infinite interactions and effects.

This also holds for the occurrence of diseases. A variety of tumour cell lines, including breast carcinomas, melanomas, and promyeloblasts, have been found to possess a $1,25(OH)_2D$-specific, DNA-regulative enzyme. Tumour cells that express this enzyme respond to the hormone by decreasing the rate of proliferation and enhancing differentiation. Being a weak ubiquitous depolarizing agent, $1,25(OH)_2D$ improves the energy exchange in all cells and protects them from transformation. Indeed, $1,25(OH)_2D$ decreases the expression of c-myc oncogene coincident with decreasing replication. When vitamin D is removed from maturing HL-60 promyelocytes, the cells revert to their original malignant state and the expression of c-myc oncogene is no longer suppressed. This is consistent with the General Theory. Specialists have speculated why this effect is of temporary character. The maintenance of energy exchange in the cells is an incessant dynamic process; low vitamin D concentrations

decrease cell metabolism in a global manner. This example also shows that the genetic code, in this particular case the expression of oncogenes, is regulated through energy exchange between the electric and metabolic levels. This can be substantiated by further pharmacological evidence.

Cell-inhibiting drugs have a reverse effect on the metabolism of $1,25(OH)_2D$. For instance, there is a close relation between chronic anticonvulsant therapy and the development of *osteomalacia* or *rickets*. Mineralization defects are worse in patients under multiple drug therapy, or when vitamin D intake or exposure to sunlight are inadequate. Anticonvulsant drugs, such as *phenytoin*, phenobarbital, primidone, etc., are cell-inhibiting compounds according to the dipole model. They have a weak dipole moment and carry two amino groups that interfere with the soliton triplets of membrane FUELs, predominantly in neurones. This results in complex inhibitory effects on calcium metabolism leading to osteomalacia and rickets. Phenobarbital, for instance, influences hepatic microsomal enzymes and alters the kinetics of vitamin D-25-hydroxylase. The serum concentrations of vitamin D and 25(OH)D are usually decreased under treatment with this drug. In addition, both phenytoin and phenobarbital can inhibit intestinal calcium transport and mineral mobilisation in the bone. These facts confirm that cell-inhibiting drugs cannot be specific agents, as usually propagated by the manufacturers, because they affect all body cells. Hence their multiple adverse effects.

Indeed, anticonvulsant drugs are an adequate example that illustrates the ubiquitous deleterious effects of cell-inhibiting drugs in the organism. This will be demonstrated for *phenytoin*. Phenytoin is said to exert a stabilizing effect on excitable membranes, but, according to the General Theory, all physiological membranes are excitable. In particular, it inhibits voltage-sensitive Na^+-channels. These FUELs are found in all body cells. As the electrochemical plasma potential is largely modulated by the flow of Na^+-ions in and out of the cell, this fact explains the numerous side effects of phenytoin. In fact, phenytoin inhibits various other channels (U-sets). At concentrations higher than 10 μM, this drug delays the activation of outward K^+-currents during propagation of action potentials along the nerves and causes an increased refractory period. Phenytoin can also reduce the size and duration of Ca^{2+}-dependent action potentials in cultures of neurones in about 20 μM by inactivating the Ca^{2+}-channel. The toxicity of phenytoin depends on the route of administration: it is greater when the drug is administered intravenously. This aspect was elucidated with respect to polyenes. In higher concen-

trations, phenytoin causes cardiac arrhythmia and hypotension. The cardiac toxicity is observed more frequently in elderly patients. In these patients, the dielectric properties of the cell membrane are reduced through a higher cholesterol-phospholipid ratio and low levels of steroid hormones, including vitamin D. The cell-inhibiting effect of phenytoin is thus augmented in elderly patients. But cardiac toxicity is also observed in younger patients. This reflects the potent suppressive effects of this drug. High doses of phenytoin can produce marked cerebellar atrophy.

While phenytoin decreases the excitation (depolarisation) in neurones by inhibiting the Na^+-inward current, it also inhibits the Na^+-dependent symport of amino acids and glucose: cell metabolism is blocked and this explains the cerebellar atrophy. Further adverse events are: behavioural changes, increased frequency of seizures, gastrointestinal symptoms, and megaloblastic anaemia. Hirsutismus is observed in young females. This effect should be attributed to a decreased susceptibility of the cells to female sexual hormones. Phenytoin inhibits practically all sexual hormones: its blocking effect on oestrogen and gestagen in females leads to virilization. Phenytoin inhibits the production of many proteins. The drug inhibits the release of antidiuretic hormone (ADH) and reduces the concentration of vitamin K-dependent proteins. The latter effect is thought to be responsible for the occurrence of vitamin D-resistant osteomalacia. Hypersensitivity reactions, including Steven-Johnson syndrome, indicate that phenytoin is a potent cell-inhibitor of the immune system. This is confirmed by additional adverse events in the immune system, such as the occurrence of systemic lupus erythematodis, neutropenia, and leukopenia, agranulocytosis, red-cell aplasia, mild thrombocytopenia. Lymphadenopathy resembling Morbus Hodgkin's disease and malignant lymphoma associated with reduced IgA has also been observed with this drug.

The toxicity of phenytoin was extensively reviewed in a symposium in 1982. It was confirmed that there is virtually no organ or system that is not affected by the adverse effects of this classical cell-inhibiting drug. Phenytoin is paradigmatic for the toxicity spectrum of all cell-inhibiting drugs. The latter comprise more than 90% of all drugs currently available on the market. It is, indeed, impossible to perceive how such chemical compounds could have been considered beneficial and been registered world-wide, even without knowing the existence of the Universal Law.

In this chapter, we have arbitrarily chosen bone metabolism to dem-

onstrate the universal validity of the General Theory based on the Law. We have shown that the vast array of phenomena associated with this important and intricate aspect of human metabolism can be explained in a logical and consistent way. This review is paradigmatic for all other physiological processes and systems in the body, including the effects of pharmacological agents. In the following, we shall discuss the pathogenesis of some common chronic immunological disorders, some of which involve bone metabolism.

2.6.2 The Pathogenesis of Rheumatoid Arthritis (RA)

RA is a common chronic inflammatory disease that involves the synovial membranes of multiple joints. The potential of the synovial inflammation to cause cartilage destruction and bone erosions, and subsequently joint deformities, is a hallmark of the disease. Although RA is considered paradigmatic for the progress of autoimmune diseases, its aetiology is still unclear. The identity of the original antigenic stimulus is unknown, but as type II collagen is found to be arthritogenic in animal models, it is considered to be an important candidate. The involvement of the MHC class II antigens suggests that a single or limited set of antigens triggers this autoimmune process. The genetic origin of RA has been established by demonstrating an association with the MHC II gene allele, HLA-DR. Infectious agents such as bacteria, mycoplasma, and viruses are also considered. Epstein Barr virus (EBV) and HTLV-1 are favoured. From this it becomes evident that the pathogenic mechanisms considered responsible for RA are quite similar to those suggested in cancer and virus infections. This fact clearly indicates that modern medicine has virtually no idea of how these diseases actually develop.

Therefore, we shall begin with the established facts and interpret them within the General Theory. The genetic connection of RA is well established. A restricted set of genetically determined MHC class II molecules point strongly towards RA. The HLA locus occupies a small segment on a single chromosome. Within this segment, there are many genes coding for functions concerned with the immune response. The locus is highly polymorphic, so that many alleles exist in the population. Genes for some other functions are also located in this region. The coding from this locus is highly dynamic and variable - it includes alternative splicing and DNA rearrangement (see above). A single de-

fect may thus affect different proteins.

Increased risk of RA is associated with HLA-DR and involves mutations of Glu (–) and Lys (+) residues at positions 70 and 71 on the HLA-DRβ1 chain. The β1 macroglobulin protein consists of an external domain, a transmembrane region, and a short cytoplasmic chain. These findings are analogous to those observed in collagen arthritis and in myelin-basis-protein-induced experimental allergic encephalomyelitis; both disorders show a close association between disease susceptibility and specific MHC class II antigens. Thus RA patients seem to share a nucleotide sequence in a gene that encodes a key constituent of a particular HLA-DR molecule. As previously mentioned, the exact structure of MHC class II is not known, but it can be predicted from the MHC class I molecule when the soliton triplet concept is applied. Structural analysis confirms that the soliton-specific Glu and Lys are located in the middle portion of the α-helix that surrounds the antigen-binding groove of HLA-DR molecules. From this it can be assumed that MHC class II alleles associated with RA exhibit an impaired soliton triplet in the MHC groove. This interaction leads to an impaired binding and presentation of peptides and infringes upon the first and second selection of the immune cells. The pathogenesis of RA confirms this conclusion, which should be substantiated by further data on the structure of HLA-DR molecules.

Osteoblasts and osteoclasts of bone metabolism are immunocompetent cells that are regulated by hormones, such as PTH, vitamin D, and lymphokines. RA is considered a T cell-mediated disease. Predominantly, CD4 T cells are involved in the inflammation. These cells interact with B lymphocytes. The involvement of CD4 T cells in RA is very pronounced in the synovial pannus. Synovial T cells show an enhanced expression of αβ receptor for IL-2 (depolarizing lymphokine) and transferrin receptors. The pannus of RA patients displaces a large number of mature (repolarized) T cells. Mature T cells proliferate poorly and release only small quantities of IL-2. Hence the enhanced expression of IL-2 receptors. CD4 cells promote lymphokine release and the production of antibodies by B cells. Rheumatoid factors are regularly found, mainly auto-antibodies of the IgM isotype. They interact preferentially with determinants of the Fc portion of IgG. One study showed that Ig production of synovial B cell populations in 13 out of 14 patients with RA was distorted towards anti-type II collagen activity. This effect was confirmed in other trials. Substantial immune deposits are present in the articular cartilage of patients with RA and have the propensity of binding the cartilage matrix.

The cytokines measured in RA are of macrophage origin. As osteoclasts evolve from macrophages, it is quite normal that lymphokines participate in bone metabolism. The cartilage destruction is ascribed to cells of the monocyte-macrophage lineage; this suggestion is compatible with the presence of T cells at the site of inflammation.

These basic clinical and pathogenic facts of RA fully comply with the energetic mechanisms that regulate the immune system. Impaired soliton triplets in the MHC-groove of class II molecules of the HLA-DR type should be regarded as the key event that triggers RA. This also applies for most other genetic defects of soliton triplets at the supramolecular level (for further details see chapter 2.9). This fact is documented by the association of RA with functionally non-equivalent substitutions of the two soliton-specific amino acid residues Glu (–) and Lys (+) in the MHC groove, which presents extracellular peptides in the first and second selection. When the soliton triplet of the MHC active site is deficient, this automatically influences the energy interaction between the MHC-peptide complex of B cells and the CD4 T cell receptor. For instance, an impairment of Fc-gamma receptor-mediated energy exchange was observed in one study[58].

From this evidence, it can be assumed that collagen peptides are poorly presented in the first and second selection. The immunocompetent cell lineage for collagen produces defective osteoclasts that cannot resorb collagen efficiently in the process of bone regeneration. This triggers additional compensatory reactions. The increased expression of IL-2 receptors in T cells is one of them. We can therefore postulate that in RA the T cell selection is distorted as a result of the functional deficiency of the MHC class II molecules. This has an impact on the activation of B lymphocytes. These cells produce auto-antibodies, which can be measured for diagnostic purposes - they are referred to as “rheumatoid factors”. Their presence indicates that the debridement of collagen is insufficient because the MHC molecules cannot bind and present self-collagen peptides to the immune cells in an adequate manner. Instead, free circulating collagen II type peptides are bound to immunoglobulins and are deposited as complexes on the collagen matrix in RA patients (compare with AS below), where they contribute to the sinovial inflammation. From this we arrive at an important conclusion:

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58 Ann Rheum Dis, 1992, 51: 594-9.

> In the absence of a causative organism, an inflammation is always a manifestation of an impaired immune system and never the result of an immunological "over-reaction", as is erroneously believed in medicine today.

The initial cause of an immunogenic inflammation is a genetic defect that leads to an impaired energy exchange of individual membrane FUELs at the supramolecular level. At present, RA is considered a classical cell-mediated immune disease, just like *multiple sclerosis*, which will be discussed below. However, the conventional classification of immune diseases in four categories makes no sense in the light of the General Theory and should be dropped as an artificial categorical system. It is only of historical interest.

2.6.3 The Pathogenesis of Multiple Sclerosis (MS)

MS is characterized by patches of demyelination of CNS that result from an auto-inflammatory process. The disease has a relapsing and remitting course caused by fluctuations of immune deficiency. This course is typical for many chronic immune diseases. Such diseases can be effectively treated with depolarizing drugs that activate the immune system. As in RA, the pathogenesis of MS involves T cells of the CD4 type, B lymphocytes, and macrophages at the site of inflammation. The pathogenesis of MS will be presented in a very concise form.

Specific MHC class II alleles (DRw15 and DQw6) are associated with an increased risk of MS. This is consistent with our energetic interpretation that certain HLA alleles exhibit impaired soliton triplets and bind less effectively particular self-peptides. This fact confirms that the immune system is actively involved in the clearing of debridements which are produced during tissue regeneration. Therefore, future research should focus on the structural components of these HLA-class II alleles, so as to find out which specific soliton triplets and residues are impaired and which peptides are poorly bound because of these defects. This will permit the development of specific immunisations.

Demyelination is considered central to the pathogenesis of MS. Demyelination and remyelination go hand in hand. The persistence of demyelination suggests that the repair mechanisms are defect. *Oligodendrocytes* are considered responsible for remyelination. These cells

proliferate and migrate within the developing CNS. Oligodendro-cytes persist in the adult mammalian CNS, so that this system retains the ability of producing new myelin. The remyelination in MS is incomplete because of repeated attacks of demyelination. The associated cell repolarisation with this type of immune disease may also suppress the activity of oligodendrocytes. In this context, it is important to recall that cell repolarisaton is more common in CNS than in any other human tissue due to high concentrations of GABA and other central repolarizing neurotransmitters. Their concentration in the brain is more than 10 times higher than that of depolarizing neurotransmitters. This reflects the specific organisation of the CNS. Astrocyte hyperplasia is another typical feature of MS. Astrocytes have been implicated in the inhibition of axon outgrowth in the adult CNS. Cell growth due to depolarisation is always counter-balanced by repolarisation.

The two chronic immune diseases, RA and MS, have a similar energetic pathogenesis, although they involve different organs and tissues. They are representative for all the other chronic immune diseases that can be encountered in humans. None of these diseases can be effectively treated at present, because the energetic background of their pathogenesis has not been appreciated. The clinical symptoms of chronic diseases can be improved and the progress stopped when the patients are treated with cell-stimulating drugs such as polyenes, which are the most potent immunostimulators available on the market. When these drugs are administered in the early phase of the disease, they may even cure it completely by reversing the pathogenic process. The more advanced the disease, the more unlikely it is that a complete reversal of symptoms can be achieved. For instance, I have successfully treated patients in the early acute stage of RA with nystatin (1 g per day for 1 year or more); the symptoms disappeared after 6 months of treatment and in the follow-up (2-3 years). There are further reports of complete cures of early MS with nystatin.

2.6.4 The Pathogenesis of Atherosclerosis

Atherosclerosis (AS) is the most common disease in western civilisation and the principal cause of death. Contrary to popular belief, AS begins in early childhood and reaches the threshold of manifestation in adulthood. The advanced occlusive lesion of AS represents a fibroproliferative re-

sponse that involves intimal smooth muscle cells, together with numerous macrophages (foam cells), T lymphocytes, and other morphological changes (e.g. "vasa vasorum"). The lesions are arbitrarily divided into three morphological categories: fatty streaks, fibrofatty lesions, and fibrous plaques. The fatty streaks consist of intimal lipid-filled macrophages and muscle cells, usually found below the macrophages. Most of the lipid is in the form of free *cholesterol* and cholesterol ester. This is considered as basic evidence that individuals with AS are *hypercholesterolemic*. The fibrofatty lesions are a progression of fatty streaks. The fibrous plaques represent lesions, which are the result of continued smooth muscle migration and proliferation coupled with proliferation of monocyte-derived macrophages and continued accumulation of T lymphocytes. The clinical manifestation and the most reliable indicator of advanced AS is *ischemic heart disease* (IHD). Further synonyms are: *coronary heart disease* (CHD) or *arteriosclerotic heart disease*.

There are several hypotheses regarding *atherogenesis* that exclude each other. The "reaction to injury" hypothesis considers primarily the vessel lesions. The "monoclonal hypothesis" considers the lesions as a result of the multiplication of single smooth muscle cells, as seen in benign tumours. The "focal clonal senescence hypothesis" deals with the contribution of ageing processes to atherogenesis. The "lysosomal theory" suggests that altered lysosomal functions may contribute to atherogenesis.

Apart from these local hypotheses, there is a broad agreement that LDL is atherogenic and that the risk for AS can be quantified by measuring LDL and HDL. An alternative hypothesis, the so-called "atherogenic remnant hypothesis", pays more attention to VLDL, which is the product of postprandial accumulation. The large number of AS hypotheses clearly indicates that the pathogenesis of the most common disease in humans is still unknown. This is symptomatic for the cognitive misery of modern medicine. Let us therefore proceed with the facts.

The association of AS with elevated cholesterol alimentation was clearly demonstrated in large epidemiological trials. In the *Framingher Study*, cholesterol levels in men below 40 years were closely related to the development of IHD; this relation was much less pronounced in the elderly. In the *MRFIT trial*, men with cholesterol levels above 6 mmol/L (240 mg/dL) had more than a threefold increase in the risk of IHD death compared to men with levels below 5 mmol/L (200 mg/dL). There was a continuous risk gradient as the cholesterol level ascended. Hyperlipidemia

(hypertriglyceridemia) is also associated with a high risk of AS, but the evidence is less clear. There is a general upward shift of average cholesterol and triglyceride consumption in highly developed countries as a result of the rapid change in culture, life-style, and diet. Dietary changes in migrant populations from more primitive societies usually include an increased intake of total calories, animal fats, cholesterol, and salt. This leads in most cases to obesity, hypercholesterolemia, diabetes, hypertension, and IHD. Before we explain the pathogenesis of AS in the light of the General Theory, we must first discuss the structure and function of the *LDL receptor* and *apolipoprotein-B*, which are basic atherogenic FUELs of cholesterol and lipid transport.

The new methodology concerning the aetiology of chronic diseases is rather simple and straightforward. We first look for structural deficiencies at the supramolecular level of common FUELs. They can be easily established when the *dipole model* and the *soliton triplet concept* are applied. This **structural analysis** reveals an impaired energy exchange between the supramolecular and cellular levels in all chronic diseases that have been genetically investigated in an appropriate manner. When the propagation of solitons (E_A) at the supramolecular level is impeded, this affects the action potentials of the cellular level (axiom of CAP). As all levels and systems of space-time are open U-sets that contain themselves as an element, any deficiency at the supramolecular quantum level is propagated to the level of the organism and is manifested as a disease. In order to establish the *pathogenesis* of any disease, we should begin with the lowest microscopic level that can be evaluated with current sophisticated methods of diagnosis and then follow systematically the pattern of energetic imbalance throughout the various levels of organic matter. This method permits a consistent explanation of all phenomena associated with the pathogenesis of chronic diseases that have been observed in the bio-sciences and medicine. This method includes all the known facts; it only excludes some of the wrong interpretations of these facts which circulate in present-day medicine. In this sense:

> The study of the *pathogenesis* of diseases within the General Theory is a **study** of **impaired energy exchange** at different levels of organic matter, beginning with the quantum level.

This insight effects a great simplification in our medical view. The only problem of this axiomatic approach is that the facts are scanty at the supramolecular quantum level and basic molecular processes are still not investigated. Therefore, this presentation of the pathogenesis of diseases is as incomplete and imperfect as the available data in the literature. However, as it is based on the Law, it anticipates all future results and incorporates them without contradictions. This is a prospective verification of the General Theory. In terms of cognition, the facts are of secondary importance - it is the consistency of the approach and the new outlook that revolutionizes medicine and bio-science. This will be demonstrated for AS.

The LDL receptor was first discovered in 1973 in fibroblasts, but subsequently it was found to be expressed in all cells[59]. LDL receptors are clustered in coated pits. When an LDL is bound to the receptor, it is carried into the cell by endocytosis where it is further processed. Cholesterol can also be synthesized *de novo* by all cells starting from *mevalonate*, which is a precursor of various physiological carriers of π-electron systems. Mevalonate is obtained from HMG-CoA (3-hydroxy-3-methylglutaryl CoA) by HMG-CoA reductase in the cytosol. This enzyme is considered pace-limiting for the de novo synthesis of cholesterol. LDL and VLDL contain mainly an apolipoprotein B, apoB (sometimes given as apoB-100), but also other apolipoproteins, such as apoE. For the sake of clarity, we shall discuss only LDL, but our arguments also hold for VLDL.

LDL is a large spherical particle, the lipid core of which is composed of cholesterol. Each cholesterol molecule is attached by an ester linkage to a long-chain fatty acid. Again, we encounter a recurrent motif of cholesterol. This compound is always bound to other phospholipids, most often in a molar ratio of about 1:1, as is observed in physiological membranes. Evidently, the function of this vital molecule can only be explained in conjunction with phospholipids, which are ubiquitous biomolecules. In the LDL, the core of cholesterol esters is enclosed in a layer of phospholipids and unesterified cholesterol molecules. The organisation of the molecules is similar to that in lipid bilayers. The hydrophilic heads of the lipids are orientated to the outside and face the ionic solution. Large proteins such as ApoB or ApoE are embedded in this lipid particle. ApoB is bound by the LDL receptor, which is a trans-

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[59] Sci Amer, 1984, 251: 52-66.

membrane glycoprotein of the C_cN_e-type (depolarizing type). ApoE is a polymorphic glycoprotein similar to ApoB that can interact with the apoE receptor (remnant receptor) or with the ApoB receptor in LDL, which is sometimes defined as the ApoE/B receptor. It cannot be excluded that there are some more membrane FUELs that bind apolipoproteins.

When an apoprotein binds its corresponding receptor, the soliton triplet(s) of their binding sites are activated and the LDL is incorporated into the cell by endocytosis. Recall that endocytosis is always associated with depolarisation of the plasma membrane. Intracellular LDL is delivered to lysosomes and incorporated into newly synthesized surface membranes. The synthesis of membranes is an extremely dynamic process which has not been adequately appreciated. For instance, the membrane lipids in lymphoblasts are completely renewed within one hour. Therefore, the turn-over rate of cholesterol and other membrane lipids is enormous, especially in growing and proliferating cells.

Another aspect that has been totally overlooked by all current hypotheses in respect of atherogenesis is that more than 99% of organic cholesterol is *membrane-bound*, so that the serum levels of LDL and VLDL measured for diagnostic purposes are only the "tip of the iceberg". This situation is very similar to that in AIDS, where the relatively constant peripheral counts of CD4 and CD8 over a long period of time do not adequately reflect the continuous progression of the disease in the secondary lymphoid organs that causes their irreversible destruction. From this observation we can derive a **general diagnostic rule** of medicine:

> Pathological plasma levels of various physiological factors that belong to the supracellular regulation only indicate an impairment of the energy exchange at the cellular level, but are not the primary cause for the pathogenesis of diseases, as is generally believed today. The primary defects occur at the supramolecular quantum level of the FUELs, e.g. a point mutation that impairs a soliton triplet, and affect in the first instance the energy exchange in the cell.

Each disease at the level of the organism is a manifestation of a reduced (impaired) energy exchange at the cellular and supramolecular levels. This rule is without exception.

Alimentary cholesterol is used in the production of steroid hormones in the ovary, adrenal gland, prostate, and other sexual organs, and in the

production of bile acids in the liver. The entry of cholesterol modulates three processes: 1) It reduces the de novo synthesis of cholesterol in the cells. 2) It promotes the storage of cholesterol in the cells by activating the ACAT enzyme (the enzyme reattaches a fatty acid to excess cholesterol, to produce cholesteryl esters that are deposited in storage droplets). 3) The accumulation of cholesterol in the cell drives a feedback mechanism that makes the cell stop synthesizing new LDL receptors. These three processes fully comply with the Law.

Cholesterol is defined in the General Theory as a **central regulatory molecule** of the *dielectric* properties of physiological membranes. As a basic constituent of the lipid bilayer, it is contiguous to all membrane FUELs and co-regulates their activity (all systems are U-sets). According to the dipole model, cholesterol is an *electroneutral* moiety and is thus a perfect **molecular insulator**[60]. Phospholipids are the second major component of the lipid bilayer. In comparison to cholesterol, these compounds have much more pronounced dielectric properties. This is especially true for unsaturated fatty acids, which carry more or less extended π-electron systems. A higher concentration of cholesterol in the membrane, that is, a higher *cholesterol-phospholipid ratio* increases the insulating properties of the membrane and decreases the amount of energy exchange across the membrane in the form of action potentials. This is simple electricity applied to organic matter (see vol. I & II) - it can be demonstrated at any time at the macroscopic level.

The modulation of the dielectric properties of biological membranes is also confirmed by numerous in vitro studies in membrane research. The cognitive problem of this kind of empirical research is embodied in the so-called "*membrane fluidity model*."[61] For instance, we read in the standard textbook of biochemistry written by L. Stryer that "cholesterol is a key regulator of membrane fluidity."[62] From this quotation, it be-

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60 Cholesterol is the most highly decorated small molecule in biology. Thirteen Nobel Prizes have been awarded to scientists who devoted major parts of their career to cholesterol. Ever since it was first isolated from gallstones in 1784, cholesterol has exerted an almost hypnotic fascination for scientists from most diverse areas of science and medicine. Nevertheless, the role of cholesterol as the universal insulating molecule of membranes has not been appreciated yet.

61 For details, see Biomembranes, Physical Aspects, ed. M. Shinizky, VCH, Weinheim, 1993.

62 See p. 298, 3rd edition.

comes evident that the current scientific approach to biological membranes is that of classical mechanics and not of electromagnetism. Although gravitation is defined in classical mechanics as an "action at a distance", the mechanics (kinetics) of fluids is described as contiguous action. As already pointed out, I have proved in volumes I and II that gravitation and electromagnetism are interrelated abstract levels of space-time, which have been defined within mathematical formalism and only then confirmed in the real physical world (mathematical U-sets that adequately assess space-time). However, only the concept of electromagnetism (Maxwell's equations) gives us a correct idea of the delocalized action of electromagnetic waves, which are systems of photon space-time. This explains the cognitive and experimental deadlock in this important area of bio-science.

We showed that DNA regulation is electromagnetically coupled to the cellular action potentials that generate electromagnetic waves in the cell (for further details on this energy exchange, see quantum Hall effect in vol. I & II). The action potentials are modified by the dielectric properties of the cell membrane, which operates as a spheric capacitor and establishes the electric LRC. This is precisely the universal energetic function of cholesterol, as revealed for the first time in the light of the Law:

> The energetic function of **cholesterol** in organic matter is to **regulate the dielectric (insulating) properties of biological membranes** and to modulate the energy exchange in the cell in a global manner. This is also true for all cholesterol-like molecules found in eukaryotes and prokaryotes, such as *steroid hormones*.

This particular knowledge is sufficient to revolutionize medicine and the bio-sciences. To underline its importance, we should stress that we can only assess electromagnetism and gravitation in a direct manner. All other forces are of hypothetical character - they are indirectly observed through these two forces. As gravitation is a very weak force and of minor importance to organic matter, the regulation of the latter is essentially based on electromagnetism. So far, this has been overlooked. In this respect, it is important to stress that all spatial forms which we encounter in the physical world are shaped by electromagnetism - for instance, all mountains and other relief forms on the earth would be flattened by gravitation unless

this force was counter-balanced by the electromagnetic forces in matter. The microscopic spatial structure of chemical compounds is also a product of electromagnetism. In fact, all the spatial forms which we encounter in the physical world can be presented as a result of two opposite forces - gravitation and electromagnetism (axiom on the reciprocal behaviour of the LRCs of two contiguous levels; see also space of the visible universe in vol. I & II). In reality, the forces (systems and levels) of space-time are infinite, just as is the mathematical ability of our consciousness to put them into distinct categories (U-sets).

As previously noted, it is not the absolute concentration of cholesterol which is relevant for the dielectric properties of membranes, but its relative ratio to phospholipids, which are major structural elements of the lipid bilayer (U-sets). A higher cholesterol-phospholipid ratio increases the insulating properties of the membrane and permits the establishment of a higher resting potential (repolarisation). At the same time the excitability of the cell is reduced in a global manner (*f* goes down). This lowers the energy exchange in the cell. On the other hand, the energy of the action potential E_A is increased, because the amplitude of the resting potential is augmented. The fluctuations become greater, that is to say, within one turn-over, more energy is exchanged in the cell. These energetic adaptations of the cell are *relativistic* and depend on the overall energetic condition of the organism (all systems are open). They can be easily quantified by employing the Lorentz transformations of the theory of relativity, as presented in the new physical axiomatics. When the cholesterol-phospholipid ratio decreases, that is, when there is relatively less cholesterol in the membrane, the energy exchange increases in the cell (*f* grows), but the energy amount of the action potential E_A is reduced. In this case, the conductance of the membrane is improved, as the phospholipids, being better dielectrics than cholesterol, prevail in the membrane. Therefore, the paramount importance of cholesterol in regulating the energy exchange in the cell should be cogent to everybody. It can be precisely assessed by the universal equation $E = E_A f$.

