EU.L.E.N-SPIEGEL

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Die Heilkraft unserer Nahrung - das Ende eines Dogmas

Irrtümer werden in der Wissenschaft bekanntlich nicht durch neue Erkenntnisse widerlegt; sie sterben aus. Zu diesen Irrtümern gehört die These, Proteine würden in unserem Körper nach den Gesetzen des Zufalls abgebaut. Da auch Nobelpreisträger diese Auffassung vertreten, scheint die These über jeden Zweifel erhaben.

Alle Lebewesen bilden ihre Eiweiße bedarfsgerecht und mit höchster Perfektion: etwa 500 Billiarden pro Sekunde, mit einer mittleren Lebensdauer