Among others, cholesterol regulates the production of Apo receptors, for instance the dynamics of their endocytosis upon activation; alimentary cholesterol begins to accumulate when the cells are quiescent. The receptor production and expression can be reduced as much as ten-fold in such cells. An excess in cholesterol reduces the transcription of the LDL-receptor gene in cell cultures, while cholesterol deficiency stimulates its transcription. This confirms the reciprocal behaviour of the LRCs

of contiguous levels and demonstrates how the cell is modulated by the amount of membrane cholesterol.

The fat transport system in the organism is subdivided for didactic purposes into two pathways: an *exogenous* pathway for cholesterol and triglycerides, which are absorbed from the intestine and enter the liver (liver cells express large amounts of HDL receptors and clear chylomicrons and chylomicron remnants), and an *endogenous* pathway for cholesterol and triglycerides, which enter the bloodstream from the liver and other non-intestinal tissues (HDL and VLDL). When a VLDL particle reaches the capillaries of adipose tissues or muscles, its apoproteins bind the Apo receptors and triglycerides are extracted. This results in a new particle, which is decreased in size and enriched in cholesterol esters, but still retains the two apolipoproteins. It is called an *intermediate density lipoprotein* (IDL). In humans, about half of the IDL is removed from the circulation within several hours by liver cells, to which this lipoprotein has a high affinity. This tight binding is attributed to apoE. The affinity of this apolipoprotein to LDL receptors on the liver cells is greater than that of apoB. ApoE is dissociated from IDL particles which are not taken by the liver. These are now converted into *low density lipoproteins* (LDL) that carry only ApoB. These particles circulate for about 1 to 2 days before they bind LDL receptors and are removed from the circulation.

These pathways represent the redistribution mechanisms of cholesterol in the organism. ApoE seems to bind stronger to Apo receptors than ApoB and is thus responsible for the quick transport of cholesterol and triglycerides, while ApoB regulates the slower distribution of lipids. The binding of ApoB and ApoE to Apo receptors is competitive and follows essentially the same selective pattern as described for the immune response. ApoB and ApoE can only operate in the lipid milieu of HDL, IDL, or VLDL. This confirms again that the function of the FUELs is closely associated with the composition of the lipid bilayer (see also reconstitution experiments above). In addition, it is important to observe that in the absence of alimentary cholesterol, each cell can switch its metabolism and produce de novo cholesterol.

The central role of the LDL receptor-ApoA/B interaction was first appreciated in *familial hypercholesterolemia* (FH). There are two forms of FH: a more common heterozygous form (about 1:500) and a rare homozygous form (1:250 000). Patients with homozygous FH have circulating levels of LDL more than six times higher than normal (twice in the

heterozygous form). Such patients may experience heart attacks at the age of two and almost inevitably up until the age of 20. It is notable that such children do not have any other risk factors, such as blood pressure, cigarettes, or high blood glucose. This confirms the primary role of elevated cholesterol in atherosclerosis.

LDL receptors in FH homozygotes cannot appropriately bind LDL-apoB and internalize them. The primary defect has been localized in the gene of the LDL receptor. Studies of DNA from affected individuals indicate that at least 150 mutant alleles occur at the locus. As already suggested, these mutations inevitably involve sequences that carry soliton triplets and thus infringe upon the ability of the receptors to propagate solitons. Depending on the kind of mutations (functionally equivalent or non-equivalent), the degree of energetic impairment may vary greatly. In FH, the mutant alleles are therefore grouped in three classes. The most common is designated *receptor negative* and specifies a gene product that is totally ineffective. Such mutants must definitely carry functionally non-equivalent mutations in the soliton triplets of the active site. This issue should be further investigated. The second most frequent class is designated *receptor-defective* and includes mutant receptors with a very poor binding activity (1 to 10% of the normal binding activity). Such FUELs harbour mutations that only partially impair the soliton triplets. The third class includes receptors that are *internalization-defective*. Such FUELs carry impaired soliton triplets, which are not in a position to propagate an adequate soliton at the supramolecular level; they cannot induce a conformational change in the quaternary structure of the ApoB and trigger its endocytosis. We come across the same kinetic mechanism as described for all membrane FUELs. Thus, FH illustrates the common energetic background of the pathogenesis of chronic diseases.

In patients with FH and other hypercholesterolemic disorders, cholesterol is accumulated in the circulation and induces AS of the vessels. Thus, atherosclerosis, as histologically and pathologically observed, is the consequence of impaired FUELs, which are involved in the energetic transport of cholesterol in the cell. This results in increased cholesterol levels in the circulation. Before we proceed with the macroscopic phenomena of AS, we should discuss why elevated cholesterol is also observed in patients who do not carry defective genes and have intact apo-receptors. Then, while FH is an extreme case of AS triggered by a blockade in the cellular uptake of cholesterol, the most common cause of AS is a relative excess in cholesterol due to over-alimentation and immobil-

ity (although other genetic defects cannot be wholly excluded in such individuals). This kind of atherosclerosis is especially common in the elderly and is closely associated with *ageing*. This process goes hand in hand with an increase in the relative ratio of cholesterol in physiological membranes.

The pathogenesis of AS is very slow and begins most probably after the second decennium. Indistinguishably, the energy exchange declines in the cells over the years, but this becomes manifest only after the sixth decennium. Parallel to this change, the function (susceptibility) of the FUELs diminishes. Because of the growing insulating properties of physiological membranes and a higher resting potential, the integral proteins need more energy from the extracellular regulation to be activated and to propagate solitons across the membrane (axiom of CAP). Gradually, the energy exchange in the cell (the transformation of the cell gradient into cell metabolism) slows down. This process can be easily quantified by the energy balance as presented above, but it should also be cogent to anybody who closely observes biological changes in human and other organisms during ageing.

An excess in circulating cholesterol in the elderly organism is therefore an aspect of the reduced energy exchange in the body cells. The alimentary cholesterol in excess cannot be accommodated in the membranes because they are "over-loaded" with cholesterol. Any additional storage of cholesterol in the lipid bilayer will fatally impair cell metabolism, as the function of the integral FUELs will be irreversibly impaired (see the results of reconstitution experiments). The observed hypercholesterolemia indicates the narrow range of cholesterol homeostasis in physiological membranes which is energetically pre-determined. The cholesterol imbalance can be additionally aggravated by over-alimentation and immobility. To understand cholesterol metabolism, it is important to bear in mind that the lipid turn-over in cell membranes which account for more than 50% of the total cell (and body) weight is very rapid. The turn-over rate correlates with the total energy exchange in the organism. Physical exercise leads to a greater turn-over of cholesterol and phospholipids. If the amount of alimentary cholesterol is not sufficient, de novo cholesterol can be rapidly produced in the cells to compensate for this deficiency. Cholesterol is essential to the organism and at the same time pathogenic - hence the Janus character attributed to this molecule.

For this reason sportsmen exhibit no hypercholesterolemia, unless

they are genetically predisposed. Therefore, elevated levels of circulating cholesterol and its deposition in the vessel walls compensate for the impaired energy exchange of this vital molecule at the supramolecular level. As the organism cannot store the excess cholesterol in the membranes, it stores it in the vessels, which is an interim mechanism of compensation. This insight enables the development of clear-cut therapeutic strategies for AS.

Let us now summarize the facts: atherosclerosis is the macroscopic (histological) manifestation of cholesterol imbalance; it involves the tissue (intima) remodelling of vessels. Such processes are immunologically regulated. Although AS is the result of a compensatory mechanism in response to an excess of cholesterol in the body, it can, nonetheless, end up with a singularity at the organ level (e.g. with a heart attack) or at the level of the organism (death). Both events fulfil a condition of destructive interference.

2.6.5 The Pathogenesis of Morbus Alzheimer (AD)

Genetic changes may affect apoliproteins, as is the case of *Morbus Alzheimer* (AD, *Alzheimer Disease*). This fact illustrates that similar changes at the supramolecular level may lead to different diseases. ApoE is involved in the mobilisation and redistribution of cholesterol in the repair, growth, and maintenance of myelin and neuronal membranes during development or after injury (this finding is also important for the pathogenesis of other CNS diseases associated with demyelination). The importance of ApoE in AD is underscored by its presence in plaques and dystrophic neuritis that characterize AD, and by the fact that apoEmRNA, which has a critical role during CNS sprouting and synaptogenesis, is reduced in the hippocampus in AD. In addition, apoE binds tightly the soluble and insoluble forms of β-amyloid in AD patients.

ApoE is encoded in chromosome 19 and is polymorphic. Common alleles of ApoE are designated as ε4, ε3, and ε2. The ancestral isoform of the protein is ApoE3. It has a Cys(−) residue at position 112 and Arg(+) residue at position 158. In the apoE4-allele, both positions are occupied by Arg (Arg-112 and Arg-158), while in ApoE2, Cys occupies both positions. This polymorphism results in six phenotypes: E2/2, E3/3, and E4/4 in homozygotes, and E3/2, E4/2, and E4/3 in heterozygotes. ApoE2 has lower affinity for the LDL receptor than either E3 or E4. Lipoproteins

associated with apoE4 are cleared more efficiently than alleles containing apoE3 and apoE2. Evidently, the presence of Arg-112 and Arg-158 in the soliton triplet(s) of ApoE4 enhances its binding to the LDL receptors and stimulates cholesterol uptake in the liver.

In this context, we should mention again a common motif of amino acid sequence observed in most integral proteins: a patch of two or more Arg (or Lys) amino acid residues, which are found in the negatively charged, intracellular side of the membrane and anchor the transmembrane part to it. This interaction determines the orientation of each integral protein in the membrane; it cannot be changed because each FUEL operates as a specific biological semiconductor. We define this interaction as "*electric anchoring*". In addition, these soliton-specific (+)-residues participate in the formation of transmembrane soliton triplets. For instance, all the α-helices analysed exhibited one or more aromatic π-amino acids (Tyr, Trp, Phe) in the transmembrane part and negatively charged residues (Glu, Asp) on the positively charged extracellular side of the membrane. This arrangement is especially pronounced in the ubiquitous class of seven-loop-receptors or in the one-loop integral proteins, such as glycophorin A.

The above mutations of apoE seem to have direct consequences on brain reinnervation, which relies heavily upon cholesterol and triglyceride transport by apoE. An epidemiological study on the distribution of ApoE alleles in a selected Canadian population revealed a significant prevalence of the E4/4 and E4/3 alleles (3-fold) in the AD population. The ε4 allele was much more frequent in AD patients than the ε3 and ε2 alleles. 83% of all homozygotes (E4/4) were diagnosed with AD. Two peaks in the ε4 prevalence in the AD population were found at 55-65 and 75-85 years. These findings are consistent with the concept of an early and a late onset of the disease[63]. These results are confirmed by other trials.

Plasma cholesterol, LDL-cholesterol, and apoB levels have been found to rise with increasing allele number (ε2 to ε3 to ε4). Especially E4/4 homozygotes are at high risk of AS. ApoE can interact directly with βA4 amyloid to form a stable product also found in senile plaques and neurofibrillary tangles. This co-localization of apoE with the major neuropathological features of AD and the prevalence of the ε4 allele suggests a relationship to the cause of AD.

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[63] Lancet, 1993, 342: 697.

At first glance, there is an apparent paradox. The ε4 allele exhibits a higher affinity to Apo-receptors and other proteins, such as amyloid, but individuals with this allele have higher cholesterol levels. In fact, this finding reflects a compensatory mechanism of the organism. The ApoE4/4 allele containing Arg-112 and Arg-158 binds avidly non-physiological proteins, such as amyloid, and the complex is deposited as plaques in the CNS. In this case the unbound form of Apo E4/4 is decreased; this leads to a lower uptake of LDL in the cells. This explains why ApoE-βA4 complex found in senile plaques contributes to the pathogenesis of AD. To counter-balance this effect, the expression of ApoE4/4 is decreased by endocytosis through depolarisation. The increased cholesterol and HDL levels in AD can be explained by the fact that some of the ApoE bindings are not physiological, so that its expression is down-regulated. This down-regulation of ApoE is associated with a compensatory increase of ApoB. However, elevated ApoB cannot fully compensate for the functional deficiency of ApoE4/4. Hence the elevated levels of cholesterol and LDL. In this case, one should look for distorted soliton triplet(s) that impede the effective function of ApoE. This is a recurrent motif in the pathogenesis of chronic diseases.

2.6.6 Summary

We discussed the pathogenesis of five diseases in the light of the Law. The method of analysis was presented and its epistemological background revealed. This method can be applied to any other disease. The new presentation of the pathogenesis and treatment of chronic diseases establishes the edifice of the General Theory in medicine. It also includes a thorough evaluation of the pharmacological effects of drugs in the light of the dipole model. Together with the soliton triplet concept, it establishes an operational method with which the Universal Law can be applied to organic matter. These two concepts are similar to the *covalent bonding* and *molecular orbit* in chemistry. While these terms permit a simple descriptive presentation of the energy exchange at the chemical level, they include (as U-sets) complex mathematical models of quantum mechanics. I have proved in volumes I and II that the mathematical methods of quantum mechanics can be derived from the universal equation and in particular from the *classical wave equation*, which is the differential form of the universal equation. This has been proven in par-

ticular for *Schrödinger wave equation*, which is the basis of any quantum approach. In addition, I have proved that the theory of probability, as embodied in Kolmogoroff's axiomatics, can also be deduced from the primary term (= probability set).

This concise methodological survey permits two clear-cut conclusions: 1) As space-time is a unity, there is in principle no difference between *inanimate matter* and *organic life*; 2) As mathematics is the only adequate reflection of space-time, all natural sciences can be mathematically presented. They can be reduced to mathematical applications for the levels and systems of space-time which these disciplines have selected as an object of study in the short history of their evolution. This is the epistemological background of the **Unified Theory of Natural Science** based on the Law. However, until all biological and medical concepts have been completely axiomatized, that is, mathematically expressed, we have to put up with semi-mathematical, descriptive presentations. While these concepts take into consideration the diversity of facts and information as inherited by traditional bio-sciences and medicine, they nevertheless abide by the rules of deductive logic and mathematical formalism, which operate on one single principle - the **principle of circular argument**. Only in this way is it possible to avoid introducing logical failures of the type which vitiate the categorical systems that are currently employed in the natural sciences[64].

2.7 THE ENERGETIC APPROACH TO POLYENES - NEW FRONTIERS IN THE TREATMENT OF AIDS, CANCER, AND CHRONIC DISEASES

Amp, Nys, and other related polyenes are **polyene macrolides** that form a clearly defined subgroup of macrolides. There are about 200 polyenes, whose structure is partially or completely known. Most of the isolated samples contain minor contaminants that impede their exact characterisation. Polyenes are produced by *Streptomyces* species and some of these compounds can be partially synthesized.

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[64] Indeed, one would need the power of Heraclitus to undertake the hard and unrewarding job of cleansing the Augean stables of the natural sciences of the numerous epistemological errors that have accumulated through the history of science. This should be the task of future scientists on the basis of the Unified Theory of Science.

2.7.1 Polyene Structure in the Light of the Dipole Model

The determining character of polyenes is the presence of an extended π-electron system in the macrolide ring. It consists of 4 to 7 conjugated double-bonds. The polyenes are subdivided into tetraenes, pentaenes, hexaenes, or heptaenes based on the UV absorption spectrum:

$$-CH_2-(CH=CH)_X-CH_2-$$

where X = 4 (tetraene), 5 (pentaene), 6 (hexaene), and 7 (heptaene). Some conjugated double-bonds may be separated by a methylene bond. For instance, in Nys four double-bonds are separated from two double-bonds by one methylene bond. Except for the UV absorption spectrum, Nys behaves in the same way as the heptaene Amp. Therefore the classification of polyenes according to their UV absorption spectrum may not always correspond to their pharmacological behaviour. In fact, the pharmacological behaviour of polyenes is more or less identical when the dipole model is applied. They only differ in the magnitude of their pharmacological activity.

All polyenes have two component moieties, namely, a macrolide ring and an amino sugar. Some polyenes have an aromatic p-aminoacetophenone (or N-methyl p-aminoacetophenone) moiety. All polyenes, except perosamine, have the amino sugar mycosamine (3-amino-3,6-dideoxy-D-mannose) glycosidically attached to the macrolide ring. Perosamine has 4-amino-4,6-dideoxy-D-mannose. The macrolide ring of carbon atoms is closed by the formation of an internal ester or lactone. It forms a stable rod-like structure with a *hydrophobic* polyene chain at one side and an opposite *hydrophilic* side consisting of hydroxyl groups. Due to this chemical structure, polyenes behave *amphipathic*. They avidly assemble with other lipids in aqueous solutions and build reversible complexes in the form of lipid bilayers (*black membranes*). The structure and physical properties of the polyenes are very similar to those observed in the α-helix of integral proteins. The conjugated double-bonds of most polyenes are in the *trans*-position. In some polyenes, e.g. candicidin, a *trans*- to *cis*-isomerism is observed. The sugar moiety is bonded at one ending of the macrolide rod and carries a primary amino group. At this ending, a carboxyl group on the main macrolide ring is present in all polyenes, the structure of which has been completely determined. A single hydroxyl group (–OH) or a carbonyl π-electron group is positioned

at the other ending of the macrolide rod. Both groups are strongly polarized and hydrophilic. The amphoteric character of polyenes is co-determined by these groups. The occurrence of a sugar moiety with an amino group and a carboxyl group on the same ending of the macrolide rod and a hydroxyl-group and carbonyl-group at the other ending of the polyene rod determines the dipole character of polyenes and the direction of their insertion in the lipid membrane. The sugar moiety and the carboxyl group are placed at the extracellular side of the membrane, just as in all membrane-bound glycoproteins, while the hydroxyl- and carbonyl-groups are situated towards the cytoplasmic side of the membrane.

The orientation of polyenes in biological membranes and artificial bilayers is determined by their unique structure that enables them to operate as **integral non-proteinic FUELs**. The carboxyl group on the macrolide ring is the electron donor. The amino group on the sugar moiety is the electron acceptor. The hydrophobic π-electron system is inserted into the membrane and interacts predominantly with cholesterol, but also with other membrane phospholipids. The three groups form a complete soliton triplet. The polyene chain is responsible for the energy exchange across the membrane by establishing a delocalized anion that can propagate solitons. All polyenes are cell-stimulating drugs of the depolarizing type. The soliton concept postulates that electron transport along a π-electron system is associated with an ionic (proton) transport in the opposite direction. This explains why polyenes have **ionophoric** properties and are used in the *patch-clamp* technique. The ionic transport flows most probably along the opposite hydrophilic side of the macrolide ring.

Thus the analysis of the chemical structure of polyenes in the light of the dipole model and the soliton-triplet concept reveals that polyenes possess the typical supramolecular structure that is also found in physiological integral proteins of eukaryotes. As polyenes are produced by most *Streptomyces* species in great quantities, it can be concluded that they represent a special, **non-proteinic type of physiological FUEL** used by these yeast species, which are prokaryotes.

The ionophoric properties of polyenes are well established. Several models have been proposed, the *de Kruiff's model* being the most widely accepted[65]. This hypothetical model is based on the steric structures of polyenes and cholesterol and has been further modified to comply with

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[65] Biochimica et Biophysica Acta, 1974, 339: 57-70.

the ubiquitous ionophoric properties of polyenes[66]. For Amp and Nys, it postulates a complex of 8 polyene molecules associated in a ring with 8 cholesterol molecules. The inside of the ring is hydrophilic, while the outside is hydrophobic. This model suggests a similar orientation of polyenes in the membrane to that assumed for transmembrane α-helices of integral proteins, e.g. of seven-loop proteins. While the immediate association of polyenes with cholesterol in aqueous solution is beyond any doubt, there is no experimental evidence that directly confirms the de Kruiff's model. This model is static and cannot explain the rapid and discrete ionophoric properties of polyenes, including the transport of various ions, such as Na^+, K^+, and Cl^-, along their electrochemical gradients.

This can be explained in the General Theory by introducing the soliton concept. It implies a dynamic exchange of electrons for ions along the supramolecular structures of membrane FUELs, which operate as biological semiconductors and propagate solitons in the cell. These standing waves induce conformational changes to the FUELs that affect adjacent structures.

In this context, it is important to observe that the terms "ion", "proton", and "electron" are circumscriptions of superimposed standing quantum waves at the particle level (see Bohr model and Schrödinger wave equation in vol. I & II). In this sense, the term "soliton" is a synonym for a standing wave at the supramolecular level; it can be regarded as the *nth-harmonic* of the standing waves of the underlying particles - in the first place, electrons - under a condition of constructive interference. With the help of the soliton concept we can consistently explain the experimental data concerning the ionophoric properties of polyenes. This is another powerful verification of this basic idea of the General Theory.

2.7.2 Pharmacological Effects of Polyenes

In eukaryotes, polyenes depolarize the cell membrane mainly by increasing its permeability for Na^+ and K^+ ions. They cause Na^+-influx into the cell and K^+-efflux out of the cell. These ionic currents influence the per-

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[66] J General Physiol, 1975, 65: 515-526; J Membrane Biol, 1986, 90: 231-240; Am J Physiol, 1986, 251:C1-C-9; J Membrane Biol, 1984, 77: 213-222; Vox Sang, 1987, 52: 182-85; Biochimica et Biophysica Acta, 1986, 860: 57-65; etc.

meability of other ions that participate in the electrochemical gradient, such as Cl^- and Ca^{2+} (U-sets). Therefore, the ionophoric effect of polyenes may be direct or indirect. Cells incubated with polyenes experience a rapid increase in intracellular calcium which is proportional to their concentration. Polyenes have been found to depolarize all eukaryotic cells - therefore, they can be defined as **universal cell-stimulating agents**. During cell stimulation, polyenes can activate various membrane effector systems, such as DAG, PIP_3-cascade, adenylate cyclase, G-proteins, etc.[67] These effects are indirect - they are mediated by the depolarisation of the electric LRC in the presence of polyenes. In addition, polyenes stimulate amino acids and glucose transport into the cell, which is linked to Na^+-transport (symport) during the rapid depolarisation. They can also stimulate various DNA-regulatory proteins and enhance protein synthesis. Polyenes also stimulate the de novo synthesis of phospholipids and glycolysis. This experimental evidence is established in many in vitro studies. Nys is used as a **depolarizing ionophore** in the *patch-clamp technique*, which is a basic method of analysing the electrophysiological properties of cell cultures. All the effects observed with this technique are, in fact, intrinsically associated with the cell-stimulating effect of this polyene[68].

The pharmacological effects described above result from the ubiquitous depolarizing properties of polyenes and confirm the basic principles of the General Theory. This is proof that the group of polyenes has the same mode of action as integral proteins of the depolarizing type. Until now, there was no adequate explanation for the effects of these drugs. Depolarisation is associated with endocytosis of integral proteins, which is part of the self-regulation of the cell. Polyenes can decrease the expression of integral proteins depending on the initial energetic conditions of the individual cells.

It is an established dogma that polyenes are specifically fungicidal in that they form complexes more avidly with *ergosterol* in yeasts than with cholesterol in human cells, but this subjective interpretation, which goes back to the beginning of the antibiotic era, has not been experimentally verified. On the other hand, there is abundant evidence that polyenes

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67 Agents & Actions, 1988, 24: 343-350, Can J Biochem, 1978, 56: 801-807, etc.

68 There are thousands of publications in this field which cannot be discussed in this chapter.

readily assemble with both cholesterol and ergosterol. It is not clear why most textbooks still stick to this dogma. The cytotoxic effect of polyenes in yeasts can be explained with the excessive depolarisation of the yeast membrane. This causes a dissipation of the electrochemical gradient and apoptosis of yeasts. The same effect can be observed in eukaryotes when they are incubated with a high concentration of polyene for a long period of time. The specific cytotoxic effect against yeasts can be explained with the higher threshold of apoptosis of eukaryotes in comparison to yeasts (prokaryotes) - while certain polyene concentrations may be toxic to yeasts, they are well tolerated by human cells.

We have stressed on many occasions that any difference in nature that is conventionally described as a specific quality is in fact a quantitative energetic difference (quants, different action potentials). When this fundamental insight is applied to antibiotics, their antibacterial effects can be explained for the first time in the history of medicine in a stringent way. Bacteria establish a protonic gradient with the help of a few membrane FUELs, which is very similar to that of mitochondria. This gradient is more easily dissipated by cell-inhibiting drugs than the plasma potential of cells. The latter is the aggregated product of numerous ions (see Nernst's equation) and involves the participation of many different FUELs. The greater the number of ionic components (U-sets) that contribute to an electric membrane gradient, the more unlikely its dissipation by ionophoric agents because of the numerous compensation mechanisms. This is in fact a consequence of constructive interference - the more waves with a different frequency interfere (participate) in a wave packet, the more stable the packet (see vol. I & II). Recall that ions are circumscriptions of standing quantum waves. The same holds true for cells and prokaryotes.

Antibiotics are not only *bactericid*; they can also cause lysis to any type of cell at sufficiently high concentrations. This is a well known fact. For instance, they depress the immune system by cell lysis. The regular occurrence of antibiotically induced candidiasis during a prolonged treatment with these drugs correlates precisely with the depression of the immune system. It is well established that candidiasis is the most sensitive indicator for the degree of immunosuppression. For this reason antibiotics should be administered *lege artis* only for a few days during the acute infection so as to support the immune system in the acute reaction by killing bacteria in the peak of their growth. Any prolonged antibiotic treatment leads to a depression of the immune system of the patient and

aggravates the consequences of the infection (condition of destructive interference). Although antibiotics gave birth to modern pharmacology, and have been celebrated as a milestone in the treatment of diseases, even the simple energetic principle of their putative specific bactericidal effect has not been realized yet. This is a convincing demonstration for the power and validity of the General Theory based on the Law. This elaboration of antibiotics is indispensable, because polyenes are often defined as "macrolide antibiotics" in the literature, which is an erroneous taxonomy.

In lower concentrations, polyenes stimulate both yeasts and eukaryotes. This fact is deliberately neglected in pharmacology. This is however not surprising, as both yeasts and eukaryotes are stimulated by depolarisation. There is simply no other way of stimulating organic matter. The treatment of yeasts by polyenes in the human organism is accomplished not only by the direct elimination of over-growing species which are more vulnerable to depolarisation than eukaryotes, but also indirectly by stimulating the immune system, which in turn eliminates the yeasts.

In this context, it should be observed that yeasts are commensurals of the intestinal tract, so that they cannot be totally eliminated without causing irreversible damage to the whole organism. Yeasts contribute to the intestinal flora as *colony-resistant factors*, and their growth is regulated by the local immune system of the gastrointestinal tract. An over-growth of yeasts is the most sensitive indicator of a depressed immune system. This fact also explains why yeast superinfections are regularly observed during prolonged antibiotic treatment, and especially during chemotherapy and radiation in neutropenic (immuno-compromised) patients.

In eukaryotes, there is a strong dissociation between the stimulating and lytic effects of polyenes. We say, the therapeutic range of polyenes is very broad. This explains their extreme tolerability after oral administration (see below). In concentrations of up to 50-100 µg/ml, polyenes stimulate most eukaryotic cells without causing cell lysis. The latter is observed in concentrations above 100 µg/ml when the cells are incubated for 24 hours or longer. Eukaryotes have the propensity to recover from depolarisation below this incubation time. This propensity is less pronounced in yeasts. The lytic concentrations of polyenes exceed more than 10 times the necessary therapeutic concentrations which we have found to be safe and effective in humans (about 10 µg/g body weight).

It is believed that polyenes are not resorbed, or very poorly resorbed, after oral administration. This belief is based on the low plasma concen-

trations which are measured after oral administration of Nys or Amp. These polyenes are commercially available for the therapy of yeast infections. However, the kinetic behaviour of these drugs is very poorly investigated. For example, the kinetic results officially quoted by the manufacturer of Amp are based on the results of only 2 patients[69].

Based on several explorative pharmacodynamic studies (e.g. challenge-dechallenge trials, histological evidence, etc.) and the evaluation of published trials, we came to the conclusion that Amp and Nys must be almost completely resorbed from the gastrointestinal tract after oral administration. Oral polyenes exhibit pronounced systemic effects that have been overlooked until now, most probably because the periods of treatment involved have been too short.

Their systemic effects can be predicted from the energetic analysis of their unique supramolecular structure. Due to their amphipathic character and high affinity to cell membranes, polyenes avidly associate with adjacent cells after resorption and do not appear in blood plasma. Oral polyenes distribute immediately in the so-called "deep" (second) compartment of the body, predominantly in the liver, lymphatic organs, and spleen, and are found only in negligible quantities in the first compartment, including blood circulation. This explains why serum levels of polyenes are very low after oral administration. Due to their lipophylic character, their plasma concentrations are also very low after i.v. administration.

Polyenes are most probably absorbed in the jejunum with the help of bile acids, to which they exhibit a very high affinity and spontaneously associate. After resorption from the intestinal mucosa, polyenes are transported via the lymph to the liver (enterohepatic pathway) and, from there, to other lymphatic organs where they interact with cells of the immune system and stimulate them through depolarisation. Due to their lipophilic character, orally administered polyenes do not reach vital organs, such as kidney, heart, and lungs in high toxic concentrations. For this reason oral polyenes do not cause any of the serious adverse events which are commonly observed after i.v. administration. This explains the extraordinary safety of polyenes when administered orally compared to their high toxicity when given intravenously. A research in the literature (3000 publications) did not yield a single serious adverse event reported with an oral polyene during the last 50 years. So far the safety of oral polyenes

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69 Antimicrob Agents & Chemoth, 1978, 13: 271-276.

is unmatched by any other registered drug.

This dichotomy in the safety profile of polyenes - high toxicity after i.v. application and no toxicity after oral administration - is determined by their pharmacokinetic behaviour. Unfortunately, this circumstance has evoked the erroneous impression that these drugs are not resorbed from the gastrointestinal tract. For this reason polyenes are given orally only for a short-term gut decontamination, while their long-term stimulating effects were not known until I discovered and explained them. The therapeutic effects of long-term treatment with polyenes were established per chance during my clinical research activities and were subsequently assessed in various clinical disorders.

Polyenes bind avidly to biological membranes and disappear immediately from the circulation. When polyenes are incubated with cell cultures or interact with artificial bilayers (e.g. in patch-clamp technique), they are almost completely found in a membrane- or lipid-bound form (> 99%). Unfortunately, this fact has not been appraised in the few pharmacokinetic studies performed with these drugs. For instance, it was found that most Amp is accumulated in the liver, spleen, and other secondary lymphatic organs, and can be recovered 24 to 48 hours after i.v. administration[70]. More than two thirds of the total amount of i.v. Amp is not eliminated renally, so that its fate in the organism is unknown at present. Despite the fact that the enterohepatic route of elimination of polyenes is not properly investigated, there is strong evidence that polyenes are cleared to a large extent by the liver. As there are no indications whatsoever that polyenes accumulate in the organism, the only possible conclusion from this fact is that most of them are metabolized by β-oxidation (fatty acid metabolism) in the cytosol.

Other studies using more sensitive methods determined somewhat higher plasma concentrations of Amp and Nys after i.v. and oral administration than initially anticipated.[71] Measurements of polyene concentration in faeces confirmed that less than 1% of the total oral dose was recovered in the faeces. As there is no evidence that polyenes are degraded in the digestive tract, it must be assumed that they are almost completely resorbed from the gastrointestinal tract. We performed dechallenge-rechallenge tests in patients treated with Nys or Amp for

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70 Antimicrob Agents & Chemoth, 1989, 33: 362-268.

71 Antimicrob Agents & Chemoth, 1990, 34: 29-32; Br J Clin Pharmacol, 1983, 16: 106-108.

various indications. There was a clear-cut correlation between the systemic effects observed and the time of dechallenge or rechallenge. The intensity of the systemic effects was dose-dependent. Histological and further diagnostic findings, such as pronounced encapsulation of liver and lung carcinoma, associated with regression of tumour growth, reversal of arthritic inflammation in RA patients, cure of cholecystolithiasis, and so on, indicate that polyenes achieve sufficient concentrations in these organs to enhance the observed therapeutic effects.

Polyenes are universal depolarizing agents. They stimulate cell growth, proliferation, differentiation, and various other metabolic activities, such as protein synthesis, receptor expression on cell membranes, turn-over of phospholipid membranes, etc. The most important effects of polyenes on immunocompetent cells (in vitro and in vivo studies) are summarized below.

Polyenes induce B and T lymphocyte activation. They enhance the production of immunoglobulins in B cells and their mitosis. Further on, they stimulate the proliferative response in murine lymphocytes. Polyenes enhance the contact sensitivity in animals and the immunogenic response to infections. Amp stimulates suppressor T lymphocytes and monocytes. It triggers the response to experimental visceral leishmaniasis in T cell deficient hosts. Polyenes stimulate the tumoricidal activity of macrophages and their precursor cells. They also activate natural killer cells. Polyenes stimulate polymorphonuclear cells (PMNs) through depolarisation. At the same time, they decrease the expression of the chemoattractant receptor and inhibit chemotaxis due to excessive depolarisation. The chemotaxis of PMNs is considered the reason for many inflammatory processes, including sepsis. While chemotaxis is suppressed, lysozyme secretion in PMNs may be enhanced. Amp enhances the phagocytosis of PMNs by stimulating the Fc-mediated (fragment c of immunoglobulins) ingestion in a dose-dependent way (substrate intake in the cell coupled to depolarisation). The same effect can be achieved by cytokines. Amp enhances the oxydative burst in macrophages. The immunostimulating effects of polyenes are also confirmed in animal models. Amp induces the resistance of mice to listeriosis and schistosomiasis and enhances their contact sensitivity.

Polyenes potentiate the cytotoxic effects of anticancer drugs by stimulating their intake into the cells via depolarisation and Na^+-symport. Amp stimulates RNA and DNA synthesis in fibroblasts and other cells as demonstrated by an enhanced uridine transport. The specific antivi-

ral effects of polyenes will be discussed in conjunction with AIDS.

The discovery of the novel pharmacological properties of polyenes and the development of the General Theory was closely associated with a large international multicentre trial on the selective decontamination of the digestive tract (SDD) in severe trauma patients in ICU wards (The "European SDD Trial"), for which I was responsible between 1991 and 1994. This was the largest trial ever performed in this indication. The trial was sponsored by Hoechst AG. Altogether more than 400 patients were enrolled. The SDD regimen was compared to the standard treatment according to the individual protocols of the centres. The SDD regimen included a daily dose of 3 g Amp given parenterally, immediately after delivery to the hospital and for the duration of the ICU stay. Systemic antibiotic treatment was given for early prophylaxis during the first 4 days after trauma and thereafter at the discretion of the investigators. The assumption was that the SDD regimen significantly reduced mortality (primary endpoint). A sequential analysis was performed each month in England and made available to an independent Steering Committee.

Meta-analysis of all SDD trials performed in more than 3000 ICU patients was published during the conduct of our trial[72]; it showed a significant reduction in mortality under the SDD regimen. In our trial, early administration of systemic antibiotics was considered the most important therapeutic measure in the prevention of sepsis (and mortality) in severe trauma patients. Since some of the regimens used were only topical, while others were topical and systemic, both groups were separately evaluated. There was no major difference in the efficacy observed between the combined systemic and topical SDD regimen and the topical SDD regimen. This result repudiated the initial hypothesis of our trial that systemic antibiotics might be more effective than topical treatment in severe trauma patients.

In September 1993, we performed an interim analysis of the baseline values of the SDD trial. Data from 300 patients were entered in the analysis. This revealed that, in the standard regimen group, systemic antibiotic treatment was used as early and almost to the same extent as in the SDD regimen group. We concluded that both groups were more or less identical with respect to the systemic antibiotic treatment administered

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[72] BMJ, 1993, 307: 525-532.

to the patients. The groups differed only in the use of oral Amp for gut decontamination. At the same time, mortality was substantially reduced in the SDD regimen. An interim statistical analysis of the primary point could not be performed with respect to the pre-determined statistical power. Recall that every evaluation is an interaction (energy exchange) and should be considered in the statistical analysis. We concluded that the life-saving effect in the SDD regimen group should be attributed to Amp. In this trial, there were indications of yeast infections to a similar extent in both groups. Therefore, the reduction of mortality in the SDD group could not be attributed to the presumed *antimycotic* effect of Amp.

At that time we still believed that Amp was not resorbed from the gut, as ascertained throughout the literature and propagated by the manufacturer. Accordingly, we did not expect any systemic effect of Amp when we planned the trial. When this initial belief was shaken by the interim analysis, I looked for indices in the literature (Medline search) and discovered that Amp, Nys, and other polyenes could stimulate a variety of cells in vitro, including immunocompetent cells. They seemed to stimulate cell growth, substrate intake in the cells, protein synthesis, and proliferation. Based on this information and supported by the clinical evidence of the SDD trial, I postulated that Amp had a different therapeutic effect in trauma patients than the antimycotic effect conventionally attributed to this drug. I came to the conviction that the observed beneficial effect of Amp in the SDD group was definitely not antifungal.

During this period, I initiated a number of small explorative trials, including self-treatment of localized, self-induced injuries (e.g. burning of the extremities), and discovered that topical Nys and Amp enhance the healing of wounds and inflammations, such as ulcus cruri, decubitus, burns, recurrent aphthous stomatitis, subprosthetic stomatatis, granuloma, and other mucosal lesions in an almost miraculous way. The healing effect was astounding and unlike anything described in the literature before. This convinced me that I had discovered a new universal mechanism of pharmacological action.

In the meantime, additional experimental evidence was collected which showed that oral Nys and Amp are also effective in the treatment of acne and neurodermatitis, improve the symptoms of chronic cold-agglutinin disease (CAD), eliminate cholecystolithiasis, reverse hyperplasia of the prostatic gland, improve postmenopausal syndrome, heal endometritis, lower elevated plasma cholesterol levels in atherogenic patients and elevated glucose levels in insulin-dependent diabetic patients, etc. The thera-

peutic effects of polyenes which I and other colleagues have observed in various clinical conditions fitted in well with the extensive body of evidence from in vitro studies with this group of compounds. Based on the General Theory, this evidence enables us to predict the beneficial therapeutic effects of polyenes in the following clinical conditions.

2.7.3 AIDS Therapy with Polyenes

The treatment of AIDS with polyenes is a novel therapeutic approach based on the Law. The objective is to stimulate the immune system from the very beginning, at best immediately after infection (after seropositive testing). Polyenes stimulate all immune cells, in particular T cells, by depolarizing them. Depolarisation is always associated with an endocytosis of integral FUELs. Depolarized infected cells do not express the gp120-gp41 complex. The proviral DNA can not be replicated by the specific delocalized coupling. At the same time the metabolism of these cells is stimulated, so that they can recruit their own DNA repair mechanisms (e.g. DNA-regulatory proteins, methylation and inactivation of proviral DNA) and inactivate the intracellular HI-virus. The replication of the HI-virus requires optimal intracellular conditions and in particular the expression of the viral FUEL - the gp120-gp41 complex.

There is broad experimental evidence that many viruses are eliminated intracellularly and that only a few replicate. Stimulated cells are found to eliminate the virus more effectively than without stimulation. This is the rationale behind the treatment of AIDS patients with polyenes. It can be postulated that chronic treatment with these drugs will reduce the rate of depletion of CD4 cells and thus prolong the disease-free interval. Polyenes stimulate the infected cells and suppress the expression of the gp120-gp41 complex. These effects reduce the risk of apoptosis of CD4 cells and other immune cells in lymphatic organs, enhance their repair mechanisms for eliminating the virus, and prevent the biasing of the first and second selection by inhibiting the expression of the gp120-gp41 complex. This aggregated effect of polyenes improves the condition of constructive interference in the immune system and prevents the manifestation of the disease - the occurrence of AIDS-related complex (ARC), which ultimately leads to death.

The purpose of early treatment with cheap and safe immunostimu-

lating drugs, such as Nys, Amp, and other polyenes, is to postpone or suppress the occurrence of the disease and not to eliminate the virus from the body, which is most probably impossible. The human body is known to harbour thousands of different viruses which participate in the regulation of the organism. At present, there are no effective oral immuno-stimulating drugs on the market except the polyenes. The latter are the most potent immunostimulators we know of. Therefore, early treatment of AIDS with polyenes is a completely novel approach and contrary to the current practice of using cell-inhibiting drugs, which have been found to increase morbidity and mortality (see CONCORDE trial above and chapter 2.9). The aim of early therapy with polyenes is to increase life-expectancy and improve life-quality in HIV patients. One should also expect a dramatic reduction in the risk of opportunistic infections.

The antiviral effects of polyenes, as described above, have been confirmed in vitro[73]. 10 µg/ml Nys and Amp completely inhibited the expression of gp120 and gp41 in H9 cells, which are a line of human lymphocytes permissive to HIV-1. The inhibition of viral replication was demonstrated by the reduction of p24 and by the inhibition of the reverse transcriptase. 10 µg/ml Nys and Amp were as effective as 50 µg/ml AZT. The cytotoxity of Nys and Amp was less than that of AZT. With the effective doses of Nys and Amp the viability of the cells was in the range of 92-96%. The polymerase chain reaction (PCR) could not detect any proviral DNA in the presence of 10 µg/ml Nys and Amp. Thus cells incubated with polyenes are highly stimulated - they can eliminate the proviral DNA and impede the replication of the HI-virus. The antiviral activity of Nys and Amp remained unchanged in cells which were preincubated with the HIV-virus, and in those which were infected during treatment. Other viruses could also be suppressed when incubated with polyenes. These data clearly indicate that the antiviral effect of polyenes is due to the stimulation of the body cells through depolarisation. Identical results were observed with a new Amp derivative in two human T cell lines, Jurkat and CEM. These results credibly confirm the validity of the bioenergetic model for the pathogenesis of AIDS (see chapter 2.5).

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[73] AIDS Res & Hum Retrovirus, 1993, 9: 475-481; AIDS, 1991, 5: 1453-1461.

2.7.4 Treatment of Cholesterol-Associated Diseases with Polyenes

Polyenes normalize circulating serum cholesterol in hypercholesterolemic patients within several weeks. They improve the uptake of cholesterol in the cell and its turn-over in the membrane. Four polyenes, candicidin, filipin, Amp, and Nys, have been given orally as hard gelatin capsules in 79 pure-bred beagle dogs, weighing approx. 10 kg. Three daily doses were tested: 50, 100, and 200 mg, corresponding to 5, 10, and 20 mg/kg body weight. The dogs were treated for 21 days and blood samples were taken daily. There was a significant ($p = 0.001$) dose-dependent reduction of serum cholesterol with all polyenes. The inter-individual variation of serum levels decreased. All dogs exhibited a marked shift to the normal range of serum cholesterol levels. These results clearly indicate that polyenes are effectively resorbed from the gut and exhibit a pronounced anticholesterolemic effect in mammals. We measured plasma cholesterol levels in patients taking Amp for selective decontamination of the digestive tract (SDD) for more than 2 weeks and observed a similar shift of cholesterol levels to the normal range. Thus polyenes promote a rapid utilisation of cholesterol. This is also compatible with our observation that prolonged treatment with systemic Amp may cause a moderate loss of weight in some patients.

Old dogs with benign prostatic hypertrophy treated with oral candicidin, Amp, and a variety of other tetraenes, pentaenes, and haptaenes produced a marked reduction in the texture and volume of the glands. Microscopic biopsies exhibited pronounced histological improvements, such as reduced congestion, granularity, and papillations. These results suggest that oral polyenes are effective in the treatment of prostatic hyperplasia. Our clinical experience has confirmed these data from animal models. This indication should be further investigated in double-blind, placebo-controlled trials.

The antihyperplastic effect of polyenes is due to a stimulation of the gland and improvement of steroid metabolism. Prostatic hyperplasia is a compensatory effect caused by a reduced efficacy of the gland cells in advanced age when male sexual hormones, e.g. testosterone, usually decrease. This clinical case introduces a basic statement of the General Theory. In the light of the Law, *space* and *energy* are reciprocal magnitudes. When this reciprocity is applied to organic matter, we arrive at a **basic axiom of pathology**:

> Energy stands for *efficacy* of cells and organs, while space stands for *hyperplasia* of organs. Hyperplasia indicates an energetic deficiency of the organ function.

There is no exception to this rule. The full importance of this basic axiom of pathology has not been realized in medicine. For instance, a hyperplasia of the heart is always a symptom of heart deficiency. In this case, the ejection fraction of the heart is reduced either due to a coronary disease or congestive failure. This condition can be described as reduced energetic efficiency (the ejection volume of the heart can be regarded as an action potential or an impulse and described by the axiom of CAP); at the beginning, the coronary disease is compensated by an increase in volume (the thickness of the myocard wall increases). The greater the heart deficiency, the greater the dilatation of the heart, and the smaller the ejection fraction (E_A goes down); in the final stage, we observe the so-called "bovine heart" which is a sign of a terminal heart insufficiency. We can apply the same axiom to the liver (hepatitis with liver hypertrophy), to the spleen (leukemia, elevated leukocyte counts associated with immunodeficiency), or to any gland such as the thyroid gland (hypothyreosis with struma). We always find the same reciprocal relationship between the efficacy of an organ and its volume[74]. As we see, also in organic matter we encounter the fundamental property of space-time - the reciprocity of space and time, respectively, energy. This is cogent proof that both organic and inorganic matter abide by the Law.

2.8 TRIALS SUPPORTING THE NEW TREATMENT WITH CELL-STIMULATING DRUGS

In this chapter, we shall present some selected examples from the literature confirming the basic conclusion of the General Theory in medicine: cell-stimulating drugs are effective in the treatment of a variety of diseases for which there is no treatment at present. Therapy with cell-stimulating drugs should be *chronic*, as the impairment of energy exchange in chronic diseases is genetically determined (see chapter 2.9) and cannot be selectively repaired by the application of external chemical agents

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[74] How about muscle hypertrophy due to exercise? We leave the solution to the reader.

such as drugs. This rejects the principle of causality in therapy. Such defects can only be counter-balanced by cell-stimulating drugs in a global manner. In terms of physics (wave theory), any effective therapy is an energetically induced shift towards an improved condition of constructive interference in the body. This will be the Ariadne's thread of modern medicine based on the Law.

The number of trials that prove the validity of this statement, as first postulated in 1994, has been growing exponentially in the last few years. These results are powerful prospective confirmation of the General Theory. The most outstanding clinical trials performed in the last ten years will be presented below. They constitute a small fraction of the total clinical evidence in support of the General Theory. To begin with, cell-stimulating drugs can be subdivided into *two* classes:

1. **Oral non-proteinic agents**. This group includes:

   a) Drugs of biological origin, such as *polyenes*, *vitamins*, and *vitamin-like derivatives.*
   b) *Synthetically synthesized drugs* with a pronounced dipole moment.

   These drugs are very well tolerated and are adequate for chronic treatment. They cause no or very few and mild adverse events.

2. **Intravenous proteins of human or biological origin**. This group consists of *humoral* and *integral FUELS*, or *analogues* obtained from humans or other species by bio-technological methods. According to the General Theory, such agents are cell-stimulating. Most of them are *depolarizing*; the rest are *repolarizing*. Due to their mandatory i.v. application (proteins are digested in the gastrointestinal tract), proteinic drugs reach via blood circulation vital organs, such as kidney, heart, and lungs, and exhibit pronounced adverse events. Due to their high toxicity, complicated i.v. application that impairs life-quality, and high costs, these drugs can only be given *intermittently* and are thus not adequate for chronic treatment. This will be substantiated below.

Therefore, the key objective of future pharmaceutical research will be the **development of cheap and safe non-proteinic cell-stimulating**

drugs. This is a clear-cut aim, imperatively deduced from the General Theory. We shall show that recent pharmaceutical research has been blindly following this objective, however, without being in a position to articulate it from a theoretical and rational point of view. With the implementation of the General Theory, it can be predicted that this kind of scientific research will be rationalized and will exhibit an unprecedented development for the benefit of chronic patients.

2.8.1 Treatment with Humoral Factors, such as Interferons, Interleukins, and Other FUELs

Current clinical results with cell-stimulating drugs repudiate the central dogma of pharmacology that postulates specific therapeutic effects of drugs. The trials presented in this chapter show that such drugs are effective in various chronic diseases by improving the energy exchange in the body in a global manner. The paradoxicality between wishful thinking and reality in pharmacology becomes cogent when one considers the large number of different indications registered or applied for *interferons* and *cytokines* - the range is from cancer to multiple sclerosis. This lack of common sense and logical thinking at the collective scientific level, as demonstrated by registration authorities, pharmaceutical companies, and other corporations, is, indeed, unprecedented in the history of mankind. Although this paradox is central to the following scientific discussion, it cannot be fully resolved by it, but should also include a rigid psychoanalysis of the systemic pitfalls of collective human consciousness (and subconsciousness) in the last 2000 years.

With respect to medicine, the reader should not be surprised to discover that one and the same cytokine or interferon is effective in different diseases. This fact confirms a basic axiom of the General Theory that says: the body is an open system, so that the supracellular regulation can incorporate any external moiety and transmit its effect as an excess of depolarisation, repolarisation, or energy-induced inhibition. The particular effects of these energetic phenomena in the cell can be infinite, because they also depend on the initial energetic conditions of the body cells, which are also infinite (as space-time is infinite, all U-sets thereof manifest this property). Back to the clinical evidence.

Eleven patients with relapsed *chronic myeloid leukemia* (CML) after allogenic bone marrow transplantation were treated with *interferon* α-

2*b*, a depolarizing cytokine, and infusions of mononuclear cells from the marrow donor to induce a graft-versus-host reaction (GVHD). Six out of eight patients with stable CML after relapse had complete remissions and three patients with accelerated CML after relapse did not enter remission. Grade I GVHD occurred in 6 patients and grade III in three. The treatment was considered effective and may offer an alternative to a second marrow transplantation[75].

The next trial supports our general consideration concerning the criteria of optimal therapy (see Pareto criterion). *Interferon*-α-2*b* was given in combination with chemotherapy (CHVP, cyclophosphamide, doxorubicin, teniposide, and prednisolone) in 123 patients with advanced follicular *non-Hodgkin lymphoma* at a dosage of 5 million units three times weekly for 18 months. This treatment regimen was compared in a randomized trial with chemotherapy alone, given in 119 patients. Interferon-α-2b in combination with chemotherapy was significantly more effective for the overall rate of response ($p = 0.0006$), produced a longer median event-free survival (34 months vs. 19 months, $p < 0.001$) and a higher rate of survival at 3 years (86% vs. 69%, $p = 0.02$). However, interferon-alfa-2b had to be stopped because of toxic effects in 13 patients (11%). This result shows that chronic treatment with i.v. interleukins is rather toxic as predicted by the General Theory. Interleukin concentrations can be increased a thousand-fold during the acute reaction, but then they fall rapidly when the infection is under control. Elevated concentrations of interleukins over a long period of time, as maintained in this study, are obviously less well tolerated by the organism[76].

Interferon-α -2*a*, another depolarizing lymphokine, was found to be effective in *chronic hepatitis* D[77] and HCV-associated *cryoglobulinemia*[78]. A relapse of hepatitis was commonly observed after the treatment was stopped. We observed the same effect with Nys in chronic cold agglutinin disease (CAD). Treatment with cell-stimulating agents should be chronic in chronic diseases - in many cases life-long. The objective of this treatment strategy is to counterbalance the impaired disequilibrium of the body cells involved in the disease. We treated one patient with CAD for 9 months and achieved an improvement of acrocyanosis, which

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[75] N Engl J Med, 1994, 330: 100-106.
[76] N Engl J Med, 1993, 329: 1608-14.
[77] N Engl J Med, 1994, 330: 88-94.
[78] N Engl J Med, 1994, 330: 751-56.

normally developed when the external temperature was below 18°C. CAD is related to cryoglobulinemia. The effect reversed after stopping the therapy (challenge-dechallenge effect).

In a large trial, *interferon-α-2a* was compared to conventional chemotherapy in CML[79]. 322 patients were followed up for 6 years. The long period of treatment is an outstanding aspect of this trial. Biological systems behave in a non-linear manner and exhibit a high elasticity. An organism with a profound impairment of energy exchange responds to cell-stimulating treatment only after a long period of treatment (long Ljapunov time).

On the other hand, the pharmacological effects of cell-inhibiting drugs occur almost immediately after administration, e.g. negative chronotropic and inotropic effects of β-blocking agents, because their effects are not physiological and hence deleterious to cells and organism (short Ljapunov time). For instance, we can observe a pronounced reduction of heart frequency under β-blocker therapy within the first 24 hours after initiation of treatment ($E = E_A\, f$, E_A = ejection fraction of heart, f = heart frequency, E = work/energy exchange (power) of heart; $E \approx f$) and a reverse effect after stopping it (β-blocker withdrawal syndrome)[80]. When the decrease of heart frequency is $\Delta f = 10$ *beats/min* (15%), the power (energy) of the heart is reduced correspondingly $\Delta E \approx \Delta f$ (see also CAST trial below). This decrease in cardiac (pump) function affects the whole organism in a global manner and leads to numerous adverse events. For further information, we recommend that the reader scrutinize the official drug information sheets issued by the manufacturers of β-blocking agents.

In addition, cell-inhibiting drugs exhibit long-term deleterious effects such as the occurrence of mutations due to an energy constraint (chapter 2.9). The higher rate of mutations increases the risk of cancer, which becomes manifest after a long Ljapunov time of 10-20 years. In such cases, the relationship between chronic cell inhibition and cancer incidence can only be assessed if the observation period is longer than the Ljapunov time. Unfortunately, there have been very few trials that assess this specific relationship over a period of more than 10 years (see below).

In the above trial, the 6-year survival in the interferon-α-2a group was significantly higher than in the chemotherapy group (50% vs. 29%,

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[79] N Engl J Med, 1994, 330: 820-5.

[80] G. Stankov. Doctor thesis, Heidelberg University, 1983.

$p = 0.0002$), as predicted by the General Theory. In the following we shall present a collection of trials with cell-stimulating drugs in different indications; all of them clearly demonstrate that **cell-stimulating drugs significantly improve long-term mortality**. The explanation of their effect is a major breakthrough of the General Theory that will revolutionize future pharmaceutical research and medicine. Another major breakthrough of immense ethical relevance is the conclusion that **most current drugs are cell-inhibiting and increase mortality and morbidity** (see chapter 2.9).

The interferon α-2a trial presented above demonstrates the consistency of the new methodology in medicine. It begins with an evaluation of the chemical structure of the drug by applying the dipole model. The predicted dipole moment of the moiety is then substantiated by analysing the reported pharmacological and clinical effects (if available). This analysis considers the basic energetic principles of cell regulation as elaborated in the General Theory. In conjunction with the soliton triplet concept, the dipole model is then applied to established genetic defects at the quantum level of organic matter, as elucidated in previous chapters (see also chapter 2.9). The predicted pharmacological effects of the drug are finally confirmed in a consistent manner at the level of the human organism by evaluating the results of clinical trials with this drug (transitivity of the General Theory due to axiomatization).

As predicted by the General Theory, organisms with a chronic, usually genetically pre-determined impairment of the energy exchange, such as CML[81], have a long Ljapunov time and respond with a delay to cell-

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[81] CML is a clonal stem cell disorder characterized by markedly increased myelopoiesis and the presence of Philadelphia (Ph) chromosome. The Ph chromosome involves a translocation of the abl proto-oncogene on chromosome 9 to the breakpoint cluster region (bcr) of chromosome 22 forming a fusion gene called bcr-abl. These translocations involve soliton-specific amino acids. I treated one patient with CML who refused current treatment protocols with nystatin in the blast phase and prolonged his life by almost two years. During nystatin treatment the patient was working all the time and consciously enjoyed life. Before he died, he spent a 3-week holiday in the South Seas. The median survival of CML patients in the blast phase is about 15-20 weeks. Patients under conventional immunosuppressive therapy spend most of their time prior to exitus in a closed aseptic ICU and suffer terrible pains and exhaustion. They cannot enjoy the rest of their life - the life quality in such patients, if this parameter can be quantified at all, is virtually zero.

stimulating drugs: in the CML trial no difference in mortality was observed after the first 2 years of treatment. The toxicity of i.v. interferon-α-2a led to a high withdrawal rate of 16%. This result was also predicted by the Theory.

Cytokines are conventionally defined as "*immunomodulators*". This term is meaningless. The cognitive mess in this area is illustrated by the fact that stimulatory (depolarizing) and inhibitory (repolarizing) effects are simultaneously ascribed to one and the same cytokine, without giving an explanation as to how these antagonistic effects are actually exerted by the compound. The term "immunomodulator" has no energetic background and cannot be quantified in a stringent mathematical or scientific way. The conflicting connotations ascribed to this term are the origin of numerous misunderstandings and illogical decisions in pharmacology at the expense of the patients.

For instance, high-dose *interleukin*-2 has been recently approved for the treatment of metastatic *renal-cell carcinoma* by the FDA, despite the lack of placebo-controlled or randomized studies, and only on the basis of a rate of durable complete response of 4% in seven studies[82]. In these trials, the median duration of survival was performed with respect to historical controls. However, the two patient groups were not comparable. This is a common mal-practice that discloses why most drugs have been registered without being properly evaluated in terms of statistics (recall that mathematics is the only adequate reflection of space-time). IL-2 is principally secreted by $CD4^+$ subset of T cells and activated B cells. Although the data on its effects are contradictory, it can be concluded that this cytokine is depolarizing. It stimulates the proliferation of immune cells. As the difference between depolarizing and repolarizing cytokines is not appreciated at present, it is generally believed that any cytokine may be effective in the treatment of renal-cell carcinoma.

This erroneous conclusion led to the conduct of a placebo-controlled trial with *interferon*-γ-1*b* in 197 patients with metastatic renal-cell carcinoma in 17 centres in Canada[83]. The authors gave as the reason for this trial that "most trials with *immunomodulators* in metastatic renal-cell

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82 Proleukin (package insert, May 1992); Rosenberg SA et al., N Engl J Med 1987, 316:889-97; Weiss GR et al, J Clin Oncol, 1992, 10: 275-81; Rosenberg SA et al., JAMA, 1994, 271:901-13; Bukowski RM et al., J Natl Cancer Inst, 1990, 82: 143-6; Taneja SS et al., 1995, 45: 911-24.

83 N Engl J Med, 1998, 338: 1265-71.

carcinoma have been uncontrolled and subject to selection bias." (p. 1265).

While this observation is undoubtedly correct, the assumption that interferon-γ-1b should exhibit the same properties as IL-2 is fundamentally wrong. An analysis of the structure and properties of this humoral protein reveals that it is of the repolarizing type and should therefore exhibit opposite effects to those of IL-2 in renal-cell carcinoma or any other disorder. In terms of the General Theory, we can predict *ad hoc* that interferon-γ-1b will not be beneficial in renal-cell carcinoma (Pareto-optimal stimulation).

Our prediction is confirmed by the results of this trial. The authors found no difference in outcome: the median time of disease progression was 1.9 months in both groups ($p = 0.49$) and there was no significant difference in median survival. The median survival was even higher with placebo (15.7 months) than with interferon (12.2 months). The overall response rate was 4.4% in the interferon group and 6.6% in the placebo group ($p = 0.51$). Although no significance was reached, due to the comparatively short observation period, there was a clear-cut trend in support of the placebo treatment.

These results can be better comprehended when they are compared to those of another trial in the same indication which was published simultaneously[84]. In this trial, *recombinant IL*-2 and *recombinant human interferon*-α-2*a* (both are depolarizing cytokines) were randomly assigned as single agents and in combination to 425 patients with *renal-cell carcinoma*. The endpoints were similar to those in the previous trial. The response rates were 6.5%, 7.5%, and 18.6% ($p < 0.01$) for the groups receiving IL-2, IFN-α-2a, and IL-2 in combination with IFN-α-2a. At one year, the event free-survival rates were 15%, 12% and 20% ($p = 0.01$).

The higher response rate under combination therapy with the two depolarizing cytokines reflects the general situation in the body - the supracellular regulation consists of many different depolarizing agents, whose effects accumulate. Any Pareto-optimal, cell-stimulating therapy should imitate this natural situation. The supracellular regulation in the body is the aggregated product of many depolarizing and a few repolarizing agents. This is an urge for a radical departure from the present *purism* advocated by registration authorities, which favour monotherapies without presenting any rational explanation for this subjective preference.

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84 N Engl J Med, 1998, 338:1272-78.

The anticancer effect of depolarizing agents was explained in conjunction with the pathogenesis of cancer and the therapeutic effects of polyenes. This effect is independent of the biochemical origin - proteinic and non-proteinic agents exert similarly beneficial effects. However, the individual kinetics of each depolarizing drug plays a major role in its efficacy - the anticancer effect depends to a large extent on the drug concentration at the site of carcinogenesis. The depolarizing effect is proportional to the concentration and incubation time, that is, it depends on the clearance time from the organism. Below, we shall present some trials which show that humoral cytokines and other proteins of the depolarizing type are effective in the treatment of various cancers.

Hepatocellular carcinoma is considered to be one of the most malignant cancers for which there is no treatment at present. We have shown that polyenes are effective in this cancer due to their resorption kinetics, which leads to high intrahepatic concentrations of these drugs. It is therefore logical to assume that similar, though less pronounced, therapeutic effects can be achieved with i.v. cytokines. The effect of *interferon-α-2a* was recently investigated in patients with chronic viral hepatitis and Child's A cirrhosis; these patients are at high risk of developing hepatocellular carcinoma. The trial was conducted in 21 centres in Italy and Argentina[85]. It was found that interferon treatment lowered the rate of progression to hepatocellular carcinoma *two-fold*.

This trial confirms two basic conclusions of the General Theory: 1) One and the same cytokine may be effective in different diseases and indications: interferon-α-2a has an anticancer effect in CML, renal-cell carcinoma, and hepatocellular carcinoma. In fact, this cytokine is effective in any kind of cancer. For this reason it is not necessary to present clinical evidence in support of the efficacy of this cytokine in each particular cancer prior to registration, as is demanded today. The new principles of registration which should be adopted after the General Theory has been published will save billions of dollars of futile clinical research for the pharmaceutical industry and will permit the immediate introduction of new effective drugs and other therapeutic procedures for many cancers and other disorders for which there is no cure at present. 2) Cell-depolarizing agents should be given prophylactically in patients at high risk of cancer. Such drugs improve the energy

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[85] International Interferon-α Hepatocellular Carcinoma Study Group, Lancet, 1998, 351: 1535-39.

exchange in all body cells, reduce the risk of cell transformation and the development of metastases. These effects reduce long-term mortality and improve life quality.

In the light of the Law, the chief imperative of future medicine will be an *early treatment* (= *prophylaxis*) in patients who are identified to be at high risk of cancer or any other chronic disease. The identification or early diagnosis will be based on analysis of the genetic code - particular gene defects that are associated with certain diseases will be determined in the patient prior to treatment (see chapter 2.9). Thus the prevention of diseases will prevail over the present inefficient "management" of manifested diseases. In this stage of malaise, the energy exchange in the organism is irreversibly impaired and can be very poorly counter-balanced by treatment with cell-stimulating drugs. In this state, the condition of destructive interference in the body is more or less irreversible and the outcome fatal (dissipation of the system). Present-day medicine is more like a fire service that arrives at the place of fire after the building has burned down. Modern medicine based on the Law will follow the principle of fire prevention.

The role of an intact immune system for the prevention of cancer was realized in its full extent for the first time in the General Theory, although this kind of coalescence has been suggested on many occasions in the past. Considering the fact that immunosuppressive, carcinogenic cytostatics or other cell-inhibiting drugs are still the therapy of choice in most chronic diseases, it is amazing that this partial insight has not led to any practical consequences in medicine. Based on the Law, we discard the use of cell-inhibiting drugs because they increase morbidity and mortality. The most vulnerable system to cell-inhibition in the body is the immune system because its rate of cell proliferation is the highest.

Immunosuppression is always associated with an increased risk of cancer and vice versa. For instance, AIDS leads to a chronic suppression of the immune system, as the name suggests. For this reason the disease is associated with a high risk of cancer. The most common cancer in HIV-patients is *Kaposi's sarcoma* (see also chapter 2.9). *Human chorionic gonadotropin* (hCG), a powerful depolarizing humoral FUEL, was found to inhibit the growth of Kaposi's sarcoma cells lines in vitro and immunodeficient mice. For this purpose, hCG was recently tested in 36 patients with AIDS-related Kaposi's sarko-

ma[86]. The authors found that the "intralesional injection of hCG induces the regression of AIDS-related Kaposi's sarcoma lesions in a *dose-dependent* manner. The response of these tumours appears to be mediated by the induction of *apoptosis*." (p. 1261).

These results were predicted by the General Theory. *Apoptosis* is the only physiological mechanism for eliminating cancer cells. This mechanism makes use of the difference in the initial energetic conditions between cancer and normal cells. As the cancer cells are subjected to autocrine over-stimulation, any additional depolarisation will trigger their lysis by apoptosis. Apoptosis is usually associated with cells of the immune system. As this system regulates tissue regeneration, apoptosis is a common phenomenon in all body cells.

This was recently confirmed for heart myocytes[87]. Chronic heart failure can result from a variety of causes, including ischemic, hypertensive, toxic, and inflammatory heart diseases. However, the cellular mechanisms responsible for the progressive deterioration of myocardial function remains unclear. Explanted hearts obtained during cardiac transplantation were found to exhibit loss of myocytes due to apoptosis; this was considered the cause of end-stage cardiomyopathy that contributed to progressive myocardial dysfunction.

While repressed immune system in AIDS patients is associated with a higher risk of cancer, an intact immune system may inhibit HIV infection. As previously mentioned, the risk of AIDS infection may vary with the individual energetic state of the immune system. There is cumulative evidence that HIV-1 exposure does not inevitably lead to persistent infection. Heterogeneity in susceptibility to infection is ascribed to "protective immunity". In a cohort study of incident HIV-1 infection among 424 initially HIV-1 seronegative prostitutes in Nairobi, Kenya, between 1985 and 1994, 234 seroconverted to HIV-1 infection[88]. Modelling of the time to HIV-1 seroconversion showed that the incidence of HIV-1 seroconversion decreased with increasing duration of exposure, indicating that there is a heterogeneity in HIV-1 susceptibility or acquired immunity to HIV-1. Each weighted year of exposure through prostitution resulted in a 1-2-fold reduction in HIV-1 seroconversion risk. As the

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86 N Engl J Med, 1996, 335: 1261-69.
87 N Engl J Med, 1996, 335: 1182-89.
88 Lancet, 1996, 348: 1347-51.

persistent seronegativity in some prostitutes could not be explained by differences in risk factors, the authors concluded "that a small portion of highly exposed individuals who may have natural protective immunity to HIV-1 **are resistant** to HIV-1".

This study indicates the primary role of intact immunity in the protection of AIDS. This is also true for the progression of the disease. As we see, all clinical events are closely interrelated, because the organism is an open system, and at the same time a unity. These interrelations can be perceived for the first time in a logical and consistent way within the General Theory.

The beneficial effect of cytokine immunostimulation in AIDS was also elucidated[89]. IL-2 was given in combination with anti-retroviral therapy and compared to retroviral therapy alone in 60 HIV-patients. The combination significantly increased peripheral CD4 counts ($p < 0.001$). However, CD4 count is a surrogate endpoint. Future trials with interleukins should select primary endpoints, such as mortality (see CONCORDE trial). This trial confirms the basic prediction of the General Theory, namely, that i.v. cytokines may be rather toxic to vital organs. IL-2 treatment was associated with fever, malaise, fatigue, and hyperbilirubinemia. These adverse events are also observed with i.v. polyenes.

Treatment with cell-stimulating drugs is beneficial to all chronic diseases with immunopathogenesis. As previously stated, prominent candidates are RA and MS. This theoretical conclusion was intuitively anticipated by several studies. In one study in 180 RA patients, **TNF** (tumour necrosing factor) was compared to placebo[90]. Treatment with TNF led to a dose-dependent, significant reduction in disease activity ($p < 0.001$). However, the observation period of 3 months was too short. We showed that TNF is a repolarizing cytokine. Its effect on RA should be estimated as modest. For this indication, we recommend the use of depolarizing agents, or more precisely, a combination of depolarizing and repolarizing drugs so as to improve the effect (Pareto-optimal effect). We treated RA patients with polyenes and observed a lasting effect after 6-9 months of treatment. For instance, a combination of TNF and polyenes may be superior to monotherapy with TNF.

Similar effects were observed with *immunoglobulin* in patients with

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89 N Engl J Med, 1996, 335: 1350-56.

90 N Engl J Med, 1997, 337:141-7.

relapsing MS [91]. As all the MS trials are based on surrogate endpoints (in this case, on EDSS, Kurtzke's expanded disability status scale), their results should be cautiously interpreted. However, the trend of MS improvement during therapy with cell-stimulating drugs is beyond doubt. Reversal of MS symptoms were also reported with polyenes.

Finally, two miscellaneous trials will be presented which show that cell-stimulation is beneficial to various clinical conditions. *Nerve growth factor* (NGF) is a depolarizing humoral agent that was used in the treatment of *corneal neutrotrophic ulcers* associated with impairment of sensory innervation and loss of vision[92]. Until now there was no effective therapy for this condition. In this trial, corneal healing began 2 to 14 days after initiation of NGF treatment and all 12 patients (14 eyes) had complete healing of their corneal ulcers after 10 days to 6 weeks of treatment. Corneal integrity and sensitivity was maintained during the follow-up period of 3 to 15 months.

Goserelin is an agonist analogue of *gonadotropin-releasing hormone* (GnRH) that reduces testosterone secretion. The conventional interpretation of the *hypothalamus-pituitary-target organ* axis introduces the idea of feedback mechanisms; this is an intuitive application of the two basic axioms - CAP and the reciprocity of LRCs of contiguous levels. It is generally accepted that GnRH is released from hypothalamus and induces the secretion of LH from the pituitary gland. Increased LH in turn reduces the release of testosterone, a major androgen (steroid hormone) from the gonads and vice versa: increased testosteron decreases the release of LH and GnRH. However, this scheme is a pure abstraction, as both LH and testosterone are modulated by a variety of other agents.

The role of the *sexual steroid hormones* was explained for the first time in connection with cholesterol, which is the universal insulating molecule of biological membranes. This breakthrough effects a great simplification in our medical understanding. The approach is, however, entirely physical and may not be easily perceived by most physicians. All sexual hormones increase the dielectric properties of cell membranes proportionally to their dipole moment, which is always greater than that of cholesterol. In this way they stimulate the body cells in a ubiquitous manner by improving the energy exchange of the electric LRC into meta-

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91 Lancet, 1997, 349: 589-93.

92 N Engl J Med, 1998, 338: 1174-79.

bolic LRC (when f is increased, $E = E_A f$ is increased too) and vice versa.

This physiological stimulation occurs within a narrow range of steroid hormone concentrations that are precisely regulated in the body. When steroid hormones are given as drugs at unphysiologically high doses, they increase the dielectric properties of the cells significantly and this effect decreases the magnitude of the resting plasma potential (see physics). The total amount of electric energy stored in cell membranes (E_A) decreases in a global manner and this causes a reduction in the overall metabolism, as assessed by the universal equation $E = E_A f$ when applied to cells: $E \approx E_A$, when $f = cons$.

The multiple immunosuppressive effects observed with high-dose steroid therapy are triggered by this mechanism[93]. This also explains the various adverse effects associated with anabolic steroids (e.g. androgens) in sports. While anabolic consumption improves physical performance in the short run, its long-term effects are always detrimental to the organism. From this we conclude that the stimulation or suppression of the cells depends on the Pareto-optimal concentration of cell-stimulating agents in the supracellular regulation. The relationship is not linear and may inverse with increasing concentrations. This is another fundamental proof that all energy interactions are cyclic events (imposed rotations).

Bearing this in mind while analysing the structure of *releasing hormones* (or their analogues), we come to the conclusion that these humoral FUELs are of the depolarizing type. When their concentration is increased, the cells are stimulated and may produce more LH and testosteron. When there is an excess of releasing hormones, LH, and testosteron in the body, cell metabolism is slowed down due to excessive depolarisation and subsequently less LH and testosteron are produced. The common effector level is the electric LRC of the cells. It is the actual mediator between the various agents of the supracellular regulation, the effects of which are now rather clumsily and mechanistically explained by means of feedback mechanisms; the latter resemble electric circuits and switches, as is the case with the suggested hypothalamus-pituitary gland-target organ axis.

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93 A common manifestation of excessive steroid therapy is *Cushing's syndrome*. The obligatory *truncal obesity* is a typical example that increased space is always associated with a reduced efficacy of organs (reduced energy exchange). This is another confirmation of the transitivity (lack of contradictions) of the General Theory in medicine.

The common mechanism of energy exchange in the body explains the functional antagonism between GnRH and testosterone. In fact, it holds in any pair of physiological agents at the supramolecular level which we can arbitrarily select (axiom of reducibility). The correlation between the concentrations of these agents is effected through the common electric LRC of the cells. It embodies the open character of all systems in space-time. At the same time, its openness is the origin of redundant and useless research in the bio-sciences, as any researcher can always find a correlation between any two randomly selected agents of the supracellular regulation, and declare this relationship causal; even worse, he may decide to crown this "discovery" with a paper. This proliferous tendency has led to the present confusion in the bio-sciences, as documented in the numerous journals in this area, and explains the cognitive deadlock with respect to biological regulation.

This introduction is important for our understanding of the effects of goserelin as a depolarizing RH in the treatment of *advanced prostate cancer*. It was found that adjuvant treatment with goserelin, when started simultaneously with external irradiation, significantly improved local control and survival in patients with locally advanced prostrate cancer[94]. We treated patients with benign prostate hypertrophy with Nys and observed a marked reduction of the gland. As Nys is a polyene that stimulates cholesterol metabolism, the effects of goserelin and Nys on the prostate are of the same energetic (depolarizing) character.

2.8.2 Treatment Effects of Depolarizing, Non-Proteinic Drugs

In the previous section, we discussed proteinic drugs that have to be administered intravenously. In the last decade, some very interesting cell-stimulating, non-proteinic drugs have been developed and registered. They comprise a small fraction of the total amount of registered drugs. Most of them are involved in the regulation of *cholesterol metabolism* and *blood pressure*. These cell-stimulating drugs will be the topic of this chapter.

We shall begin with the outstanding and rapidly expanding group of **HMG CoA reductase inhibitors**. The very name of this group embodies the cognitive mess in pharmacology. Although these drugs are de-

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[94] N Engl J Med, 1997, 337: 295-300.

fined as "inhibitors", they are cell-stimulating drugs of the depolarizing type. The mode of action that is postulated for this group of drugs is paradigmatic for the paradoxical approach in pharmaceutical research today[95]. The interpretation is essentially based on the effects of HMG CoA reductase inhibitors observed in cell cultures. The results of such in vitro studies are regularly misinterpreted, as becomes evident when they are analysed in the light of the General Theory.

For instance, when cultured cells are incubated with HMG CoA reductase inhibitors, one should expect from the name that the enzyme is inhibited by the drugs and its concentration decreased. This is however not the case. The enzyme is increased in the cells. This increase is attributed to "an increase in the rate of transcription of the HMG CoA reductase gene, an increase in the rate of translation of the messenger RNA, and a decrease in the rate of degradation of the protein. Through these compensatory mechanisms, cultured cells can increase the amount of HMG CoA reductase sufficiently to restore rates of cholesterol synthesis almost to normal, even in the presence of relatively high concentrations of the inhibitor. An increase in HMG CoA reductase also occurs in the livers of rabbits, rats, and hamsters treated with these inhibitors.[96]" As if these results and conclusions did not exist, we read further down in the same textbook: "Inhibitors of HMG CoA reductase block synthesis of cholesterol in the liver, thereby triggering compensatory reactions that lead to a reduction in plasma LDL.[97]" However, it remains a mystery how these drugs lower plasma cholesterol when they actually stimulate its de novo synthesis in the cells. In addition, nothing is known about the "compensatory reactions" which are held responsible for the hypocholesterolemic effect of these inhibitors.

From this short introduction to the "state of the art" in modern pharmacology, it is obvious that the confusion in this field is profound. The results quoted above clearly indicate that these "inhibitors" stimulate the cells and their various effector systems. Thus, HMG CoA reductase inhibitors are cell-stimulating drugs of the depolarizing type. This example is typical of the inconsistencies one always encounters whenever one decides to scrutinize pharmacological models in a logical and stringent

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95 See Goodman's and Gilman's The Pharmacological Basis of Therapeutics, 8th ed, p. 883-886.

96 See p. 883.

97 See p. 883.

way (what most pharmacologists have obviously failed to do). What is the explanation of the hypocholesterolemic effect of HMG CoA reductase inhibitors in the light of the General Theory?

When we analyse the chemical structures of the registered HMG CoA reductase inhibitors, such as *lovastatin*, *mevastatin*, *simvastatin*, and *provastatin*, with the dipole model, we come to the conclusion that they have a moderate dipole moment. None of the compounds carry an amino group that would melt the midgaps of soliton triplets and thus inhibit the energy exchange at the supramolecular level. Instead, they carry two conjugated π-electron bindings in the ring and one or two polar groups (C = O) at the endings. Therefore, these drugs exhibit a modest depolarizing effect on cells when they interact with their membranes. As all supracellular agents are incorporated into the cell where they are metabolized, we shall follow the suggested metabolic pathways of HMG CoA reductase inhibitors and interpret them within the General Theory.

HMG CoA is a precursor of **mevalonate**, that is, HMG CoA is transformed into mevalonate by the enzyme HMG CoA reductase. Mevalonate is a key molecule in lipid biosynthesis. It is a basic molecule from which all *squalenes* are synthesized. Squalenes are the precursors of cholesterol and its derivatives, e.g. *bile salts*, which are polar derivatives of cholesterol or *sexual hormones*. At the same time, squalenes (C_{30}) are the basic molecules, from which a remarkable array of compounds carrying conjugated π-electron structures (a basic five-carbon building block) are formed. This group of biomolecules includes *vitamin K*, *ubiquinone* (coenzyme Q_{10}) of the respiratory chain, *isoprenoids*, β-*carotenes*, various other *polyenes*, and cyclic compounds. All these compounds participate in the electron-ion exchange in soliton triplets at the supramolecular level and thus play a key role in the cellular energy exchange. Without the ability of the cell to synthesize such molecules, none of the basic metabolic pathways would function. We recall that ubiquinone is a basic component in the electron transfer in the respiratory chain of mitochondria.

Obviously, lipid biosynthesis offers a remarkable *bifurcation*, the key step of which is mevalonate. From this molecule the cell synthesizes cholesterol, the basic *insulating* molecule of human cells, and a vast array of compounds with extended conjugated π-electron structures, which act as *conductors* of electron-ion transfer at the supramolecular level. This electric aspect of lipid biosynthesis was elucidated for the first time within the General Theory. It credibly con-

firms the basic concepts of the soliton triplet and the dipole model.

Indeed, from a teleological point of view it does make sense for Nature (the Law) to group the production of biological compounds with insulating and conducting properties in one common pathway. In this way the dielectric properties of the cell, upon which the global energy exchange in organic matter depends, can be precisely regulated. This insight effects another great simplification in our biochemical and medical view; this will be demonstrated for HMG CoA reductase inhibitors.

These drugs are said to be structural analogues of the half-reduced intermediate of HMG CoA. As lipid biosynthesis has the propensity to incorporate any kind of compounds with similar structures, it is not too far fetched to assume that lovastatin or simvastatin participate in the lipid biosynthesis. Their effect is two-fold: 1) The immediate depolarizing effect of these drugs through energy interaction with the electric LRC stimulates the cell in a global manner. This also includes lipid biosynthesis as proven by many in vitro experiments. 2) The drugs participate as substrates in the lipid biosynthesis and can induce the de novo production of cholesterol and other compounds with conjugated π-electron structures. To provide an intact energy exchange, the insulating and dielectric properties of the cell must stay in a narrow relationship; therefore their production is balanced. The overall energy exchange is, however, augmented.

Thus HMG CoA reductase inhibitors stimulate the cell through their dielectric properties and as cellular substrates that participate in the lipid synthesis. This is paradigmatic for all biochemical compounds. As all systems are open, the two aspects of this energy exchange can only be distinguished in the mind, but not in real terms - space-time is a unity. We recommend that the reader apply this approach to any other cell substrate.

This energetic mechanism explains the hypocholesterolemic effect of HMG CoA reductase inhibitors. The overall stimulation of the body cells in the presence of these drugs augments their energy exchange $E = E_A f$. In the first place, this increase in metabolism affects lipid biosynthesis, as phospholipids and cholesterol in cell membranes comprise more than 50% of the total body weight. The HMG CoA reductase inhibitors increase the intracellular metabolism of cholesterol. This effect can be registered by a decline in circulating plasma cholesterol. Whenever there is a higher demand for cholesterol in the cells, its plasma concentration is decreased. The same effect can be achieved by *physical exercise*; vice

versa, *immobility* and *over-alimentation* lead to an increase in circulating cholesterol because cellular demand is decreased (low energy exchange). As we see, increased energy exchange in the body induced by either physical exercise or cell-stimulating drugs normalizes plasma cholesterol levels. The same holds true for all the other lipids. This is the actual mode of action of HMG CoA reductase inhibitors in the light of the General Theory. It is consistent with all biological facts and medical results, which we shall now discuss in detail.

The general statement of the General Theory concerning medical treatment is that cell-stimulating drugs reduce morbidity and mortality, while cell-inhibiting drugs increase morbidity and mortality. We shall now quote the results of some pivotal trials with HMG CoA reductase inhibitors which have been performed in the last few years and confirm this basic conclusion.

The *Scandinavian Simvastatin Survival Trial* [98] (**4S-trial**) is one of the most outstanding clinical trials ever performed. Before this trial was published in 1994, drug therapy for hypercholesterolemia was controversially discussed, mainly because of insufficient clinical trial evidence for improved survival. An analysis of international clinical research revealed that the first statistically impeccable, placebo-controlled, mortality trials were started in the late 80s and most of them were first published after 1990. At the beginning, only a few studies involved cell-stimulating drugs, as such drugs were rare on the market. This situation gradually changed after 1993 when cytokines and some non-proteinic, cell-stimulating drugs, such as HMG CoA reductase inhibitors, penetrated into the market. As more than 90% of all registered drugs are cell-inhibiting, a large portion of these trials was performed with such drugs. As their results were negative for the active treatment, they were called "**negative trials"**, that is to say, they proved that the mortality in the active group was significantly higher than in the placebo group, where the active treatment was a cell-inhibiting drug. In the next chapter, we shall discuss the results of such negative trials.

Unfortunately, there is strong evidence that many negative trials have not been made public. Instead, their results have disappeared into the archives of the pharmaceutical companies that sponsored them because they involved registered drugs, which might otherwise have been withdrawn from the market, as was the case with some antiarrhythmics after

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[98] Lancet, 1994, 344: 1383-9.

the CAST trial was first published (see below). I have personal information on two such trials sponsored by large pharmaceutical companies which were prematurely withdrawn because the mortality was significantly greater in the active group compared to that in the placebo group. The legal excuse for this highly immoral behaviour on the part of the pharmaceutical companies is that there is still no law in any country (at least in any European country) that obliges pharmaceutical companies to publish the results of the trials sponsored by them[99]. This deplorable legal situation should be abolished as soon as possible, preferably immediately after this publication of the General Theory. The obligation of the sponsor to disclose the results of all negative trials will prevent any further performance of similarly negative trials, which are in fact statistically verified massacres on patients under the veil of scientific research[100].

The 4S-trial is a milestone in clinical research, not only because of its unprecedented quality in terms of statistical design, but also because it was published only one month after I had outlined the General Theory in 1994 (its final development was accomplished in 1997-98, after the new axiomatics of physics and mathematics was established). At a time when only a few placebo-controlled trials with cell-stimulating drugs were published, this was an important prospective confirmation of the basic axioms of the newly elaborated theory. In this large trial, 4444 patients with *angina pectoris* or previous *myocardial infarction* and serum cholesterol of 5.5-8.0 mmol/L on a lipid lowering diet were randomized to double-blind treatment with *simvastatin* or placebo. The median follow-up period was 5.4 years. An outstanding characteristic of this trial was the long observation period, which exceeded the Ljapunov time for this indication.

Simvastatin reduced total cholesterol, LDL-cholesterol, and HDL-cholesterol by 25%, 35%, and 8% respectively. 256 patients (12%) died in the placebo group, compared with 182 (8%) in the simvastatin group.

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99 Phase-III trials are registered by the FDA, but this does not necessarily mean that their results are made public to the general scientific community.

100 Although both the freedom of scientific research and the physical inviolability of the individual are safeguarded in most democratic constitutions, in practice the innocent individual often ends up as a victim of irresponsible scientific research. There are numerous examples in the recent history of mankind that confirm this conclusion (see the discussion in my popular book on the Law published in the Bulgarian language in 1998).

This result is *highly significant* ($p = 0.0003$). As both groups were evenly distributed, this trial showed that **74 lives (4%) were saved with simvastatin** during the observation period. The medical progress achieved with this drug should thus be cogent to everybody. The 6-year probabilities of survival in the placebo and simvastatin groups were 87.6% and 91.3% respectively. 622 patients (28%) in the placebo group and 431 (19%) in the simvastatin group had one or more major coronary events. The relative risk was 0.66 and thus highly significant ($p < 0.00001$). This risk was also significantly reduced in subgroups consisting of women and patients of both sexes aged 60 or more. Further benefits of the treatment included a 37% reduction ($p < 0.00001$) in the risk of undergoing myocardial revascularisation procedures, that is, simvastatin increased life quality and decreased morbidity.

The 4S-trial showed irrevocably that a long-term treatment with simvastatin as a cell-stimulating drug of the depolarizing type is safe and improves survival in CHD patients. In fact, this holds in any other patient population, e.g. in the elderly.

A remarkable aspect of this trial was the specific Ljapunov time, after which the difference in the outcome of the two regimens became manifest. Although this aspect was not considered by the authors, it can be easily perceived from the Kaplan-Meier curves for all-cause mortality (see figure 1. in the original publication on p. 1385). In the 4S-trial, the decrease of mortality in the placebo group began after 2 years of treatment. This "incubation time" was also observed in other trials (see CONCORDE trial). Evidently, chronic treatment with cell-stimulating drugs needs at least 2-3 years to significantly improve mortality when compared to no treatment. The Ljapunov time after which a significant treatment difference is observed is, however, shorter in a direct comparison between a cell-stimulating drug and a cell-inhibiting drug (see below). Any trial with a shorter follow-up period than the intrinsic Ljapunov time, which is a specific constant time quantity for each clinical disorder and patient population, is futile in the light of the General Theory, as it will inevitably miss the difference. For instance, all trials which did not find a negative difference between placebo and active treatment with a cell-inhibiting drug had a shorter period of observation than the specific Ljapunov time for this treatment indication. The same holds true for trials with cell-stimulating agents, which do not find any treatment difference with respect to placebo. The optimal period of observation should be 5-7 years. Such trials are obviously not cheap and involve many clini-

cal centres and huge human resources (international multicentre trials).

The 4S-trial also illustrates another major aspect of clinical research which has not been realized so far. Most clinical results are given in terms of statistical probabilities (power); this renders the real information meaningless to most physicians, who are as a rule very poor in mathematics. They simply cannot comprehend what kind of information is hidden behind the numerical probabilities given in such trials and consequently tend to disregard basic clinical results in their day-to-day job. Until the discovery of the Law, not even the mathematicians could explain the probability set in real terms. This has hindered an understanding of applied statistics in clinical research.

In the new axiomatics, we clearly state that the probability set of Kolmogoroff is a synonym for energy/space-time and is thus equivalent to the primary term (principle of last equivalence). Therefore, all probabilities which we assess from real samples (systems of space-time, e.g. organisms) are space, time, or space-time relationships. Hence the importance of Ljapunov time, which is reciprocal absolute time in the exponent. The differences, e.g. treatment differences, which we statistically assess in clinical trials merely indicate the occurrence of different energetic conditions in the patient - for instance a condition of illness versus a condition of health. This difference is defined as a "response" (healing or improvement of mortality) and is usually measured by different *surrogate* parameters. As a rule, it is assumed in an *a priori* manner that their magnitudes correlate with the outcome without presenting any valid proofs. However, when the new axiomatics is applied to such secondary parameters, and their space-time dimensionality is properly assessed, it emerges that most of the surrogate clinical parameters used in trials are inversely related to an appropriate response such as healing or reduction in mortality. As space-time has only two dimensions, we can only assess space-, time- or space-time quantities of real systems (see vol. I & II). In this respect, the primary endpoints of clinical research, such as "healing" (E) and "reduction of mortality" (f), are *direct* space-time quantities. They are proportional to the energy exchange in the body $E \approx f$. This observation can be explained in a simple manner: the longer the organism lives, the greater the amount of exchanged energy in the form of metabolism (see energy balance of the organism). Most surrogate endpoints which are currently used in clinical trials are direct quantities of space, e.g. *surrogate clinical parameter* $\approx$ [*space*] $\approx 1/f \approx 1/E$, and are thus inversely proportional to healing or reduction of mortality.

Instead, they correlate with an increase in mortality and morbidity. Typical parameters of this kind are negative inotropic and chronotropic effects observed with most cardiaca, such as β-blocking agents, antiarrhythmica and calcium antagonists. All cardiaca have been registered on such mistaken surrogate endpoints. Therefore, it is not surprising to find that they increase mortality and morbidity when compared to placebo in mortality trials (see chapter 2.9). This aspect has been grossly overlooked in clinical research.

As space-time is infinite, there are infinite systems and energetic differences. This axiomatic approach in mathematics effects the greatest possible simplification in science. Its realisation is not a question of intelligence, but of a psychological rearrangement of the mind. It is a question of integrity of character, ethical behaviour and ability to think logically[101]. It is cogent that when we apply this maxim to the representatives of current clinical research and pharmacology, most of them may not qualify. However, there is no reason why this situation should not change in the future. The social systems and levels of space-time are created by man and are thus a function of his will - the will, just as consciousness, is a system of space-time; it abides by the Law. For instance, consciousness is subject to evolution, while the latter may occur in quantitative leaps. The knowledge of the Law is such a leap. Translated into ethical and theosophical categories: man is prone to sin as long he does not comprehend the Law. As soon as he begins to behave according to the Law, he liberates himself from his "eternal sin". Back to medicine.

The same results as observed for simvastatin were confirmed for *privastatin* in another trial of similar design and scope[102]. Had the authors been aware of the existence of the General Theory (a manuscript of this theory had been sent to N Engl J Med in 1994), they might not have performed this rather expensive trial. According to the dipole model, simvastatin and privastatin have almost the same dipole moment and should therefore exhibit identical therapeutic effects. This was confirmed by the above trial. The same observation holds true for another trial performed with *lovastatin*[103]. This trial showed that lovastatin significantly improved endothelium-mediated responses in the coronary arteries of

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101 Apply this conclusion to Einstein's character to explain why he failed to discover the "universal field equation".

102 N Engl J Med, 1996, 335: 1001-9.

103 N Engl J Med, 1995, 332: 481-87.

patients with atherosclerosis. These results also confirmed the pathogenesis of atherosclerosis as outlined in the General Theory.

Thus, the new Theory appears to be of immediate practical relevance. It will streamline clinical research and will dramatically *reduce* its current costs, which are mainly due to a lack of any theory of biological regulation. The revenues in pharmaceutical research will be augmented and this will enhance further progress in this field. However, the new theory makes the withdrawal of many cell-inhibiting drugs from the market an ethically imperative step which does not need to be further substantiated by futile negative trials that will only involve an additional sacrifice of patients. Recent clinical research has already accumulated enough evidence for the deleterious effects of cell-inhibiting drugs, which are theoretically explained by the General Theory (see next chapter).

Chronic treatment with cell-stimulating drugs raises the question of the cost effectiveness of such treatments. As medical health care evolves within rigid financial and fiscal constraints, it is important to analyze whether the expenses of such chronic treatment will not exceed the present financial capacities of medical care systems. Since the 4S-trial, this question is being debated in medicine with respect to HMG CoA reductase inhibitors in CHD patients. It is a typical case of Pandora's box, readily opened by unyielding obstructionists of medical progress.

A recent trial evaluated the indirect costs gained from treatment with *simvastatin* compared to the direct costs of the treatment[104]. The results of this trial are highly instructive. The cost per year of life gained because of cholesterol-lowering treatment with simvastatin was estimated in relation to age, sex, and the pretreatment cholesterol level of patients with pre-existing coronary heart disease. When only direct costs were studied, the costs ranged from $3,800 to $27,400 in the various groups of patients. When the reduction in the indirect costs associated with morbidity was included, treatment led to *savings* among men and women 35 years old, and the cost per year of life gained ranged from $1,200 to $13,300 in the older groups of patients. These results have been confirmed by other trials. Therefore, the use of cell-stimulating drugs is *cost effective* when compared to present treatment. It will become even more cost effective when most cell-inhibiting drugs are withdrawn from the market and only a few cell-stimulating drugs are registered and employed.

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104 N Engl J Med, 1997, 336: 332-336.

Generally, we can conclude that:

> Any medical treatment that abides by the Law is *cost effective*. Any medical treatment that infringes upon the Law is cost ineffective[105]. This is called the "**axiom of cost effectiveness**".

This is a fundamental ethical and financial principle, on which any future medical health care should be based[106]. Although HMG CoA reductase inhibitors are propagated as "specific" cholesterol-lowering agents, they stimulate all body cells in a global manner and thus induce various other positive effects. Vice versa, there are many other, chemically unrelated compounds that exhibit hypocholesterolemic effects. Polyenes, such as Nys and Amp, decrease elevated cholesterol levels too, but they also increase very low cholesterol levels. In fact, they produce a shift towards the mean physiological range. The same holds true for HMG CoA reductase inhibitors.

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105 The same conclusion holds true for morality. Although individual experience may not confirm this conclusion, it is nonetheless true when applied to society and scientific research. For instance, any energy source that abides by the Law is cost-effective. The present combustion of organic fuels, such as petroleum, gas, and coal, is highly cost-ineffective because it is associated with a depletion of oxygen in the atmosphere and will soon cause the annihilation of mankind (see vol. I). The same holds true for nuclear power - the storage of radioactive products from this energy exchange is not solved (because of its cost ineffectiveness), and this also endangers human life. These developments were possible only because moral considerations did not play any role in modern scientific research. This deplorable situation can be reversed by developing new energy sources based on artificial photosynthesis, which will supply new oxygen for the atmosphere and promote the survival of mankind (see vol. I and II). The ethical basis of this new scientific behaviour will be a true understanding of the Law and the General Theory of Natural Sciences as summarized in the present tetralogy.

106 It is important to observe that the discovery of the Law reconciles ethics with financial considerations for the first time in the history of mankind. The new theory of economics explains the nature of money - it is an artificial metaphysical level of space-time created by man to facilitate the social organisation of the human community. The nature of money reflects the nature of space-time/energy (U-set). An understanding of this fact will profoundly change our attitude towards money and establish a new valid ethics of human behaviour.

In a recent trial the effects of another cell-stimulating agent, *raloxifene*, was evaluated in 601 postmenopausal women[107]. Raloxifene is a non-steroidal benzothiophene that is classifed as a selective oestrogen receptor modulator on the basis of studies in which it has prevented bone loss and lowered serum cholesterol concentrations. When the dipole model is applied to this compound, it is cell-stimulating. Although this drug has a different chemical structure than that of steroid hormones, it nonetheless modulates their effects - for instance, it reduces *osteoporosis* as determined in the above mentioned trial. This confirms the common effector level of energy exchange in the cell - the electric LRC across the plasma membrane. At 24 months, the mean difference in the change of bone mineral density between women receiving raloxifene and those receiving placebo was 2.4% for the lumbar spine, 2.4% for the total hip and 2.0% for the total body ($p < 0.001$). Serum concentrations of total cholesterol and LDL-cholesterol decreased under raloxifene, while HDL cholesterol and triglycerides did not change.

From this discussion, the reader may gain the impression that the General Theory advocates the broad use of cell-stimulating drugs, especially in the elderly. This is not necessarily so. In fact, it only advocates cell-stimulation as a method of prolonging human life, but cell-stimulation can be induced in many different ways. The chief objective is to maintain Pareto-optimal supracellular regulation (= condition of constructive interference).

For instance, we strongly advocate physical and intellectual activity in the elderly as a key factor that increases life quality and life expectancy. This common experience was recently confirmed in a large epidemiological trial of immaculate statistical design[108]. It showed that physical activity improves both cardiovascular and non-cardiovascular mortality in men with no history of CHD, stroke, or any “other heart trouble”. These results support our recommendations for sedentary elderly to increase physical activity and for active middle-aged individuals to continue their mental activity into old age. Actually, this behavioristic strategy was already advocated by the epicureans in antiquity, so this trial only confirmed the redundancy of collective human insight[109].

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107 N Engl J Med, 1997, 337: 1641-47.

108 Lancet, 1998, 351: 1603-8.

109 Although epicureanism is interpreted from the point of view of strict religious puritanism as a hedonistic philosophical system propagating luxury or in-

We shall finish this section by briefly introducing another major group of cell-stimulating drugs that has gained broad acceptance in the last few years - the group of **ACE-inhibitors**. Again, we encounter the paradox in the name: these drugs are cell-stimulating according to the dipole model, although they are described as inhibitors. We leave the elucidation of this group to the reader and advise him to adhere to the approach applied to HMG CoA reductase inhibitors.

The insight that ACE-inhibitors lower mortality in patients with myocardial infarction goes back to 1987, when the first **CONSENSUS trial** (Cooperative North Scandinavian Enalapril Survival Study) was published[110]. This was one of the first placebo-controlled trials ever performed with a cell-stimulating drug; it initiated a series of similar trials which proved the beneficial therapeutic effects of this group of drugs. The result of the CONSENSUS trial was subsequently confirmed by other trials. In one study, *captopril* was given to 2231 patients with left-ventricular dysfunction after a myocardial infarction and compared to placebo[111]. Mortality from all causes was significantly reduced in the captopril group; the reduction of risk was 19% ($p = 0.019$). The incidence of both fatal and nonfatal major cardiovascular events was also reduced in the captopril group.

Similar results were obtained for *enalapril* in patients with heart failure (ejection fraction of 0.35 or less) in another placebo-controlled trial in 4228 patients[112]. The conduct of this trial symbolizes the redundancy in clinical research, which will be eliminated when the General Theory is fully implemented. This also holds true for further trials with ACE-inhibitors, such as the AIRE study on *ramipril* [113], its follow-up study[114],

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dulgence in sensual pleasures, this school of thought actually perceives the highest good in the freedom from any mental or intellectual disturbance, or physical pain. This should be precisely the objective of any true medicine, which is at present more influenced by the religious notion of the necessity of patients' drug-induced suffering (many hospitals in the West are still run under the auspices of the church) than by the conviction that man has the natural right of pleasure during his short life.

110 N Engl J Med, 1987, 316: 1429-35.

111 N Engl J Med, 1992, 327: 669-77.

112 The SOLVD investigators, N. Engl J Med., 1992, 327: 685-691.

113 Lancet, 1994, 342: 821-28.

114 AIREX, Lancet, 1997, 349: 1493-97.

and GISSI-3 study on *lisinopril* [115]. All these studies confirmed the significant decrease in mortality and morbidity in CHD patients under chronic treatment with ACE-inhibitors, as anticipated for all cell-stimulating drugs.

Only one trial, the CONSENSUS II trial[116] seemed to constitute an exception in this respect: it did not find any difference between enalapril and placebo with respect to mortality. However, when the design of this trial is thoroughly analysed, it becomes evident that its observation period is much shorter than those of the other trials. The survival effect of enalapril, given within 24 hours after the onset of acute myocardial infarction, was evaluated only during the first 180 days after infarction. This observation period is significantly shorter than the specific Ljapunov time of manifested treatment difference in this indication (> 2-3 years), so the trial should be evaluated as "useless".

Thus, all clinical results, when properly obtained in double-blind, placebo controlled, long-term trials, fully comply with the General Theory. According to it, cell-stimulating drugs are effective in different indications. This was shown not only for proteinic drugs, such as cytokines, but also for non-proteinic drugs, such as ACE-inhibitors. The latter drug group is not only beneficial in CHD, but also in *normotensive patients* with *insulin-dependent diabetes mellitus* (IDDM) and normoalbuminia, or microalbuminia.

In a placebo-controlled trial in 530 patients with IDDM, the ACE-inhibitor *lisinopril* was found to slow the progression of renal disease with little or no albuminuria[117]. The greatest effect was observed in patients with microalbuminuria ($p = 0.001$). Similar results were obtained with *ramipril* in patients with *non-diabetic nephropathies*[118]. This ACE-inhibitor decreased the risk of *terminal renal failure* and reduced the *rate of GFR decline* "to an extent that seems to exceed the reduction expected for the degree of blood-pressure lowering", as the authors concluded. Had they been aware of the General Theory and the mechanism of energy stimulation of ACE-inhibitors, they would have certainly attributed this effect to the depolarizing property of these drugs.

Despite present ignorance with respect to the actual effect of ACE-

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115 Lancet, 1994, 343: 1115-22.
116 N Engl J Med, 1992, 327: 678-84.
117 The EUCLID study group, Lancet, 1997, 349: 1787-92.
118 The GISEN Group, Lancet, 1997: 349: 1857-63.

inhibitors, the results of this trial prompted a commentary in the same journal[119], entitled "ACE-inhibitors: *panacea* for progressive renal disease?" Indeed, in the light of the General Theory, we can correctly proclaim that chronic treatment with cell-stimulating drugs is a "panacea" for most patients with chronic diseases because it abides by the Law. Any action that fully abides by the Law can be described as part of the **human panacea** - it brings us nearer to the teleological purpose of human survival, given the fact that the destiny of mankind has been dramatically endangered by hazardous industrial activities during the last century of this Millennium.[120]

2.8.3 Vitamins and Other Essential Compounds Exhibit Cell-Stimulating Effects

With the exception of *vitamin C*, all known vitamins have a more or less pronounced dipole moment and are thus cell-stimulating drugs. They are referred to as *fat-soluble vitamins*. The role of *vitamin A* (retinol) in vision and that of *vitamin D* in bone metabolism have been worked out. *Vitamin K* is a product of lipid biosynthesis and is obtained from the precursor mevalonate (see above). *Vitamin E* (alpha-tocopherol) shows a striking similarity to coenzyme Q of the respiratory chain and is also a product of lipid biosynthesis. To this class of vitamins we should also attribute the large group of β-*carotenes*.

β-*Carotenes* are polyenes with extended π-electron systems and have a pronounced dipole moment. *Vitamin E* (*alpha-tocopherol*) belongs to this group. According to the dipole model, it is a depolarizing compound with a strong dipole moment. It carries an aromatic ring at one ending and an aliphatic chain at the other. As defined in the dipole model, it does not have any amino groups that interfere with soliton triplets of membrane FUELs and impair their function.

Such substances are conventionally called **antioxidants**. Various ben-

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[119] Lancet, 1997, 349: 1852-53.

[120] For instance, the dramatic increase of antibiotic resistance (meticillin-resistant Staph. aureus epidemia) in the last few years is the result of erroneous treatment strategies with antibiotics. These strategies are mainly advocated in North America and Japan and merely reflect the vested interests of major US and Japanese pharmaceutical companies which are leaders in antibiotics.

eficial effects have been ascribed to these substances in recent years. In fact, antioxidants are depolarizing agents carrying extended π-electron systems, which contribute to electron-ion exchange across biological membranes or simply accommodate unpaired electrons in the cell.

Thus the positive therapeutic effects of antioxidants fit in very well with the soliton triplet concept. In the EURAMIC trial (European multicentre case-control study)[121], *vitamin E* and β-*carotene* concentrations were measured in 683 patients with acute myocardial infarction and in 727 controls. The results confirmed the hypothesis that high concentrations of β-carotenes reduce the risk of first myocardial infarction. Evidently, depolarizing cell-stimulating agents are beneficial in this indication. These results are compatible with previous observations of a reduced risk of infarction among users of vitamin E supplement only.

One of the most exciting trials in the last few years is the one with all-*trans*-retinoic acid (*tretinoin*) in patients with *acute promyelocytic leukemia*[122]. This study was carried out world-wide, and as early as 1993 approximately 1500 patients were treated with tretinoin. The mean incidence of complete remission was found to be 84%. All-*trans*-retinoic acid was defined by the authors as the "most effective single agent for the treatment of any type of acute leukemia" and "compared with most anticancer drugs used in oncologic practice, all-*trans*-retinoic acid must be considered highly safe, with few serious adverse reactions."

All-*trans*-retinoic acid is a derivative of retinol (vitamin A), which provides the photosensitive prosthetic group in rhodopsin and bacteriorhodopsin. This key compound is responsible for the propagation of solitons in these FUELs. According to the dipole model, all-*trans*-retinoic acid is a cell-stimulating drug with a strong dipole moment. It has a conjugated triene chain with a carboxyl group at one ending and carries no amino groups whatsoever. From its pharmacological effects at the cellular level, it can be concluded that it acts as a repolarizing drug - it enhances predominantly maturation and differentiation of leukocytes. As predicted by the General Theory, all-*trans*-retinoic acid is effective for the duration of therapy. All investigators participating in this trial observed that the remissions induced by this drug were short-lived. This observation is true for most chronic diseases with a genetically pre-determined impairment of cellular energy exchange. In some other condi-

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[121] Lancet, 1993, 343: 1379-84.

[122] N Engl J Med, 1993, 329: 177-89.

tions, the patients may be completely cured with cell-stimulating drugs.

The all-*trans*-retinoic acid trial showed that the various forms of leukemia can be effectively treated with any cell-stimulating drug. We presented the results of clinical trials that confirm the beneficial effect of cytokines in leukemia. These results prove that the body is a unity and that all systems can be energetically modulated in the same manner by various cell-stimulating drugs. This eliminates the central dogma of pharmacology, which postulates that drugs have specific activities, as a cognitive failure with grievous consequences for the patients. At the same time this realisation represents the most radical simplification in pharmaceutical research and forms a leitmotif of the present volume.

The beneficial effects of all-*trans*-retinoic acid in acute promyelocytic leukemia were further substantiated. In another trial the effect of this cell-stimulating drug given in combination with chemotherapy was compared to chemotherapy only[123]. Before we present the results, we must clearly state that all chemotherapeutics (cytostatics) are cell-inhibiting agents and thus exert deleterious effects on the organism (see next chapter). In the case of acute leukemia with a poor and rapid outcome, chemotherapy may be preferential to no treatment in the short run, but the adverse events are substantial (see also below). In such cases, a combination of chemotherapy with cell-stimulating drugs is *Pareto-optimal* and may increase the survival rate when compared to chemotherapy only. The overall cell-stimulating effect reduces the adverse effects of chemotherapy that determine the rate of mortality in these patients.

The protective effects of cell-stimulating drugs (Nys) have also been confirmed in post-cancer patients undergoing radiation therapy. Therefore, such drugs will play a role in future protective therapy in cancer by improving morbidity and life quality in those rare cases where chemotherapy and radiation will still be administered[124].

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[123] N Engl J Med, 1997, 337: 1021-27.

[124] This form of treatment is repudiated in the General Theory. Meta-analyses of radiation trials have not confirmed any beneficial effect of radiation on mortality when compared to no radiation. However, it is unlikely that radiation will be immediately abolished in cancer therapy. This inertia can be counter-balanced in the initial phase by the simultaneous use of cell-stimulating drugs, which will protect the patients from the severe adverse events of radiation. In practice, this is already done in most neutropenic patients subjected to chemotherapy and radiation - without knowing the immunostimulating effect of polyenes, such pa-

In the all-*trans*-retinoic trial, the rate of overall survival at one, two, or three years after entry into the study were 75, 57, and 50 percent respectively among patients assigned to chemotherapy, and 82, 72, and 67 percent among those assigned to all-*trans*-retinoic acid ($p = 0.003$). Observe the relative increase in survival rates after the third year (increase in treatment difference with growing Ljapunov time).

The protective effects of cell-stimulating vitamins in AIDS have been appreciated in the last few years. They can best be evaluated in the pregnancy outcome in HIV-1 infected women. A recent placebo-controlled trial from Tanzania performed in 1075 HIV-1 infected pregnant women evaluated the role of *vitamin A* and *multivitamins* in protecting fetal AIDS transmissions[125]. Vitamins stimulate the immune system and enhance the organism's self-defence (see above). In the light of the General Theory, one should expect that vitamins decrease the rate of fetal AIDS transmissions and deaths. Indeed, this trial confirmed that significantly less deaths (30) occurred among women assigned multivitamins compared to those (49 deaths) among women receiving no vitamins ($p = 0.02$). Multivitamins also decreased the risk of low birth weight by 44%, severe preterminal birth by 39%, and small size for gestational age at birth by 43%. Additional supplementation of vitamin A to multivitamins had no significant effect on these variables. This clearly indicates that the aggregated cell-stimulating effect of multivitamins is responsible for the beneficial outcome, and that this Pareto-optimal effect may not be improved by additional supplementation of vitamin A. However, vitamin A supplementation alone is beneficial when compared to no supplementation, as found in previous trials. These results do not contradict one another, but are complementary. Multivitamins, but not vitamin A, also resulted in a significant increase in CD4, CD8, and CD3 counts. One can expect similar, though more pronounced, cell-stimulating effects with Nys and Amp in AIDS.

Finally, the results of another major clinical trial with a cell-stimulating agent will be presented. The second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2) performed in 2316 patients with suspected *acute myocardial infarction* examined the effect of intravenous

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tients are treated with high doses of Nys or Amp for opportunistic candidiasis and the survival rate is improved (Am J Med, 1987, 83: 17-26; Am J Med, 1988, 84: 826-32, etc.).

[125] Lancet, 1998, 351: 1477-82.

magnesium sulphate (Mg) in a double-blind, placebo-controlled, randomised protocol[126]. Mg treatment was started with a loading injection before any thrombolytic therapy and continued with a maintenance infusion for a further 24 h. Cause-specific mortality of randomised patients was examined over 1 to 5.5 years (mean 2.7) of follow-up. The mortality rate from ischaemic heart disease was reduced by 21% ($p = 0{,}01$) and the overall mortality rate by 16% ($p = 0.03$). A 25% reduction in the early ventricular failure was measured in the Mg group.

These data are consistent with the protective effect of Mg on the contractile function of the myocardium from reperfusion injury seen in experimental models. In the context of the General Theory, Mg^{2+} is a universal electron acceptor for incomplete soliton triplets in various regulatory proteins, such as ATP-ases. Decreased Mg concentration impairs the function of the FUELs and the body cells. For instance, the $Na^{+}K^{+}$-ATPase needs Mg to pump sodium and potassium ions against their gradient. In the absence of this metal ion, the ATP-ases are deficient and cannot restore the plasma potential after its rapid depolarisation. This causes a profound impairment of cell metabolism.

In this trial, the propensity of heart muscle cells to perform action potentials (adequate depolarisation and repolarisation) was improved in the presence of high concentrations of Mg. It also showed that the longer the follow-up period (Ljapunov time), the more pronounced the difference between the groups.

The role of *steroid hormone substitution* in reducing *osteoporosis* in postmenopausal women is well known. The role of polar cholesterol derivatives in cellular energy exchange was elucidated for the first time in the General Theory. Their effects on bone metabolism can be deduced from the discussion in chapter 2.6. The problem of steroid hormone substitution lies in the fact that these hormones are administered at unphysiologically high doses and exhibit pronounced deleterious effects. The reason for this dose-dependent antagonism was explained. As the balance between long-term risks and benefits of oestrogen-replacement therapy for the prevention of osteoporosis in postmenopausal women is still unclear, this ambivalence of the clinical results is reflected in all recommendations in this respect. This is a classical optimization exercise that should be based on the idea of Pareto criterion. The mathematical implications of this approach are beyond

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126 Lancet, 1994, 343: 816-19.

the scope of the present survey.

Recently, the effect of postmenopausal *hormone therapy* on mortality were evaluated[127]. It was established that, on average, mortality among women who use postmenopausal hormones is lower than among non-users. However, the survival benefit diminishes with longer duration of use and is lower for women at low risk of coronary diseases. We leave it to the reader to interpret these results within the General Theory by considering the energetic mechanism of action of steroid hormones and the concept of Pareto-optimal cell-stimulation.

2.9 CELL-INHIBITING DRUGS INCREASE MORBIDITY AND MORTALITY

Before we proceed with our discussion of the deleterious effects of **cell-inhibiting drugs**, selected evidence will be presented in support of a basic statement of the General Theory: this says that an impaired energy exchange at the supramolecular and cellular levels, caused by genetically deficient FUELs or acquired mutations, creates a strong energetic constraint for the cell to transform. The data confirming this conclusion has been growing exponentially in the last few years with the introduction of new explorative techniques within the Human Genome Project.

2.9.1 Interpretational Pitfalls of Mutagenesis

Two types of FUEL impairment have emerged in malignant cells. The first type includes an unrestrained production of *growth factors*, *growth factor receptors*, and other depolarizing proteins, which directly sustain the autocrine stimulation of cancer cells. The second type includes *proto-oncogenes* that are regulated by *tumour suppressors*. When the production of tumour suppressors is reduced, mainly due to genetic mutations, cell regulation is no longer effective, and the effects of proto-oncogenes are enhanced. The final result is again an unrestrained autocrine stimulation of the cell. There may be several variations of this scenario, including a collection of intermediate steps, but the ultimate result remains

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[127] N Engl J Med, 1997, 336: 1769-75.

invariant. Transformed cells no longer obey the supracellular regulation, but exhibit self-sufficient, autocrine stimulation. Sometimes, this stimulation may be *paracrine*. Cancer cells fulfil a condition of destructive interference with respect to normal cells.

In the context of the General Theory, it is impossible to distinguish between an autocrine and a paracrine stimulation, as all systems are U-sets and contain themselves as an element. Any regulation is at once autocrine and paracrine. Transformed cells are subjected to autocrine regulation and can reproduce infinite times in vitro, while normal cells die after they have reproduced several times. The paracrine stimulation includes the co-operative self-organisation of all body cells. The two types of cell transformation - unrestrained production of growth factors and/or proto-oncogenes - will be illustrated with representative examples from recent publications. None of the authors have offered any coherent explanation of their results.

Increased secretion of *epidermal growth factor* (EGF) was observed in *primary breast carcinoma*[128]. However, EGF was not secreted by normal or malignant epithelial cells, but from characteristic cells with the morphological and immuno-phenotypic profile of activated macrophages. This study confirms a fundamental concept of the General Theory: this says that immune cells are always involved in any kind of tissue remodelling. It also demonstrates that supracellular regulation is a co-operative process that involves all cells. Another important aspect of this study is that the authors did not find any significant association between the presence or absence of EGF secretion in the primary tumour and clinical prognosis.

From this we conclude that macrophages stimulate epithelial breast cells in order to counter-balance their energetic deficiency, which has led to the transformation of some of them to carcinoma cells. Their role is to correct the condition of destructive interference in the presence of cancer. Therefore, macrophages should not be made responsible for the malignancy, as is often suggested in the literature - on the contrary, they participate in a compensatory mechanism that counter-balances the transformation to cancer cells. This mechanism can be assessed with the axiom on the reciprocity of the LRCs of two contiguous levels. We leave this exercise to the reader.

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[128] Lancet, 1993, 342: 148-49.

An increased depolarisation of malignant epithelial cells by macrophages promotes endocytosis of autocrine or paracrine enhanced receptors in these cells. For instance, it lowers the excessive over-production of steroid receptors due to gene derepression and mutation. Enhanced expression of various membrane FUELs in conjunction with malignancy indicates that the regulation of their synthesis is impaired due to somatic mutations that shift the supracellular regulation towards more repolarisation. Such genetic defects create a strong energetic constraint on the cell to transform and to become malignant, that is, to provide more stimulation through depolarisation.

At present, such FUELs are interpreted as "cancer markers". Typical examples are steroid hormone receptors - their expression is usually augmented in the epithelial breast cells of breast cancer patients. Following the wrong principle of causality, such FUELs are considered responsible for the occurrence of malignancy. This is reflected in the recommendation to use specific receptor inhibitors, e.g. *steroid hormone inhibitors* (see below), for the treatment of breast cancer. In fact, this kind of therapy only worsens the energetic condition of the cells and increases their rate of transformation to malignant cells. The macroscopic manifestation of this impairment at the quantum level is a visible or palpable tumour. Recall that any increase in space-time is inversely proportional to energy, that is, a tumour is always indicative of an impaired energy exchange (reduced metabolism) at the cellular level. There is no exception to this rule.

The authors of the above trial came, as expected, to the opposite conclusion. They suggested that macrophages were responsible for the cancer growth. This is a classical interpretation failure in cancer research that stems from the wrong principle of causality, which is the epistemological foundation of most present-day therapeutic approaches.

Another recent study clearly supports the notion that malignant breast cells may excessively express various membrane FUELs. An enhanced expression of *somatostatin receptor* (SS-R) was found in *primary breast cancer* and, in particular, in invasive ductal cancer[129]. We pointed out that somatostatin is a classical example of a repolarizing hormone that exhibits ubiquitous anti-proliferative effects - mainly on the growth of experimental cancer, including breast-cancer cell lines.

The traditional interpretation of the so-called "somatostatin receptors"

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[129] Lancet, 1994, 343: 640-43.

necessitates a critical reassessment of current concepts of cancer. "Receptor-binding research in vitro" has attributed specific binding properties to many membrane FUELs, although the evidence clearly indicates that most of them can be activated by numerous other factors of the supracellular regulation. They can enhance either agonistic or antagonistic effects. Another fact that is tacitly omitted in this respect is that many of these receptors have additional functions and operate as channels, enzymes, DNA-regulatory proteins, etc. This conflicting evidence is extensively covered in the literature, but, surprisingly enough, there are no visible efforts to eliminate the paradoxes associated with its interpretation. The pluripotent functions which are observed after an interaction between a single type of integral FUEL and various agents can hardly be reconciled with the simple notion that a specific factor binds a specific receptor to enhance a specific response (principle of deterministic causality), as embodied in the first and second messenger concept.

Receptor-binding research is based on the central dogma of "saturation kinetics", which is supposed to take place during an interaction between a receptor and a "receptor-specific" factor. However, such "saturation kinetics" cannot be observed under physiological conditions, as this presupposes a fixation of the integral proteins in the plasma membrane. In reality, when FUELs are physiologically activated by depolarisation, they are incorporated into the cell by endocytosis; when they are activated by repolarisation, they are expressed in a greater number. In addition, it has been found in numerous studies that the degree of expression of membrane FUELs is inversely proportional to the concentration of the activating factors in the supracellular regulation. This dynamics (mobility) of integral FUELs does not fit in with any saturation kinetic model that has been suggested so far.

To avoid this biological "inconvenience", receptor-binding studies are performed in *in vitro* cell cultures at temperatures near 0°C. At such low temperatures, a *phase transition* of the lipid bilayer takes place. The membrane loses its fluidity and becomes rigid. This inhibits the activation and propagation of soliton waves along protein structures, and the FUELs remain fixed to the membrane. The thermal phase transition of lipid bilayers is a specific energy interaction that abides by the Law (see thermodynamics in vol. I & II). However, it is not compatible with the existence of organic life. The fact that organic life is not possible at zero temperature is conveniently neglected in this kind of futile research. Therefore, the results of the numerous receptor-binding studies published

in the literature should be regarded as pure artefacts, which do not contribute to our understanding of biological regulation. Their interpretation in medicine is equally erroneous.

From this we can conclude that an enhanced or reduced expression of integral FUELs in malignant cells is always a consequence of the disease and should not be considered a primary cause of carcinogenesis. The primary cause is always a genetic mutation involving soliton-specific amino acids that leads to quantum defects at the supramolecular level - the propagation of solitons is impaired and the FUELs lose their function. This impairs cell metabolism and subsequently the function of the whole organism - early death is the final outcome of this destructive interference. One cannot repeat this simple truth often enough, considering the fact that at present it is totally confounded by numerous obscure religious, esoteric, and mechanistic explanations.

If somatostatin receptors are expressed at a higher level in patients with breast cancer, this evidence tells us that the supracellular regulation of the sick organism produces more somatostatin or other repolarizing agents. They repolarize the breast cancer cells which are excessively depolarized by their own autocrine stimulation to establish Pareto-optimal stimulation (a condition of constructive interference). As a result of this compensatory mechanism all body cells in the cancer patient are repolarized, particularly those in the vicinity of the tumour; such cells express a higher degree of somatostatin receptors. Therefore, “somatostatin markers” merely indicate an altered energetic condition of supracellular regulation in the breast cancer patient. They are <u>not</u> the cause of breast cancer. We conclude:

> The various levels of FUEL expression in each organism are valuable indicators for the individual energetic situation of the supracellular regulation.

Therefore, a chief objective of future clinical research will be to evaluate these different energetic states and determine the Pareto-optimal condition of health. This is essentially an optimization task that can be solved within mathematics. This kind of information will enable the clinician to choose the optimal therapy with cell-stimulating agents for each individual patient.

In this context, we must briefly discuss the role of *body temperature* for the supracellular regulation because it is of central importance. I have

proved in the new physical axiomatics that *electromagnetism* and *thermodynamics* are closely related - they can be regarded as two levels of material space-time that exchange energy. New fundamental constants (e.g. CBR-constant) and applications of the Law (e.g. Stankov's law of photon thermodynamics) were derived; they assess this particular energy exchange in a precise manner and prove that electromagnetism and thermodynamics are interrelated levels (see vol. I & II). This vertical interaction is very important for the body's regulation because the electromagnetic LRC is central to cell regulation and metabolism. At the same time organic matter exhibits a unique capacity to maintain a more or less constant temperature of 36.5°- 40°C in mammals (observe that this property is not inherent in inorganic matter). The role of this constant high body temperature in the regulation of the organism has not been appreciated in medicine (physiology) and the bio-sciences (biochemistry).

In the new axiomatics, the quantity "temperature" assesses the absolute time of the thermodynamic level $T = f_{thermo}$. Temperature fluctuations are energy fluctuations at this level. This aspect is covered by Boltzmann's law, which is an application of the universal equation (see vol. I & II). As the thermodynamic level exchanges energy with the contiguous electromagnetic level of matter, **thermal fluctuations modulate the electric action potentials of cells and their metabolism** (see axiom of CAP and axiom on the reciprocity of contiguous LRCs). For instance, *fever* during an infection increases cell metabolism in a global manner. The interrelation between supracellular regulation (electromagnetism) and body temperature (thermodynamics) is illustrated by the fact that the former may influence the latter and vice versa (see also shivering thermogenesis in chapter 1.1). For instance, fever is always associated with tachycardia; the latter measures the increase in frequency (time) of the electromagnetic action potentials of heart muscle cells. As $E \approx f$, the energy exchange at the electromagnetic level of the cell and the organism is augmented when the body temperature is increased and vice versa: during hypothermia we observe bradycardia. These examples can be continued *ad infinitum*. They prove that the electromagnetic and thermodynamic levels correlate and exchange energy[130].

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[130] This observation is closely associated with a major theoretical breakthrough in superconductivity, which will pave the way for the establishment of non-brittle superconductors that can work at normal temperatures.

Recall that energy exchange occurs in both directions - conservation of energy reflects the closed character of space-time (U-sets). Enhanced secretion of lymphokines in the CNS can elevate the setting point of body temperature, which is assumed to be located in the thalamus[131]. Elevated temperature is for instance often observed in cancer patients. Elevated temperature (thermal rubor) in a local inflammation, e.g. an inflamed injury, stimulates cell metabolism and enhances the repair mechanisms, including the migration of leukocytes, and promotes healing.

CD44 is another common membrane FUEL that is associated with cancer and metastases. While normal mucosa is CD44 negative, the expression of this receptor in *atrophic gastritis* and *intestinal metaplasia* correlates with an increased leukocyte infiltrate and expression of HLA-DR by mucosal cells. CD44 expression significantly correlates with distinct metastases at the time of diagnosis and increased mortality. In one trial, an increase in the expression of variant CD44 isoforms was associated with tumour progression in breast and colorectal carcinoma[132]. This observation simply indicates that various FUELs may contribute to an altered energy exchange at the cellular level during malignancy. In this respect, the General Theory provides a rational basis for the logical and coherent interpretation of these clinical phenomena.

The second type of cell transformation involves **proto-oncogenes** and can be illustrated by the role of the NF-1 gene in the pathogenesis of *type 1 neurofibromatosis* in children. Such children are at increased risk of malignant myeloid disorders. Analysis of the NF-1 gene suggests that the function of its product *neurofibromin* is reduced[133]. NF-1 belongs to the *tumour suppressor* class of recessive cancer genes. NF-1 shows sequence homology with yeast and mammalian GTPase-activating proteins (conservative polymorphism). This domain of neurofibromin binds Ras and accelerates the hydrolysis of GTP. The *proto-oncogenes* of the **RAS family** regulate cellular growth and differentiation by cycling between an active state, in which they are bound to GTP (Ras-GTP), and an inactive state, in which they are bound to GDP (Ras-GDP). During cancer development in humans, these genes commonly acquire activating *point*

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131 D. Adam & G. Stankov, Fever in childhood, Eur J Pediatr, 1994, 153: 394-402.

132 Lancet, 1993, 342: 1019-24.

133 N Engl J Med, 1994, 330: 597-601.

mutations that lead to elevated levels of Ras-GTP and impair the biochemical activity of Ras proteins. When the NF-1 gene is reduced, Ras-GTP complex is elevated. Ras-GTP stimulates the cell.

The energetic role of *proto-oncogenes* in cancer cells is substantiated by numerous studies. For instance, the inactivation of the *retino-blastoma tumour suppressor gene* (RB gene), the normal growth-restraining activity of which depends on the cell cycle, is common in *parathyroid carcinoma*[134]. Inactivation of the RB gene has also been implicated in the pathogenesis of some other cancers. At present, great hopes are cherished that genetic research will soon produce specific treatments for genetic disorders by establishing the exact genetic causes and impairing them. This naive illusion stems from the same deterministic and mechanistic approach, which can be encountered in any other field of bio-research and human intellectual endeavour.

The last example in this presentation deals with the retrospective evaluation and publication of the **Humphrey's case**[135], which convincingly supports the fundamental ideas put forward in this chapter. In May 1967, when Humphrey was vice-president of the USA, he was admitted to Bethesda Naval Hospital for haematuria. Voided urine specimens were obtained for cytologic examination and cystoscopy was performed. Some of the pathologists who reviewed the urine-cytology slides, among them Dr. J.K. Frost, director of cytopathology at Johns Hopkins Hospital, believed that the cytology was diagnostic for carcinoma. Other experts apparently did not agree, and a definitive diagnosis was not established. Humphrey was therefore subjected to a cystoscopy every 6 months. A biopsy revealed *in situ carcinoma* in 1969, but he was asymptomatic a further four years before a biopsy of his prostatic urethra revealed a "borderline malignancy". For this condition, he received both radiation therapy and intravesicular thiotepa. In August 1976, he developed recurrent haematuria and a new biopsy confirmed the diagnosis of infiltrating carcinoma of the bladder. A radical cystectomy was performed which revealed widely infiltrative transitional-cell carcinoma of the bladder with lymph-node metastases. Humphrey died from cancer on January 13, 1978, eleven years after the first diagnosis.

Recently, both the invasive bladder carcinoma resected in 1976 and the filters prepared from urine specimen in 1967 were analysed for *p*53

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[134] N Engl J Med, 1994, 330: 757-61.

[135] N Engl J Med, 1994, 330: 1276-78.

mutations. A transversion from adenine (A) to thymine (T) in codon 227 of the p53 gene was found in pooled clones of DNA from Humphrey's cancer resected in 1976. The same transversion was also detected in 9% of the clones of DNA obtained from the 1967 filter preparations of urine. Therefore, it was possible to detect cells harbouring p53 mutations nine years before Humphrey underwent cystectomy, six years before he received any therapy for bladder disease, two years before diagnosis of in situ carcinoma was established by biopsy, and at a time when no cancer could be identified in his bladder.

This case confirms the basic conclusion of the General Theory: any disease, including cancer, begins as an **energetic quantum defect** at the supramolecular level, before it manifests itself as a disease at the level of the organism (long Ljapunov time). In Humphrey's case, the original defect was a somatic mutation of the p53 gene. Many other genetic mutations which are commonly associated with cancer have been discovered in recent years. Mutations of the common tumour-suppressor gene p53 were found in lung cancers from *atomic-bomb survivors*[136] and in radon-associated lung cancer from *uranium miners*[137]. The high-energy photons of gamma radiation emitted from uranium interfere with the electromagnetic waves of the electric LRC of the body cells and lead to a disruption of the interference pattern in the nucleus that drives all DNA processes kinetically. The resultant interference destroys the soliton pattern (standing waves at the supramolecular level)[138] in the DNA-strings. This destructive interference of electromagnetic waves in the nucleus enhances the rate of somatic mutations. This mechanism explains why the rate of mutations in cells subjected to gamma radiation is significantly increased. Some of these mutations involve non-equivalent substitutions of soliton-specific amino acids that impair the function of the FUELs.

These energetically induced somatic mutations are responsible for

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136 Lancet, 1993, 342: 1520-21.

137 Lancet, 1994, 343: 86-87.

138 In volumes I and II, I have proved that all motions are rotations, so that there is no possibility of discriminating between waves and rotations in real terms. Therefore, the statement that the genetic code operates by establishing standing quantum waves, called *solitons* (also *phonons* or *excitons*), is beyond doubt (see also chapters 1.3 & 1.4).

the transformation of normal cells into malignant cells. Interactions with other external sources of low energy may not be as dramatic as those observed after an atomic bomb explosion or uranium exposure, but they can, nonetheless, contribute to the occurrence of cancerogenic mutations. Acquired mutations are most often the aggregated product of many factors, e.g. air pollution, food, and soil decontamination. Most cancers develop from such kinds of mutation. Most probably, the primary factor of Humphrey's bladder carcinoma belongs to this group. For instance, a carcinogenic factor that is commonly associated with bladder carcinoma is *tobacco smoking*.

There is another aspect of Humphrey's case that is of eminent medical importance. Had the diagnostic technique in 1967 been in a position to determine somatic mutations in human proteins, the outcome of Humphrey's bladder cancer might have been more favourable. However, the precision of the diagnostic procedures at that time did not permit the confirmation of the vice-president's diagnosis at the supramolecular quantum level. Adequate techniques for the screening of genetic defects have only recently been developed. The earlier we learn about pathogenic (e.g. carcinogenic) quantum defects at the supramolecular level, the better the therapeutic prospects for the patient. Had the General Theory been known at that time, the vice-president could have been treated with cell-stimulating drugs, e.g. with Nys or Amp, from the very beginning, and this might have prevented the occurrence of his bladder cancer or would have, at least, postponed its development. The vice-president's life could have been prolonged.

This example illuminates a new and exciting field of clinical research that will permit an early diagnosis of energetic defects at the supramolecular level which are associated with an increased risk of cancer. Patients carrying such mutations should be prophylactically treated with cell-stimulating drugs, even when there are no visible signs of malignancy. Such treatment strategies will undoubtedly increase life-expectancy and reduce mortality - not only in cancer patients, but also in patients suffering from chronic diseases.

The last highlight of Humphrey's case is the energetic aspect of the p53 mutation. The antisense transversion at codon 227 from A to T generated a point mutation from the soliton-specific amino acid residue, Arg (+) to Ser, which, in the light of the General Theory, is a functionally non-equivalent substitution. Obviously, the substitution of Arg for Ser impaired a functionally important soliton triplet in p53, and this trig-

gered the transformation of Humphrey's urothelium cells into cancer cells. This aspect will be substantiated by further examples in the next section.

2.9.2 Disease-Associated Point Mutations Confirm the Soliton Triplet Concept

We showed that a point mutation in p53 involving the soliton specific amino acid Arg (+) is associated with bladder carcinoma; p53 is now one of the best investigated proteins in terms of genetic mutations. Mutations of the p53 gene are linked to a variety of cancers in colon, lung, breast, oesophagus, liver, brain, and other tissues.

Recently, p53 gene mutations were found in *B-cell lymphoma*; they were associated with a poor prognosis in patients with this disease[139]. The rate of complete remission was significantly lower in patients carrying a p53 mutation than in those with the wild-type p53 ($p = 0.001$). The same was observed for overall survival: the Kaplan-Meier estimates of survival at 5 years were 16% and 64% respectively ($p = 0.001$). The most common point mutations observed in the 22 patients with B-cell lymphoma were functionally non-equivalent mutations that involved soliton-specific residues. These were: Arg248Trp, Asn148Glu, Leu194Arg, Arg196Stop, Met237Arg, Arg248Gln, His179Asp, Tyr234Cys, Cys141Tyr, and Tyr220Asn. Thirteen of the 22 patients were carriers of such mutations. There were 2 further deletions and one mutation involving the acceptor. The other point mutations were functionally non-equivalent substitutions involving *non-soliton* residues. The role of such mutations can be explained within the General Theory. We shall illustrate this with the following example.

A common point mutation in this and other studies (see below) is the one that involves proline (Pro). *Proline* is a unique residue among the 20 human amino acids. It does not belong to any subgroup. Structurally, it is associated with the large group of *aliphatic*, non-soliton residues: Gly, Ala, Val, Leu, and Ile. Like these amino acids, proline has an *aliphatic* side chain, but it differs from the five aliphatic residues in that its side chain is bonded to both the nitrogen and the α-carbon atoms. The resulting *cyclic* structure markedly influences the protein architecture. Proline is often found in the bends of folded protein chains and plays a key role

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[139] N Engl J Med, 1997, 337: 529-34.

in the shaping of the tertiary and quaternary structure of proteins. Proline is *hydrophilic* and is thus not averse to water - it contains a secondary rather than a primary amino group which makes it an *amino acid*. For this reason, it is often found to be exposed to the outer side of the protein fold, while the five aliphatic residues preferentially build the inside wall of the protein fold, where the soliton triplets are located. These residues protect the soliton triplets from unwanted interactions with the ionic plasma and guarantee the intact propagation of solitons. Whenever proline is exchanged with one of the aliphatic residues, we have a functional non-equivalent mutation.

As we see, the concept of functional non-equivalent mutations is not restricted to soliton-specific residues. For didactic and practical purposes, we introduced this concept in conjunction with the soliton triplet: the majority of functionally non-equivalent point mutations that lead to manifest diseases involve the 7 soliton-specific amino acids. This is confirmed by the above trial, where the majority of mutations concern soliton-specific residues. However, there are also functional non-equivalent point mutations that affect the remaining 13 *non-soliton* residues. As these amino acids differ in their structure, polarity, and charge, they may also contribute to an impairment of the soliton propagation at the supramolecular level and thus induce pathological conditions (U-sets). A detailed discussion of all the possible functionally non-equivalent mutations with non-soliton residues is beyond the scope of this survey. Here, we shall restrict our analysis to the two point mutations with Pro found in the above trial: Leu257Pro and Ala159Pro. Both mutations are functionally non-equivalent because they involve substitutions of aliphatic residues (Ala and Leu) for hydrophilic Pro.

While discussing the pathogenesis of atherosclerosis, we pointed out that some severe forms, such as FH (familial hypercholesterolemia), may be associated with genetic defects of ApoB or the LDL receptor. Now, we shall present some recent prospective evidence for this conclusion. In a large epidemiological trial conducted in Denmark the genotypes of 9255 subjects from the general population, 948 patients with ischaemic heart disease, and 36 patients with FH were investigated for three mutations in the ApoB gene: Arg3500Gln, Arg3531Cys, and Arg3500Trp[140]. These functionally non-equivalent point mutations with soliton-specific residues were found to be associated with FH. The prevalence of

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140 N Engl J Med, 1998, 338: 1577-84.

heterozygotes in the general population was 0.08% for both Arg3500Gln and Arg3531Cys mutations, and 0% for Arg3500Trp mutation. Among carriers of the Arg3500Gln mutation, cholesterol levels were significantly higher than among non-carriers in all three populations. The authors concluded that "the Arg3500Gln mutation in the ApoB gene which is responsible for the familial defective ApoB-100 and is present in approximately 1 in 1000 persons in Denmark causes severe hypercholesterolemia and increases the risk of ischaemic heart diseases".[141]

This result, obtained four years after the General Theory was first outlined, fits in well with the pathogenesis of *atherosclerosis* as presented in chapter 2.6. It is backed by all other relevant facts collected for this indication. These are: elevated plasma LDL cholesterol is causally related to ischaemic heart disease. Elevated plasma cholesterol can result from over-alimentation and immobility with or without association with genetic disorders. The most common genetic defects include functionally non-equivalent point mutations in the LDL receptor, for instance, in classical FH[142] or in ApoB, as found in the above trial. These mutations cause an impairment of the soliton triplets of these proteins. The consequence is reduced cholesterol uptake in the cell due to an overall reduction in cell metabolism.

The cellular demand for cholesterol is lowered in hypercholesterolemia because of the reduced energy exchange in body cells. As cholesterol is the universal insulating molecule of biological membranes, circulating cholesterol in excess cannot be deposited in cell membranes (50% of the body's weight; more than 90% of human cholesterol is membrane-bound), because it will additionally aggravate the already decreased energy exchange in the cells (see universal equation); this is not compatible with life. The "least evil" is therefore to store the excess plasma cholesterol in the vessels. The clinical manifestation of this compensatory mechanism of the organism is called "atherosclerosis" (AS). The long-term consequences of AS is CHD and an increased rate of mortality.

As genetic defects cannot be repaired, the only adequate therapy of AS is to reduce alimentation. However, one need not reduce alimentary cholesterol, as it is produced by de novo synthesis in the cells. Therefore, the recommendation to reduce alimentary cholesterol in order to

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141 See p. 1577.

142 Goldstein et al. FH, in The metabolic and molecular bases of inherited disease, 7th ed. Vol. 2 New York,, McGraw-Hill, 1995: 1981-2030.

prevent atherosclerosis is pure nonsense which only serves the pecuniary interests of the producers of cholesterin-low diets such as margarine. Another possibility of reducing plasma cholesterol levels is to increase the mobility of the hypercholesterolemic patient, e.g. through physical exercise, and to treat him with cell-stimulating drugs, e.g. polyenes or HMG CoA reductase inhibitors. All three measures increase the energy exchange at the cellular level, including the turn-over of cholesterol in lipid biosynthesis. This kind of cell stimulation reduces the concentration of circulating cholesterol in the vessels to normal ranges. Its deposition in the vessels is interrupted and the occurrence of CHD inhibited. The patient mortality is significantly reduced, as demonstrated in numerous placebo-controlled trials with HMG COA reductase inhibitors (see previous chapter).

However, the occurrence of atherosclerosis is not exclusively associated with elevated cholesterol and impairment of its corresponding FUELs. There are other causes that may lead to this condition. It has been shown that premature atherosclerosis can also occur in patients with *familial chylomicronemia* (FC) as a result of mutations in the *lipoprotein lipase* (LPL) gene[143]. Before this trial was performed, it was believed that this syndrome was non-atherogenic, because it is associated with low levels of LDL cholesterol, whereas chylomicrons are triglyceride-rich particles. Lipoprotein lipase is the rate-limiting enzyme for the hydrolysis and removal of chylomicrons and VLDL triglycerides from the circulation. However, this enzyme also affects HDL and LDL through lipolysis.

At present, over 60 mutations of the LPL gene that cause enzyme deficiency are known. The mutations of the LPL gene investigated in 4 patients with FC in this trial included functionally non-equivalent substitutions of soliton-specific residues: Gly188Glu, Arg243Cys, Asp250Asn, Gly188Arg, and one mutation with proline: Leu286Pro. As we see, we come across the same energetic pattern of mutations although the mutagenic FUELs associated with one and the same disease may be different. This is a recurrent motif in most diseases. Thus the new quantum approach to the pathogenesis of diseases greatly facilitates our understanding of this intricate process and **reduces modern medicine to applied physics and mathematics of the human organism**.

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[143] N Engl J Med, 1996, 335: 848-54.

In our previous discussion we indicated that many different chronic diseases may be caused by common genetic defects which occur in one and the same protein (gene). ApoE has been selected as a common candidate for genetic mutations that may trigger two distinct diseases: *atherosclerosis* (AS) and *Alzheimer disease* (AD). This suggestion has been prospectively confirmed in a recent trial studying the relationship between AD and *vascular dementia* associated with AS[144]. The authors found that dementia and its two major subtypes, AD and vascular dementia, were associated with AS and that there was an interaction between ApoE and AS in the aetiology of AD. As we see, all the pieces of the puzzle, called "medicine", begin to fit together. To this will be added another facet.

A substantial proportion of the *glaucoma* cases have a genetic basis. Mutations causing glaucoma have been identified in the chromosome 1 open-angle glaucoma gene (*GLC1A*), which encodes a 57-kd protein called *myocilin*. However, the role of this protein and the mechanism by which mutations cause glaucoma are not known. For this purpose 716 patients with primary open-angle glaucoma and 596 control subjects were screened for sequence changes in the GLC1A gene[145]. A variety of point mutations in this gene were found to be associated with glaucoma. The spectrum of disease ranged from juvenile glaucoma to typical late-onset primary open-angle glaucoma. As found in previous trials, the majority of mutations involved functionally non-equivalent substitutions of soliton-specific residues.

Atopic diseases are very common disorders. There is growing evidence that increased incidence of atopic diseases is associated with the broad use of cell-inhibiting drugs, as predicted by the General Theory. The **ISAAC trial** conducted on 463 801 children aged 13-14 in 56 countries has just confirmed that *asthma*, *allergic rhinoconjunctivitis*, and *atopic eczema* are increased 20- to 60-fold between centres (and countries)[146]. The highest prevalence rates were observed in industrial countries (West Europe, North America, Australia), which are characterized by high consumption of cell-inhibiting drugs (80% of world pharmaceutical sales), and the lowest in poor countries (Eastern European countries, Indonesia, India, China, and Ethiopia) with a very low drug con-

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144 Lancet, 1997, 349: 151-54.
145 N Engl J Med, 1998, 338: 1022-27.
146 Lancet, 1998, 351: 1225-32.

sumption (less than 10% in total)[147]. This distribution was independent of race and geographic position[148].

On the other hand, there is a strong genetic predisposition for atopy. According to the General Theory, acquired mutations caused by cell-inhibition increase the energy constraint in the cell and hence the risk of mutations (see above); these may add up to latent inborn mutations, which in turn may trigger a disease, e.g. an atopy. For instance, the intensity of atopic allergy depends on the actual efficacy of the immune system and may exacerbate when the latter is repressed by external factors. Thus, the occurrence of atopy or any other chronic immunogenic disorder with genetic predisposition is the aggregated product of inborn and acquired mutations (plus other predisposing factors) that impair the cellular energy exchange.

Recently, a novel *interleukin*-4 *receptor* allele was identified in atopic patients, in which a functionally non-equivalent point mutation was observed; it affected two soliton specific residues Glu576Arg. This mutation was associated with decreased energy exchange in immune cells and caused atopy[149].

And last but not least, the risk of *recurrent thromboembolism* is significantly higher in carriers of *coagulating factor* V *Leiden*, which is triggered by a functionally non-equivalent point mutation, includ-

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147 This is a classical example that illustrates the corrective mechanism of the Law. The financial and technological inequality between the poor Third World and industrialized countries is offset in medicine by the excessive use of expensive cell-inhibiting drugs in rich countries which increase mortality and morbidity. The poor countries cannot afford these drugs and this has spared them a similar disaster. In religion, this kind of compensatory justice is erroneously attributed to divine forces and vulgarized in the idea of paradise ("the first will be the last...", and so on). However, as God is a synonym for the Law (principle of last equivalence), this metaphysical religious explanation can be abolished for ever. The same is true for the idea of paradise. The only possible paradise is to live according to the Law.

148 This trend is confirmed by my own clinical experience. I have successfully treated many patients, mainly children, suffering from atopic diseases with Nys in the last four years. Most of the patients had a history of chronic depression of the immune system due to excessive and prolonged use of antibiotics or other cell-inhibiting drugs in early childhood. In many cases, the immune deficiency could be quantified by specific immunological tests.

149 N Engl J Med, 1997, 337: 1720-5.

ing a soliton-specific residue Arg506Gln[150]. This mutation resulted in resistance to activated protein C.

These selected studies illustrate the basic statement of the General Theory with respect to the pathogenesis of diseases: pathogenic mutations lead to impaired energy exchange between the electromagnetic LRC of the cell and the quantum supramolecular level of organic matter. This vertical energy exchange abides by the Law.

2.9.3 Treatment with Cell-Inhibiting Drugs Increases the Risk of Cancer

There is substantial epidemiological evidence that the incidence rates of some cancers have been continuously growing in the last two or three decades[151]. This incidence is independent of the improved diagnostic screening and therapy. In fact, medical interventions have failed to reduce cancer mortality. The following commentary of A.B. Astrow in Lancet[152] elucidates the issue:

> "An oncologist colleague lately returned from an autopsy conference at my hospital and proudly announced that his patient, who had had a widespread cancer, had died "cancer-free". The patient had succumbed *instead to chemotherapy-induced lung disease*. It is precisely this sort of thinking and practice, where our zeal to eliminate the cancer sometimes eliminates the patient as well...The discouraging statistics of cancer epidemiology provide the background for ... discussion. After a 25-year "war of cancer", with a growing armamentarium of effective anticancer drugs, ever more radical treatment strategies, and spectacular advances in our understanding of the molecular mechanisms of oncogenesis, **mortality rates from cancer in the USA are rising**. Common tumours, such as cancer of the breast and prostate, show striking increases in incidence."

Indeed, the in vivo effects of *anticancer drugs* have been strongly ques-

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150 N Engl J Med, 1997, 336: 399-403.

151 Lancet, 1994, 343: 251-5; NIH Observer, 1993, 4:1.

152 1994, 343: 494-5.

tioned in recent years[153]. In the context of the General Theory, it will be proven that increased treatment with cell-inhibiting drugs has largely contributed to the growing incidence of cancer, including cancer-induced mortality.

According to the soliton concept, the quenching of standing supramolecular waves (solitons) in the FUELs by cell-inhibiting drugs, carrying one or more positively charged amino groups and having no dipole moment, impairs the energy exchange at the supracellular and cellular levels and induces a strong bioenergetic constraint on body cells to mutate. The vast majority of registered drugs are cell-inhibitors when the dipole model is applied. They inhibit the function of the integral and cytosolic FUELs in a global manner. Hence:

> **Cell-inhibitors increase the risk of cancer and the rate of mortality and decrease life quality due to high toxicity and morbidity.**

Selected examples from recent pivotal trials that confirm this conclusion will be presented below.

Organ *transplant* recipients who receive *immunosuppressive* drugs to prevent graft rejection experience a higher rate of malignancy. In an epidemiological trial, the incidence of *non-Hodgkin lymphoma* (NHL) was assessed in 45141 kidney transplant patients and 7634 heart transplant recipients and compared to that in the general population[154]. This was the largest epidemiological trial conducted in the field of transplantation. The rate of NHL was especially high during the first post-transplant year among both kidney transplant recipients (101 cases vs. 2.7 expected in the general population; 225 per 10^5) and heart transplant recipients (93 vs. 0.6 expected; 1218 per 10^5). Thus **immunosuppressive treatment caused a 40- to 150-fold increase in the incidence of malignancy**.

During the first year after transplantation, the immunosuppressive therapy is especially "aggressive" (high-dose treatment) because of the expected high rate of rejection. In this trial, the incidence was found to decrease in subsequent years (43 and 371 per 10^5 in kidney and heart transplant recipients). This result is fully compatible with the General Theory. After the first year of transplantation, the cell-inhibiting immu-

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153 Lancet, 1994, 343: 1174; Lancet, 1999, 353: 1633, etc.

154 Lancet, 1993, 343: 1514-16.

nosuppressive treatment is less aggressive (lower dose), and some patients may not even need immunosuppressive drugs. This evidently decreases the rate of mutations and the incidence of NHL, and other malignancies. This fact confirms a fundamental statement of the General Theory, namely, that the rate of mutations depends on the actual state of energy exchange in the cell: the greater the cell-inhibition, the higher the rate of mutations and the risk of cancer and vice versa.

This was also confirmed by the fact that in this trial there was a significant increase in the cancer risk in patients who received rejection prophylaxis with antilymphocyte antibodies and in those who received both *cyclosporin* and *azathioprine* when compared to other less aggressive immunosuppressive combinations. Both drugs are potent cell-inhibitors. For instance, cyclosporine is a cyclic peptide that carries numerous positively charged methyl amide groups; except in position 9 and 10, which are in the *cis* configuration, all other methyl amide moieties are in the *trans* configuration. All amide nitrogens are either hydrogen bonded or methylated, and the biological activity of cyclosporin is very sensitive to alterations of steriochemical configurations or modification in these positions[155].

The mutagenic effect of immunosuppressive agents is well established. Recent studies demonstrated that long-term survivors of acquired *aplastic anemia* are at high risk of malignant diseases. The risk of cancer after

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[155] Cyclosporin raises an interesting question. This compound is produced by fungus *Tolypocladium inflatum Gams*, and is thus of organic origin. At the same time we postulate in the General Theory that most organic compounds are cell-stimulating. In fact, we did not say "all" for good reasons. There are some species, such as certain *fungi* and *bacteria*, which may also produce cell-inhibiting compounds. These moieties result from the *saprophytic* character of these species - enabling them to live on dead organic matter. The role of these cell-inhibiting compounds of organic origin is not to contribute to the supracellular regulation, but to impede it in the host organism and to accommodate its organic substances to the needs of the saprophytic organism. Therefore, it is not at all surprising that most immunosuppressive agents are of fungal origin. Their cell-inhibiting effect is similar to that of antineoplastic agents, e.g. *alkylating agents.* The latter are very strong electrophiles, that is, they also quench the electrons in the midgaps of π-electron system of soliton triplets and impede the propagation of solitons (Use this method to explain the cell-inhibiting effects of antimetabolites, vinca alkaloids, antineoplastic antibiotics, such as dactinomycin, daunorubicin, doxorubicin, bleomycin, mitoxantrone, etc.).

aplastic anemia treated with immunosuppression or bone marrow transplantation was assessed in 860 patients treated by immunosuppression and in 748 patients who received bone marrow transplants and compared with that in the general population[156]. 42 malignant conditions were reported in 860 patients with immunosuppressive therapy (19 cases of myelodysplastic syndrome, 15 cases of acute leukemia, 1 case of NHL and 7 solid tumours). Nine were reported in the 748 patients who received bone marrow transplantation (2 cases of acute leukemia and 7 solid tumours). The overall relative risk of cancer was 5.5 ($p < 0.001$) as compared with the general European population. The risk was 5.15 ($p < 0.001$) after immunosuppressive therapy and 6.67 ($p < 0.001$) after transplantation. The 10-year cumulative incidence rate of cancer was, however, 18.8% after immunosuppressive therapy and 3.1% after transplantation.

These results clearly demonstrate the long-term mutagenic effect of immunosuppressive treatment. The *highest risk factor* after bone marrow transplantation was the **use of radiation** as a conditioning regimen before transplantation. Radiation impairs profoundly the solitons of the genetic code, e.g. it can induce **G to T transversions**, and should be regarded as a major risk factor for malignancy not only in patients with bone marrow transplantation, but also in any other patient population subjected to this treatment. Other risk factors are the addition of *androgens* to immunosuppressive treatment, *age*, and *treatment with multiple courses of immunosuppression*. This trial substantiates our initial conclusion that radiation and immunosuppressive drugs are the most potent cell-inhibiting treatments and significantly increase the risk of cancer and mortality in humans.

The carcinogenic potential has also been confirmed for drugs whose metabolites exhibit both cell-inhibiting and cell-stimulating effects. Such drugs are most difficult to evaluate. For instance, *tamoxifen*, the best known non-steroidal antioestrogen, was found to be both carcinogenic and cancer-protective. In the first place this drug was associated with an increased risk of *endometrial cancer*. Two papers from Finland and Israel showed in a case-control study that symptom-free postmenopausal women taking tamoxifen for breast cancer had a larger uterus with thicker endometrium and more endocervical and endometrial polyps than women with breast cancer not receiving tamoxifen[157]. Two further trials from

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[156] Lancet, 1994, 343: 86-87.

[157] Lancet, 1993, 342: 452.

Holland and Denmark elucidated this issue.

The Dutch trial was a case-control study based on the Netherlands Cancer Registry[158]. 98 patients were identified with a verified endometrial cancer diagnosed at least 3 months after a diagnosis of primary breast cancer. Tamoxifen was used by 24% of patients with a subsequent endometrial cancer compared to 20% of controls (relative risk 1.3). Women who had used tamoxifen for more than 2 years had a 2.3 times greater risk of endometrial cancer than non-users. There was a significant trend of an increasing risk of endometrial cancer with the duration of tamoxifen use ($p = 0.049$) and with an increase of the cumulative dose ($p = 0.046$). This result confirms our conclusion that the duration of treatment with cell-inhibiting drugs correlates with the cumulative risk of mutations and cancer. The authors of this trial conclude that "these findings support the hypothesis that tamoxifen use increases the risk of endometrial cancer."

This result was also confirmed by the Danish trial[159]. Women taking tamoxifen had a significantly larger uterus and a lower impedance to blood flow in the uterine arteries. 39% of women taking tamoxifen had histological evidence of an abnormal endometrium compared with 10% in the control group. 10 patients in the tamoxifen group (16%) had atypical hyperplasia and another 5 (8%) had a polyp. These results were confirmed by further large trials. Nevertheless, tamoxifen is still widely prescribed. In this context, it is important to observe that before 1990 there were virtually no clinical trials that assessed the carcinogenic effects of cell-inhibiting drugs.

According to the dipole model, tamoxifen is a weak cell-stimulating drug. However, the situation with this compound is rather complicated. Tamoxifen is a derivative of chlorotrianisene, which has a more pronounced dipole moment than tamoxifen. The oestradiol cell growth effect is greatly reduced in the presence of chlorotrianisene; this indicates that this drug is repolarizing. In tamoxifen, the chlor group is substituted with an aliphatic group (CH_2CH_3) and the aliphatic chain of the B ring carries a *tertiary amino group*; these substitutions obviously alter the dipole moment of tamoxifen. The drug has partial oestrogen agonist activity when the alkylaminoethoxy side is in the *cis*-conformation and an anti-oestrogenic activity when it is in the *trans*-conformation. Recall that retinal in rhodopsin is active as 11-*cis*-retinal and dissociates as 11-*trans*-

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158 Lancet, 1994, 343: 448-452.

159 Lancet, 1994, 343: 1318-1321.

retinal from opsin after photon absorption. Obviously, this particular isomerisation modulates the physiological activity of retinal and other compounds (see also cyclosporin above). Tamoxifen is marketed as a pure *trans* isomer, but in humans both stereoisomers can be activated metabolically to produce racemic mixtures of phenolic metabolites which exhibit a 100-fold greater affinity for the oestrogen receptor than that of the parent molecule.

The carcinogenic effect of tamoxifen in endometrium prompted the FDA in 1994 to ask the manufacturer Zeneca to revise the data sheet in the US National Surgical Adjuvant Breast and Bowel Project (NSABP) sponsored by the NIH so as to include an update warning of an increased risk of uterine cancer[160]. In addition, this trial had to be halted in late March 1994 following allegations of data falsification in some centres. Notwithstanding these peripeteia, the NSABP showed that tamoxifen, when compared to placebo, reduced the rate of breast cancer by 40% in women who had never had breast cancer before[161]. Similar results were observed in another recent study in breast cancer[162].

And last but not least, recently a carcinogenic effect was established for five H_1-*antihistamines*[163]. *Loratadine*, Schering-Plough, *astemizole*, Janssen, *cetirizine*, Pfizer, *hydroxyzine*, Pfizer and *doxylamine*, Pfizer/Vicks were found to promote the growth of melanoma and fibrosarcoma in mice after intraperitoneal administration. In an accompanying editorial[164], Dr. D. Weed of the US National Cancer Institute agreed with the authors' suggestion that the subject required further investigation, including epidemiological studies.

However, such redundant clinical research may not be necessary after the publication and propagation of the General Theory, as it clearly explains from a theoretical and axiomatic point of view the energetic mechanisms of carcinogenesis under treatment with cell-inhibiting drugs. We can only hope that the new theory will evoke an urgent reaction of the registration authorities to curb the use of cell-inhibiting drugs on the basis of the present theory and the results of the numerous placebo-controlled studies that cogently document their deleterious effect.

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160 Scrip, June 14, 1994.
161 J Natl Cancer Inst, 1998, 90: 1371-1388.
162 Lancet, 1999, 353: 1993-2000.
163 J Nat Canc Instit, May 18th, 1994, p.770.
164 See p. 740.

At present, the results of such negative trials are not properly interpreted. They are regarded as solitary events, disentangled from established paradigms in pharmacology. The increase in mortality with such drugs has not raised a broad concern among specialists to question the scientific foundations of pharmacological research. This has been done in the General Theory. Therefore, a major objective of the present volume is to urge the immediate withdrawal of most cell-inhibiting drugs from the market. Their rapid substitution with new effective cell-stimulating agents will be facilitated by new rational requirements for registration on the basis of the General Theory; this will not only stimulate medical progress, but also increase the revenues of the pharmaceutical companies. With the introduction of the dipole model, the R & D costs will drop dramatically[165] and this will ultimately relieve the costs of medical care.

Before we finish this section, a brand new piece of evidence will be presented that prospectively confirms the above conclusions. AIDS is a clinical state of immunodeficiency. In the General Theory, immunodeficiency is associated with a higher risk of cancer (see also immunosuppression and bone marrow transplantation above). Immunodeficiency can be acquired by virus infection as in AIDS or induced by chemotherapy and immunosuppressive agents. The final result is the same - the incidence of cancer is increased.

In one of the largest epidemiological trials in AIDS conducted in the USA and Puerto Rico the incidence and type of cancers resulting from this viral disease were compared to those in the general population by matching population-based cancer and AIDS registries in both countries[166]. This brand-new study included 98 336 AIDS patients and 1 125 089 people with cancer aged less than 70. Among people with AIDS, there were 7028 cases of *Kaposi's sarcoma* (KS), 1793 of NHL (*non-Hodgkin lymphoma*) and 712 other cases of histologically defined cancer. Incidence rates were increased **310-fold** for KS, **113-fold** for NHL, **36.7-fold** for *angiosarcoma*, **7.6-fold** for *Hodgkin disease*, 4.5-fold for multiple myeloma, 3.5-fold for brain cancer, and 1.9-fold for all other cancers. The incidence of such cancers can be reduced under chronic treatment with cell-stimulating drugs such as polyenes. This will decrease

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165 I have roughly estimated that the broad and consistent application of the General Theory, including the dipole model, in the pharmaceutical industry will save about 100 billion $ of R&D per year.

166 Lancet, 1998, 351: 1833-39.

the mortality in HIV-patients, which is determined to a large extent by the progression of these cancers (especially KS).

2.9.4 Placebo-Controlled Trials with Cell-Inhibiting Drugs Prove the Increase of Mortality in Humans

The last section of this chapter is the most important and at the same time the most depressing one. It contains the results of some outstanding negative trials which prove that cell-inhibiting drugs increase mortality when compared to placebo. Translated into plain language, this section will furnish irrefutable evidence that **physicians have systematically killed patients** over the last 50 years by treating them with *antiarrhythmic drugs, calcium-channel blockers, immunosuppressive drugs, chemotherapy*, and *radiation*, just to mention some of the most common treatment regimens of cell-inhibition today. Although this collective crime has not been intended, its ongoing omnipresence cannot be overlooked.

We shall begin with the milestone in negative trial research - the **CAST trial**[167]. In this trial, the protective effects of the *class Ic antiarrhythmic drugs, flecainide* and *encainide*, were compared to placebo in patients after myocardial infarction. The trial was designed to test the hypothesis that suppression of ventricular ectopy by class Ic drugs *reduces* the incidence of sudden death as propagated by both manufacturers and specialists.

Flecainide and encainide are considered to be the most potent antiarrhythmic drugs in inhibiting the inward Na^+-current in sarcolemmal Na^+-channels. Plasma membrane or intracellular membrane Na^+-channels are actively involved in cell depolarisation and substrate intake through symport. According to our definition, drugs that block these channels are potent cell-inhibitors. They inhibit the rapid depolarisation and thus decrease the energy exchange according to the universal equation: when f decreases, $E = E_A f$ decreases too, as $E_A = cons.$ and $E \approx f$. In addition, class Ic antiarrhythmic drugs, such as flecainide and encainide, reduce the resting potential (the amplitude of the action potential): when E_A goes down, the energy exchange in the muscle cells is also decreased $E \approx E_A$.

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[167] N Engl J Med, 1989, 321: 406-12; N Engl J Med, 1991, 324: 781-8.

The inhibiting character of these drugs can be determined by the dipole model. The chemical structure of each of the two drugs reveals two tertiary amino groups. One amino group is found in the middle of the two cyclic rings and disrupts their dipole moment. The dipole model predicts that such drugs are potent cell-inhibiting agents and thus increase morbidity and mortality when given chronically.

This prediction was cogently confirmed by the CAST trial. It was one of the largest placebo-controlled trials in this indication and the first negative trial that led to the withdrawal of registered drugs from the market. This fact elucidates why there have been very few trials with negative results so far: if such trials were performed for other cell-inhibiting drugs, they would inevitably lead to the withdrawal of most drugs currently available on the market. Therefore, the pharmaceutical companies are reluctant to sponsor similar trials; in the rare cases when they did so, it was either from ignorance with respect to the outcome or under the pressure of the registration authorities, but never on the basis of pure ethical and scientific considerations[168].

Of 1498 patients enrolled in the CAST trial, 857 were assigned to receive encainide or placebo (432 to active drug and 425 to placebo) and 641 were assigned to receive flecainide or placebo (323 to active drug and 318 to placebo). After a mean follow-up of 10 months, 89 patients died: 59 from arrhythmia (43 receiving drug vs. 16 receiving placebo, $p = 0.0004$), 22 of non-arrhythmic cardiac causes (17 receiving drug vs. 5 receiving placebo, $p = 0.01$) and 8 from non-cardiac causes (3 receiving drug vs. 5 receiving placebo). The study had to be halted prematurely.

The authors looked for an effect of flecainide and encainide on ventricular tachycardia, which was supposed to be improved by this treatment. They were surprised to find no differences between the two groups in the incidence of non-lethal ventricular tachycardia, proarrhythmia, syncope, need for a permanent pacemaker, congestive heart failure, recurrent myocardial infarction, angina, or any other factors that might have been causally related to the outcome. The authors concluded that "the mechanisms underlying the excess mortality during treatment with encainide or flecainide remain unknown." The energetic mechanism of cell-inhibiting drugs leading to increased morbidity and mortality was

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168 This is at least my impression from 15 years in clinical research with the biggest pharmaceutical companies.

explained five years later within the General Theory, as outlined in the present volume.

This trial elucidates another important *psychological* phenomenon in clinical research. The authors of the CAST trial were very honest and, instead of proposing highly speculative hypotheses, admitted in the discussion that they did not know the actual cause of increased mortality under antiarrhythmic treatment. The practical consequence of this honesty was that the impeccable results of this trial were largely discarded in Europe (and especially in Germany, where most practising physicians, according to my experience, do not read international medical journals or original publications of clinical trials[169]). The use of antiarrhythmic drugs was not questioned in these countries, while the same drugs were banned from the US market.

This example illustrates the deep-seated quest of deterministic minds for a causative explanation. The human mind would rather accept a causal explanation which is evidently wrong than a correct result which does not suggest a causal relationship. This single fact underscores the ethical and scientific dimensions of the discovery of the Universal Law and the development of the General Theory in the proper planning and interpretation of future clinical trials. For the first time in the history of natural sciences, a stringent and logical explanation is given for all biological and medical phenomena. At the same time, the Theory represents the most radical departure from present deterministic and causative thinking.

Subsequently, the CAST trial was continued with *moricizine* and the negative results for this class of antiarrhythmic drugs was confirmed again[170]. Had the General Theory been known at that time, this trial would not have been performed. The same holds true for many other clinical

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169 If they do read such journals, most of the physicians almost certainly do not understand the underlying statistics and are hence unable to properly evaluate the results. This observation is of ubiquitous character and is not restricted to German colleages, who in addition are the worst investigators in Western Europe. For instance, while investigators from such a small country as Finland regularly publish high quality trials in international medical journals, during the last ten years I have not come across a basic double-blind, placebo controlled or epidemiological trial, performed in Germany and published by German authors in a peer journal.

170 CAST II investigators, N Engl J Med, 1992, 327: 227-35.

trials which were subsequently conducted in cardiology. The results with flecainide, encainide, and moricizine in the CAST trials are backed by further results from other class I antiarrhythmics drugs[171]. They show that *sodium-channel-blocking agents* are associated with an increased mortality and sudden cardiac death "despite suppression of arrhythmia".

In the absence of a General Theory of biological regulation, it is generally assumed that these results need not hold true for other classes of antiarrhythmics. At this point, it is important to observe that the classification of antiarrhythmics is highly arbitrary and is predominately based on morphological ECG parameters, rather than on a strict biophysical theory. This is illuminated by the fact that in the last few years many modifications in the classification of antiarrhythmics were necessary to comply with new clinical evidence. Departing from the prevailing determinism in clinical research, it has been postulated that *class* III *antiarrhythmic drugs* might be beneficial in patients with left ventricular dysfunction after recent or remote *myocardial infarction* (MI). This is the kind of empirical redundancy one always observes in clinical research and pharmacology. It stems from the prevailing theoretical agnosticism in this field.

However, the hypothesis that *potassium-channel blocking* agents may improve survival is based on sound empirical results. Studies of the class III antiarrhythmic *amiodarone*, given after MI and in congestive heart failure, established that it was safe and improved survival. We shall present these trials below. Because amiodarone is believed to prolong the duration of the action potential of muscle cells by *potassium-channel blockade*, it has been suggested that other potassium-channel blockers might be protective too. For instance, it has been assumed that *d-sotalol*, which is also assigned to class III antiarrhythmic drugs, exhibits similar beneficial effects in patients after MI. This extrapolation from one drug to another has been done despite the knowledge that amiodarone exhibits different ion-channel effects from those of d-sotalol, such as sodium-channel and calcium-channel blockade, as well as non-competitive α-adrenergic and β-adrenergic blockade, and is a coronary vasodilator, while d-sotalol is not[172]. We quote the effects of amiodarone, just as they are published in the literature, but do not ascertain that their interpretation and common presentation are correct. As it eventually transpired, this

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171 JAMA, 1993, 270: 1589-95.

172 Circulation, 1991: 84: 1831-51; Eur Heart J, 1991, 12: 1112-31.

assumption was essentially mistaken. We shall show that the highly arbitrary classification of amiodarone and d-sotalol in one and the same class of antiarrhythmic drugs has had grievous consequences for the patients.

Before we proceed with our presentation of the clinical results, we must pay attention to the chemical structures of amiodarone and d-sotalol and analyse them by means of the dipole model. Both drugs have completely different chemical structures. Amiodarone exhibits only one amino group at one ending and has two polar iodine atoms in the cyclic ring. In addition, there is an intermediary CO-group that links the two π-electron cyclic structures and contributes to the polarity of this compound. Altogether, amiodarone exhibits a modest dipole moment and carries the elements of a weak soliton-triplet. Based on its structure and pharmacological effects, this drug is classified as a cell-stimulating drug of the repolarizing type. On the other hand, d-sotalol is a pure cell-inhibiting drug. It carries two secondary amino groups at the two endings that disrupt the dipole moment of this compound. Hence the cell-inhibiting effect of this drug. Because it prolongs the slow repolarizing phase (plateau) of the action potential in muscle cells, d-sotalol is believed to block potassium channels, which are thought responsible for this phase.

In the Light of the Law, the electric LRC of muscle cells (or any other cells) is the aggregated product of all integral FUELs and agents of the supracellular regulation that interact with them. As all systems are open U-sets and contain themselves as an element, from an energetic point of view it does not make any difference which FUEL, ion, or agent is predominantly responsible for the modulation of the electric LRC. What counts is the relative change of the potential in time and space. As d-sotalol does not reduce the amplitude of the action potential, but only prolongs its plateau[173], it has a negative chronotropic effect on heart muscle cells: f is decreased and the energy exchange $E = E_A f$ is also decreased.

In this respect, it is important to observe that as energy (cell metabolism) has only two dimensions, space and time, any chronotropic effect on the heart is at the same time inotropic: thus d-sotalol is both negative inotropic and chronotropic. This correlation is a consequence of the reciprocity of space and time. In this particular case, inotropy is a synonym for energy and chronotropy is a synonym for time; as $E \approx f$, both magnitudes change simultaneously. Space-time is a unity; this holds true

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[173] Personal communication.

for any system of space-time. The present discrimination between inotropic and chronotropic drugs is an abstraction born in the cardiologist's mind. Considering this evidence, it is a mystery why both drugs are still believed to have similar effects and have been assigned to the same class III antiarrhythmics.

This detailed discussion of the two drugs has a personal background that is highly instructive with respect to modern clinical research. In early 1994, I was contacted by a representative of *Bristol-Myers Squibb* and informed that his company had sponsored a large international multicentre, placebo-controlled (phase III) trial evaluating the efficacy of d-sotalol as an antiarrhythmic drug. Sotalol had been used for a long time as β-*blocker*, but the company was searching for new indications to enlarge its therapeutic scope, as the positioning of the drug in the β-blocker segment was jeopardized by various new β-blockers ("me-too drugs"). To avoid competition, BMS decided to use the racemate form of this drug.

At that time, I had just outlined the General Theory and had finished with the verification of the dipole model on the basis of 4000 registered drugs (chemical entities). Both *amiodarone* and *d-sotalol* were among the drugs analysed. Based on the dipole model, I informed the BMS-representative that **d-sotalol was definitely a cell-inhibiting drug** and would therefore be detrimental to the patients enrolled in this trial. In this context, I quoted the results of the CAST trial as discussed above. In the presence of two other colleagues, I predicted that this trial, if properly evaluated by the company, would inevitably show that d-sotalol had increased mortality in comparison to placebo. As one would expect, the company representative was not very happy about my objections.

At the end of 1994, I had another meeting with the same representative. He informed me that the trial had been **prematurely stopped** by the safety monitoring board because **there were significantly more deaths in the d-sotalol group** when compared to placebo. He showed me confidentially the interim statistical results of this trial. The only two figures which I remembered were that more than 3000 patients were enrolled in the trial and that there were more than **20 excess deaths** in the treatment group. For the first time after many years of clinical research I realized during this intercourse that clinical researchers in particular and doctors in general could quite easily become "statistical murderers".

Two years before this meeting I finished a similar large trial programme in osteoarthritis with a new non-steroidal antiinflammatory drug (NSAID), for which I had written the protocols. According to the dipole model

NSAIDs are potent cell-inhibiting drugs. We had to stop one trial because of life-threatening adverse events (gastrointestinal bleedings) in the high-dose treatment group. Being the only one to have realized the full magnitude of the fatal potential of cell-inhibiting drugs, I was somehow relieved not to have had any drug associated deaths in any of my previous trials. That evening I came to the conclusion that I would no longer be in a position to carry out clinical trials with cell-inhibiting drugs. From that moment onward, my only occupation was to develop and popularize the discovery of the Law and its consequences in medicine and to convince the scientific community and the authorities to stop this world-wide genocide of patients. I was bewildered, staggered and depressed by the silent, clean, and efficient character of this collective capital crime in which I had participated for many years, financed by the taxpayers and disguised under the moral impeccability of the Hippocratic oath. One year later, I closed my institute (DIAS institute), which conducted clinical trials for the international pharmaceutical industry, and dedicated myself to the elaboration of the new theory of the Law.

But a true story must have an epilogue. In 1996, I red in Lancet the results of the **SWORD trial**[174] and felt, as if I had been "stabbed with a sword". I recognized the trial that made me quit my profession as a clinical researcher. It is an established practice to justify the conduct of each trial in the introduction of the paper. The authors' justification of this trial is as follows:

> "Among available potassium-channel blockers, *d*-sotalol has been most widely used. It is the dextrorotatory optical isomer of the racemate *d,l*-sotalol and blocks I_{kr}, the rapid component of the delayed-rectifier current. *d*-sotalol lacks clinically significant beta-blocking activity and would be expected to be well tolerated by patients with severe left ventricular dysfunction. Antifibrillatory activity of *d*-sotalol has been shown in some experimental models but not in others. The Survival With Oral *d*-Sotalol (SWORD) trial was a multinational, multicentre, placebo-controlled, randomized, double-blind trial of d-sotalol to test the hypothesis that a drug with a pure potassium-channel-blocking action *reduces all-cause mortality* in patients with previous MI and left ventricular dysfunction."

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[174] Waldo AL et al., 1996, 348: 7-12.

As I had anticipated, it turned out the other way round. After 3121 of the planned 6400 patients were recruited, the trial had to be stopped on Nov 1, 1994 after 2.3 years of recruitment. Among 1549 patients assigned d-sotalol, there were 78 deaths (5%) compared with 48 deaths (3.1%) among the 1572 patients assigned placebo ($p = 0.006$). Thus **30 patients in excess were killed by treating them chronically with d-sotalol**. This means that approximately **1% of all the patients participating in the trial and 2% of those treated with d-sotalol were actively exterminated.** This figure is quite instructive if one wants to estimate the *cumulative killing rates* of cell-inhibiting drugs world-wide in the second half of this century.

It is important to observe that, according to the dipole model, d-sotalol is somewhat less cell-inhibiting than the more common racemate of d,l-sotalol, which has been widely used as β-blocker for many years. Thus we can assume similar or even higher killing rates with this β-blocking agent in patients with heart diseases, such as CHD and hypertension. Although we do not have any direct comparisons, the killing rate of d-sotalol can be considered representative for the large group of β-blocking agents, many of which are more potent cell-inhibiting drugs than this agent when the dipole model is applied (see also below). The survival curve in the SWORD trial (see figure 1 in the original publication) showed that the difference in the mortality rate increased significantly after the first 180 days of treatment and had its maximal value after 300 days (specific Ljapunov time). This indicates that the observation period in this condition must be at least 1 year. Shorter observation periods may miss the difference in treatment. The results of this trial do not need any further discussion. They illuminate the dreadful truth of modern pharmacology.

There are many reasons why this truth has not been unveiled yet. We cannot consider all of them. Instead, a trial with antiarrhythmic drugs, including sotalol, has been arbitrarily selected; it will suffice to elucidate some common causes for the theoretical and empirical mess in clinical research today. In this study, seven antiarrhythmic drugs, *imipramine*, *mexiletine*, *pirmenol*, *procainamide*, *propafenone*, *quinidine*, and *sotalol* were given to only 486 patients with ventricular tachyarrhythmias[175]. Each patient received up to six drugs *in sequence*. Each drug was tested

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[175] ESVEM trial, N Engl J Med, 1993, 329: 452-8.

when a specified dose or concentration was reached. If the dose could not be achieved because of intolerance on the patient's part, a lower dose was used as long as it exceeded a specific minimum. Testing was performed once for each drug until one drug was predicted to be effective, or all six drugs failed. Patients did not undergo testing of a particular drug if they could not tolerate the minimal dose or had serious ventricular arrhythmia before the efficacy test. Patients did not receive any drug they had previously received if the drug had been ineffective or had caused adverse events. In the analysis, only adverse events that resulted in the discontinuation of the study drug were presented. In this trial, only secondary, that is, *surrogate* endpoints, were evaluated for efficacy (adverse effects, holter monitoring, electrophysiological study). There was no *intent-to-treat analysis*; most of the data was censored. Although the trial was not designed as a mortality trial, this endpoint was evaluated *posteriori*. There were too many statistical tests that devalued the statistical power, if any, considering the small number of patients, the sequence design, the numerous drop-outs, and the short periods of observation for each treatment regimen.

Indeed, this trial exemplifies all the possible mistakes which an investigator should avoid in clinical research. Most of the publications in scientific journals are based on such deficient trials. Their results are without any value and should be discarded for medical or registration purposes. The portion of high-quality trials, as quoted in this book, is extremely low. When we analysed the publications in 10 famous international medical journals during the last 10 years, beginning in 1988, we found that less than 5% of the clinical trials published there were *long-term, double-blind, randomized, placebo-controlled, mortality trials*. However, this is the only clinical design that renders adequate medical information. Therefore, we should not be surprised to find in the literature an overwhelming *optical* majority of useless studies and clinical results that should be weighed against a few solid results from large, placebo-controlled, mortality trials as presented in this chapter. This is beyond the powers of most readers (and editors).

Two further causes for the present scientific mess in medicine should also be mentioned: 1) There are too many medical journals, which are desperately searching for any kind of clinical trial to publish; 2) There is an established policy of "perish or publish" in research today. The latter is the visible carcinogenic effect of prevailing scientific empiricism over theory. This atomization of action over theoretical insight has precluded

the establishment of a universally valid theory of biological regulation and pathogenesis of diseases. This has been achieved in the General Theory.

Therefore, we should not be surprised to read in the above trial that sotalol is "more effective than the other six antiarrhythmic drugs in preventing death and recurrence of arrhythmia". The only "benefit" of such erroneous conclusions is to propagate the broad use of cell-inhibiting drugs and contribute to their impressive killing rate.

In the late 1980s, it became evident that the only antiarrhythmic drug which promised to reduce all-cause mortality was *amiodarone*, but the number of patients studied so far was too small to allow definite statistical conclusions. All placebo-controlled trials with other antiarrhythmic drugs delivered negative results: they showed that chronic therapy with cell-inhibiting antiarrhythmic drugs was associated with increased mortality, in most cases, with a sudden and presumably arrhythmic death (cardiac singularity due to destructive interference). Thus most antiarrhythmic drugs were, in fact, found to have a proarrhythmic effect. This is a classical example of the paradoxicality between wishful thinking and dreadful reality in pharmacology.

Based on the Law, I proved that mathematics (the continuum *n*), and in particular statistics (Kolmogoroff's probability set $0 \leq SP(A) \leq 1$), is the only adequate perception of space-time, that is, of being: $n = SP(A) =$ principle of last equivalence (see vol. I & II). This stringent conclusion of the new axiomatics has been intuitively anticipated in clinical research. In the last few years, a new trend of performing **meta-analysis** has emerged: this statistical method assesses the efficacy and safety of drugs and other therapeutic procedures based on the cumulative evidence of previous clinical trials. Meta-analysis is an application of the intuitive notion that space-time is discrete (individual trials and sample sizes of the whole), but *continuous* - all trials assess the unity of the patient population. The trials considered in the meta-analysis are regarded as U-sets of space-time, in this case, of the total patient population, which itself is a level of organic matter. Thus, for the first time in the history of applied statistics we can present objective arguments in support of this abstract mathematical procedure:

> Meta-analysis is a mathematical method that adequately reflects the nature of the primary term.

A fundamental meta-analysis of trials with antiarrhythmic drugs given after MI was performed in 1993[176]. It proved that *sodium-channel blockers* were harmful and that *calcium-channel blockers* had no beneficial effects. The latter evasive conclusion was offset by subsequent trials: **calcium-channel blockers also increase mortality**. On the other hand, when meta-analysis of placebo-controlled trials with amiodarone, given after myocardial infarction or in patients with heart failure, was performed[177], it was found that this *cell-stimulating drug of the repolarizing type* substantially improved survival. The latter meta-analysis based on 138 trials of antiarrhythmic drugs confirmed the results of the previous one by showing a significant excess mortality among survivors of MI who received class I antiarrhythmics. This is commensurate with the CAST trials and confirms the consistency of any appropriate clinical statistics, which is part of the new physical and mathematical axiomatics.

According to the General Theory, repolarizing drugs exert modest beneficial effects on mortality. However, in cardiology such drugs may be as effective as depolarizing drugs, especially in the antiarrhythmic patient. This kind of cell-stimulation may be more appropriate in improving the conditions of destructive interference, especially in patients with repetitive *ventricular premature defibrillations* (VPDs) or *torsades de pointes*. The beneficial effects of the cell-stimulating antiarrhythmic drug amiodarone predicted by the meta-analysis were subsequently confirmed by two recent trials (consistency and lack of contradictions of the mathematical approach).

In the double-blind, placebo-controlled **CAMIAT trial**, the effect of amiodarone was evaluated on the mortality of patients with resuscitated ventricular fibrillation or arrhythmic death among survivors of MI with frequent or repetitive VPDs[178]. This patient population was found to have a much higher mortality 1 to 2 years after the event than those without VPDs. 1202 patients were recruited in this study (606 in the amiodarone group and 596 in the placebo group): the mean follow-up was 1.75 years and thus longer than the estimated specific Ljapunov time in this indication. In the efficacy analysis, resuscitated ventricular fibrillations or arrhythmic deaths occurred in 31 (6.0%) patients in the placebo group and in 15 (3.3%) in the amiodarone group ($p = 0.016$). This means that **16**

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[176] Am J Cardiol, 1993, 72: 51F-58F.

[177] JAMA, 1993, 270: 1589-95.

[178] CAMIAT trial, Lancet, 1997, 349: 675-82.

patients (2.6%) were saved by treating them with amiodarone.

When an analysis of major trials with cell-stimulating drugs was performed, it was established that the improvement of mortality with these drugs ranged from 3 to 5%, depending on the indication, patient population, and observation period (see also the *life-saving rate* of HMG CoA reductase inhibitors). These results should be compared with those of d-sotalol and other cell-inhibitors. In comparison to the latter, we estimate that the life-saving effect of cell-stimulating drugs exceeds 5-8%. In medicine, this is a very big difference. For instance, if amiodarone were to be directly compared to d-sotalol in patients with MI, we would expect that **in the amiodarone group at least 5% of the patients would be saved;** vice versa, **5% of the patients would be killed by treating them with d-sotalol** when compared to amiodarone. This figure is indicative not only for the killing rates of most current cell-inhibiting drugs in different indications, but also for the significant medical progress which will be achieved when these drugs are substituted by cell-stimulating drugs after the publication of the present volume.

When we extrapolate this figure to the treatment prevalence with cell-inhibiting drugs in the general population of industrialized countries (Europe and North America), we quickly come to the conclusion that in these two continents alone millions of patients have been prematurely killed with wrong therapies during the last 50 years. This figure may exceed by far the holocaust of Jewish and Slavonic people by the Germans during the Second World War. On the other hand, the extensive use of cell-stimulating drugs will save millions of human lives. The difference in outcome becomes evident from the few available trials which have evaluated a cell-stimulating drug with a cell-inhibiting drug in a direct comparison (see the results of the ABCD trial below).

However, the results of placebo-controlled trials reveal the Janus character of clinical research. For instance, we can also say that in the amiodarone trial 16 patients were killed by treating 596 patients with placebo instead of amiodarone. This fact questions the ethical appropriateness of placebo-controlled trials. This is a completely new aspect that has not been appreciated in clinical research yet. In the light of the General Theory, it emerges as a central ethical problem of modern clinical research. This aspect needs further elucidation. In my personal opinion, we shall no longer need placebo-controlled trials because the dipole model clearly indicates which compounds are cell-stimulating and which are not. The only comparison which should be allowed from an ethical point

of view is that between a standard cell-stimulating drug and a new cell-stimulating drug or a combination thereof, to establish the Pareto-optimal stimulation in the body and further reduce mortality. This kind of clinical research will be evolutive and interdependent. It demands the establishment of treatment protocols which are followed world-wide in most clinical centres and are incessantly improved on the basis of the General Theory (international, interdependent clinical research).

Placebo-controlled mortality trials are the state-of-the-art in present-day clinical research. In the absence of any theory of biological regulation, the only possibility of finding out whether a drug is beneficial or detrimental to the patient is to compare it with no treatment. As conditions should be made equal, placebo is given. The necessity of performing placebo-controlled trials illuminates the simple truth that clinical research and pharmacology operate in a state of profound agnosticism. With the development of the General Theory this agnosticism is eliminated once and for all. Based on the dipole model, we are in a position to predict the therapeutic effects of any chemical moiety. In addition, we can perform various in vitro tests to find out the relative energetic specificity of the drug candidate during its interaction with various integral and cytosolic FUELs in cell cultures. This limited kind of research will be sufficient to establish the complete pharmacological profile of the drug. Animal kinetic studies will give additional information on the pharmacodynamic behaviour of the compound in the organism. As animal and human cells are regulated in the same way, animal-disease models can be employed to establish the therapeutic potential of the drug in vivo. The present kind of placebo research in humans will no longer be possible on purely ethical considerations: knowing the General Theory, we cannot justify the deliberate killing of patients suffering from severe disorders by treating them with placebo, instead of giving them cell-stimulating drugs. This would be tantamount to murder.

As the reader may perceive, the discovery of the Law will bring about the most radical departure from present registration policies. At the same time, it will facilitate the quick development of cheap and effective cell-stimulating drugs for most incurable chronic diseases. In this context, it is important to observe that one of the greatest injustices in modern times is the fact that most of the drugs are too expensive and the majority of mankind cannot afford them. For instance, more than 90% (approx. 30 million) of HIV-patients live in poor countries and have no chance of receiving an adequate treatment. These patients can immediately profit

from chronic treatment with cheap Nys or Amp, which are cell-stimulating agents of the depolarizing type and decrease mortality. If we assume that polyenes decrease mortality by 1% per 5 years, which is a conservative estimate, we can save about 300 000 human lives during this period only in the HIV-infected population. If we extrapolate this figure to other diseases in which polyenes are highly effective, we can estimate that within the next 10 years we can easily save more human lives with these drugs than were lost in the First, Second, and Third (Cold) World Wars together. So much for the practical and ethical implications of the General Theory.

In the CAMIAT trial, an intent-to-treat analysis was performed. The results were comparable with those obtained in the efficacy analysis (recall that in the ESVEM trial no intent-to-treat analysis was performed). It showed that primary outcome events occurred in 24 patients in the placebo group and in 15 patients in the amiodarone group ($p = 0{,}029$). This outcome proved that the results were *robust*. The absolute risk of reductions were greatest among patients with congestive heart failure or a history of MI.

These results were confirmed by the second recent trial with amiodarone - the **EMIAT trial**[179]. This placebo-controlled, mortality trial included 1486 patients with impaired LVEF of 40% or less after MI and was also based on *intent-to-treat* and *efficacy analysis*. The patient population in this trial exhibited a lower rate of mortality during the first 2 years after event than that found in the CAMIAT trial, despite the fact that the mean observation period in the EMIAT trial was 21 months and thus similar to that of the CAMIAT trial. Altogether 1496 patients were enrolled in the CAMIAT trial. All-cause mortality did not differ between the two groups. When the mortality rate caused by arrhythmic deaths was evaluated, there was a risk reduction of 35% in the amiodarone group ($p = 0.05$).

At first glance the results of the EMIAT trial seem to be less convincing than those of the CAMIAT trial. However, this trial exhibits another common pitfall that should be considered in the interpretation of clinical trials. The *drop-out rate* in the EMIAT trial was unevenly distributed between the two groups. During this trial, 284 (38.5%) patients in the amiodarone group discontinued their medication compared with only 158 (21.4%) in the placebo-group (see figure 4. of the original publication, p.

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[179] Lancet, 1997, 349: 667-74.

671). In the CAMIAT trial, the drop-outs were more evenly distributed between the two groups (36.4% in the amiodarone group and 25.5% in the placebo group). This partially explains the less pronounced treatment effect of amiodarone in the EMIAT trial. The most common reason for discontinuing amiodarone was the occurrence of adverse events. The most common reason for discontinuation in the placebo group was the occurrence of ventricular tachyarrhythmia. This biased the results of the EMIAT trial.

The spectrum of side effects in the amiodarone group showed some similarities with those of i.v. Amp. Both drugs affect vital organs such as heart and lung. However, there are notable differences, which indicate that Amp and polyenes are depolarizing agents, while amiodarone is a repolarizing drug. While amiodarone depresses some hormone systems (e.g. hypothyroidism) because of its repolarizing effect, or interfere with the CNS (sleep disturbances) because of its kinetic distribution in the body, i.v. polyenes exhibit mainly renal toxicity. On the other hand, oral polyenes have virtually no adverse events due to their pronounced amphipathic character.

We have worked out the adverse event profile of amiodarone in comparison to that of polyenes in order to demonstrate that **side effects are pharmacological effects**: they support the dipole model by giving additional information as to whether a cell-stimulating drug is depolarizing or repolarizing. In the long run, we shall be able to establish sophisticated pharmacological profile maps for each compound and chemical group. Equipped with such techniques, we shall no longer need clinical trials to determine the therapeutical spectrum of cell-stimulating drugs. In this respect, the General Theory offers some dazzling new perspectives for the pharmaceutical industry that cannot be discussed here.

The deleterious effects described above are not restricted to *antiarrhythmic drugs*. The increase in mortality has been observed with most **cardiaca**: according to the dipole model, they are potent cell-inhibitors. We shall not discuss their structure and leave this exercise to the reader[180]. Short-term and long-term treatments with **calcium-channel blockers** were found to worsen heart failure and increase the risk of death in pa-

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[180] This application of the dipole model is a good on-the-job training for any pharmacologist or clinical researcher.

tients with advanced *left ventricular dysfunction*[181]. This toxic potential was established for most calcium-channel blockers, including many of the newer agents which have become available for clinical use in the last few years[182].

The first evidence that calcium-channel blockers may increase mortality dates back to the early 70s and includes some of the classical calcium-channel blocking agents. Short-term treatment with *verapamil*, *nifedipine*, and *diltiazem* produced clinical deterioration[183] and long-term therapy with these drugs increased the risk of worsening heart failure, myocardial infarction, and death in patients with left ventricular dysfunction[184]. These detrimental effects have been correctly attributed to the propensity of these drugs to depress cardiac contractility (apply the universal equation). In addition, the activation of endogenous neurohormonal systems has been discussed, but the importance of these mechanisms could not be elucidated.

The subsequent approach of using sustained-release formulations or "vasoselective" agents, e.g. *nicardipine*, *nisoldipine*, or *felodipine*, did not prevent the development of cardiovascular complications. Immediate-release formulations of nicardipine[185] and nisoldipine[186] resulted in the worsening of heart failure, as did sustained-release formulations of verapamil[187] and felodipine[188].

These results were recently confirmed for *amlodipine* in the **PRAISE trial**[189]. As a consequence, a recommendation was issued to "*avoid the use of calcium-channel blockers in patients with heart failure*", even if

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181 Circulation, 1990, 82: 1954-61; Circulation, 1991, 83: 52-69; The Multicentre Diltiazem Postinfarction Trial Research Group, N Engl J Med, 1988, 319: 385-92.

182 Am Coll Cardiol, 1987, 9: 622-30; Br Heart J, 1987, 58: 122-8; Br Heart J, 1995, 73: 428-33.

183 Nouv Press Med, 1975, 4: 337-8; J Am Coll Cardiol, 1987, 10: 1303-11; Circulation, 1985, 72: Suppl III: III-275.

184 Circulation, 1990, 82: 1954-61; Circulation, 1991, 83: 52-69; The Multicentre Diltiazem Postinfarction Trial Research Group, N Engl J Med, 1988, 319: 385-92; Circulation, 1984, 70: Suppl. II: II-305.

185 J Am Coll Cardiol, 1991, 17: Suppl A: 274A.

186 J Am Coll Cardiol, 1987, 9: 622-30.

187 JAMA, 1989, 261: 994.

188 Br Heart J, 1995, 73: 428-33.

189 N Engl J Med, 1996, 335: 1107-14.

these drugs might still be considered for the treatment of coexisting angina or hypertension. This was the first half-hearted step in the right direction in cardiology.

So far, there have been no attempts to withdraw these drugs from the market, as was the case with the class I antiarrhythmics after the CAST trials. Instead, calcium-channel blockers are among the *most frequently* prescribed antihypertensive drugs in the USA and Europe[190], despite the fact that they are suspected of being detrimental to hypertensive patients with and without diabetes.

As ACE-inhibitors were found to be effective in patients with IDDM and NIDDM, recently the ACE inhibitor *enalapril* was compared to the calcium-channel blocker *nisoldipine* in hypertensive patients with NIDDM (ABCD trial)[191]. This is one of the rare trials in which a cell-inhibiting drug, nisoldipine, is directly compared with a cell-stimulating drug, enalapril. While the beneficial effects of nisoldipine were questioned in previous trials, the mortality lowering effect of enalapril was well established (see above). Therefore, it is very difficult to fathom why this trial was ever performed. Based on ethical considerations, its conduct should have been prohibited. Considering our previous discussion, we should expect that the treatment difference between the cell-stimulating enalapril and the cell-inhibiting nisoldipine will be more pronounced than that between enalapril and placebo.

Indeed, the difference in mortality rate was found to be extremely high in the ABCD trial. Although the number of patients enrolled in this trial was restricted (470, 235 in each group), the difference in mortality and morbidity rate was unusually high: nisoldipine was associated with 25 (10.6%) fatal or non-fatal MI compared to only 5 (2.1%) in the enalapril group. Thus **nisoldipine increased mortality and morbidity (occurrence of SAEs, serious adverse events) by 8.5% when compared to enalapril**. We have already estimated this figure from the results of placebo-controlled trials with cell-stimulating or cell-inhibiting drugs. The result of the ABCD trial cogently confirms the consistency of the General Theory and its full coalescence with clinical experience. The chief asset of this trial is that the observation period was 5 years. This long Ljapunov time favoured the considerable treatment difference observed in this trial.

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190 Arch Intern Med, 1995, 155: 829-37.

191 The ABCD trial, N Engl J Med, 1998, 338: 645-52.

Thus, all clinical results in cardiology fit in with the basic predictions and conclusions of the General Theory. As cardiology has produced the most sophisticated placebo-controlled trials based on mortality, we have focused on this field. In addition, *cardiaca* contain many potent cell-inhibiting drugs, which interact directly with the electric LRC of the cells, and a few cell-stimulating drugs, which have also been evaluated in high-quality, placebo-controlled, mortality trials. The level of clinical research in other indications and drug classes is much lower, e.g. antibiotics in infections. There are no obvious reasons for this apparent disparity.

The better the quality of the clinical research, the more obvious the beneficial effects of cell-stimulating drugs and the more pronounced the detrimental effects of cell-inhibiting drugs. For this reason we have basically quoted trials performed after 1990. Such trials comply with the recommended statistical standards of clinical research, as prescribed in the last few years. This "vademecum" effects another major simplification in the interpretation of clinical results.

The General Theory postulates that cell-inhibiting drugs increase mortality and morbidity. Above, we have mainly focused on mortality. However, **increased mortality is always associated with increased morbidity.** For instance, calcium-channel blockers do not only increase mortality, but also morbidity. The most common pathogenic effect of such drugs is **increased risk of cancer** due to increased energy constraint in the cells to mutate under drug inhibition. Higher morbidity caused by cell-inhibition leads automatically to higher mortality. Therefore, the two phenomena are closely interrelated - they are aspects of one and the same thing: the infringement against the Law by treating humans with cell-inhibiting drugs.

This fact was confirmed in a recent trial that evaluated the risk of *cancer* of *calcium antagonists* compared with β-*blockers* and *ACE-inhibitors*[192]. A previous study suggested that the relative risk of cancer in patients taking calcium antagonists was increased by 2.02 times when compared with users of β-blockers[193]. In the light of the Law, this com-

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192 Lancet, 1997, 349: 525-28.

193 Hypertens, 1996, 9: 695-99. However, not all β-blockers are cell-inhibitors; some of them are cell-stimulating agents and reduce mortality (Lancet, 1999, 353: 2001-7).

parison is inadequate, as both groups are cell-inhibiting. As β-blocking agents also have a carcinogenic potential, they are not an appropriate baseline. In this case, a comparison with placebo should have been selected. Fortunately, this trial also included ACE-inhibitors, which are cell-stimulating drugs and thus reduce the risk of cancer. Based on the General Theory, we should expect that ACE inhibitors exhibited a lower incidence of cancer than calcium antagonists and β-blockers.

Indeed, the above trial confirmed this prediction: the relative risk estimates for all cancers combined was 1.27 for users of calcium-channel blockers and 0.79 for users of ACE-inhibitors. In this case, the risk of cancer for users of β-blockers was set 1. The study was based on 446 cases of cancer and 1750 controls. The number of cancer cases was 183 (24.2%) compared to 755 controls in the β-blocker group, 85 (20.1%) compared to 422 controls in the ACE-inhibitor group, and 178 (31%) compared to 573 controls in the calcium antagonist group. Thus, the risk of cancer was increased by 4% under β-blocker treatment and by 10% under therapy with calcium antagonist when compared with the cancer risk under ACE-inhibitors. The relative risks were even higher: 26% under β-blocking agents and 60% under calcium-channel blockers when compared to ACE-inhibitors. These results clearly indicate that cell-stimulating drugs such as ACE-inhibitors reduce the risk of cancer, while cell-inhibiting drugs such as β-blockers and calcium-channel blockers increase it. This is a clear-cut message.

Any therapeutic procedure which inhibits the energy exchange in the cell increases the risk of cancer. This holds true not only for cell-inhibiting cardiaca, but also for *radiation* and *chemotherapy*. Although chemotherapeutics (cytostatics) are administered as anti-cancer drugs, most of them have a pronounced carcinogenic potential, which has been well known since the early 60s[194]. Considering the broad use of cytostatics, this is one of the most embarrassing paradoxes of modern medicine that should be cogent to anybody with a modest command of medicine and logical thinking. According to the dipole model, all cytostatics and immunosuppressive drugs (some cytostatics are also used as immunosuppressive agents) are potent cell-inhibitors. We shall not discuss their in-

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194 For non-specialists, I recommend the highly instructive book "Cancer: the misguided cell" by DM Prescott & AS Flexer, Spectrum, Heidelberg, 1986, which covers this issue.

dividual chemical structures and suggest that the reader test the dipole model on these drugs by himself.

Radiation is also cell-inhibiting and highly carcinogenic. This is well established for *gamma-radiation* (see above). Any high-energy photon radiation can interfere with the electromagnetic waves of the cellular action potentials and destroy their intracellular and nuclear pattern by destructive interference. As the DNA-code is regulated by these electromagnetic waves, inducing discrete and highly specific solitons in the DNA-string, the rate of mutations significantly rises during and after radiation. We have quoted some outstanding results that confirm this phenomenon.

Cytostatics, *immunosuppressive drugs*, and *radiation* depress the immune system. This effect mainly contributes to the occurrence of cancer. This issue has been discussed on many occasions throughout this book (see cancer in AIDS patients). To substantiate the carcinogenic potential of *radiation* and *chemotherapy*, we shall present the results of a large epidemiological trial recently conducted in the USA[195]. This study evaluated the risk of developing new solid cancers after bone marrow transplantation in 19,229 patients who received allogenic transplants (97.2%) or syngeneic transplants (2.8%) between 1964 and 1992. Bone marrow transplantation has been the therapy of choice in most leukemia cases for more than 20 years. However, despite growing concern about possible late consequences of compromised immune function and treatment, particularly with total-body radiation and high-dose chemotherapy used as conditioning regimens for transplantation, there have been no adequate studies that assess the risk of cancer among long-term survivors of bone marrow transplantation. This example illustrates the broad neglect of the toxicological effects of common therapies in past clinical research. The situation has gradually improved in the last 5-8 years.

This trial confirmed that **transplant recipients are at significantly high risk of solid cancer due to radiation and chemotherapy** when compared to the general population ($p < 0.001$). The risk was **8.3 times** higher than expected among those who survived 10 or more years (long Ljapunov time) and 2.7 times higher than expected for the total population of transplant recipients. The cumulative incidence rate was 2.2% at 15 years (the reader should compare this rate with the killing rates of

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195 N Engl J Med, 1997, 336: 897-904.

cell-inhibiting drugs). The risk was significantly elevated for malignant melanoma (5.0 times) and cancers of the buccal cavity (13.4). It is noteworthy that the mucosa has a high proliferative rate and is easily damaged by cell-inhibition caused by chemotherapy or radiation. This is the most common severe adverse effect of this kind of treatment. High risk of solid cancer in transplant recipients included various other organs, such as liver (7.5), brain, and other parts of the central nervous system (7.6), thyroid (6.6), bone (13.4), and connective tissue (8.0). The multivariate analysis revealed that higher doses of total-body radiation were associated with a higher risk of solid cancers as predicted in the General Theory. The risk was higher for recipients who were younger at the time of transplantation and received concomitant chemotherapy and radiation ($p < 0.001$).

The latter result needs further elucidation. The immune system is still in the process of development during childhood. The evolution of the immune system reaches a peak at puberty. After that it more or less sustains this energetic level. If the immune system is repressed in early youth by radiation and/or chemotherapy, it may not mature and remains chronically repressed for the rest of life. This is associated with increased risk of cancer and chronic diseases. The same, though less pronounced, effect is observed during excessive antibiotic treatment in early childhood. Many of these patients exhibit an impaired immune system and suffer from various atopic diseases (see above). In this trial, the risk of cancer was 36.6 times higher than expected in children who were under 10 years of age at the time of transplantation, but only 4.6 times higher than expected in patients who were 10 to 29 years old at the time of transplantation and nearly normal for those who were 30 years or older ($p < 0.001$). This is another convincing confirmation of a basic tenet of the General Theory.

CONCLUSIONS

The last two chapters have confirmed the dreadful truth that pharmaceutical and clinical research - two of the most ethical disciplines of experimental research - have infringed upon the Law and evolved in the wrong direction. As a consequence **many cell-inhibiting drugs that increase mortality and morbidity in humans have been developed and registered**.

High-quality clinical trials, conducted in the last several years according to appropriate statistical standards, have documented in an irrevocable manner that medical doctors, pharmacologists, and the like have contributed to a **collective scientific holocaust** under peaceful conditions that exceeds by far - in terms of the number of victims - recent historical holocausts, such as the extermination of Jewish and Slavonic people by the Germans during the Second World War, or by Stalinists during the Russian civil war and thereafter. This scientific holocaust in the name of medical ethics has been accomplished unconsciously, on the basis of wrong paradigms, and is by no means comparable to the historical German or Stalinist sin. The result is, however, the same.

Every specialist in this field who has been educated to believe in these scientific paradigms and has ardently followed them in his job has contributed to this ubiquitous and unique crime in the history of modern civilisation. This accusation includes the author himself before he discovered the Law. There is no other option but to admit this stark and shocking fact.

This scientific holocaust is going on in front of our very eyes - statistically, every second somewhere on this planet a patient is prematurely killed by a treatment with a cell-inhibiting drug or regimen. The rate of **iatrogenic killing** is growing parallel to the consumption of cell-inhibiting drugs. Based on current prescription statistics, we can estimate that approximately 8 out of 10 patients are treated with cell-inhibiting drugs and are likely to die earlier than without this treatment. As almost every individual becomes seriously ill during his life, especially in advanced age, practically everybody is subjected to a cell-inhibiting treatment and

faces the risk of dying earlier than physiologically predetermined. Like nuclear contamination, all people are equal in the face of this medical peril, independently of their origin, social status, welfare, age, or sex. Therefore, urgent and radical political decisions are called for to curb this self-inflicted evil on mankind, before the present-day diminishing belief in humanity and ethics (see the bombing and exodus in Kosovo) is completely lost and new, more dreadful calamities than those of the 20th century are engendered.

The only way to atone for this collective sin and establish a novel and **universally valid ethics** is to begin asking questions about the causes of this global scientific agnosticism in medical and biological research. I will leave the answers to the reader and instead present the results of a unique trial entitled "Conflict of interest in the debate over calcium-channel antagonists", which was recently published[196]. As far as I am informed, this is the first trial of its kind. I shall leave the authors to speak for themselves:

> "Physicians' financial relationships with the pharmaceutical industry are controversial because such relationships may pose a conflict of interest. It is unknown to what extent industry support of medical education and research influences the opinions and behaviour of clinicians and researchers. The recent debate over the safety of calcium-channel antagonists provided an opportunity to examine the effects of financial conflicts of interest.
>
> We searched the English-language medical literature published from March 1995 through September 1996 for articles examining the controversy about the safety of calcium-channel antagonists. Articles were reviewed and classified as being *supportive*, *neutral*, or *critical* with respect to the use of calcium-channel antagonists. The authors of the articles were asked about their financial relationships with both manufacturers of calcium-channel antagonists and manufacturers of competing products (i.e., beta-blockers, angiotensin-converting-enzyme inhibitors, diuretics, and nitrates). We examined the authors' published positions on the safety of calcium-channel antagonists according to their financial relationships with pharmaceutical companies.

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> Authors who supported the use of calcium-channel antagonists were significantly more likely than neutral or critical authors to have financial relationships with manufacturers of calcium-channel antagonists (96%, vs. 60%, and 37% respectively; $p < 0.001$). Supportive authors were also more likely than neutral or critical authors to have financial relationships with any pharmaceutical manufacturer, irrespectively of the product (100%, vs. 67% and 43%, respectively; $p < 0.001$).
>
> Our results demonstrate a strong association between authors' published positions on the safety of calcium-channel antagonists and their financial relationships with pharmaceutical manufacturers. The medical profession needs to develop a more effective policy on conflict of interest. We support the complete disclosure of relationships with pharmaceutical manufacturers for clinicians and researchers who write articles examining pharmaceutical products." (p. 101)[197]

In my opinion, it is a basic mistake to discriminate between "seducers" and "seduced". This trend results from misguided religious education. Everybody can be at once a seducer and seduced (U-sets). The only panacea for the present pathological state of ethics in scientific research is not to look for who is the seducer and who is the seduced, as is usually done in jurisdiction, because in the present-day "paradise of scientific ignorance" sin does not make any sense. Instead of wasting time in searching for the culpable, we should resort to the quick and full mental acceptance and strict implementation of the new **Unified Theory of Natural Science** based on the Universal Law. But this Tantalus act may appear to be an insurmountable challenge to many a scientist, as my experience tells me.

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[197] The outstanding characteristics of this remarkable trial is that it cogently demonstrates that human ethical behaviour can be mathematically quantified in an objective manner. This proves the basic conclusion of the new theory that space-time, including society, abides by the Law and can be mathematized. This is the basis of a Unified Theory of Natural Sciences as founded in the present tetralogy (see also vol. IV on philosophy and ethics). This theory will pave the way to a new, better world based on universally valid ethical principles - those of the Law.

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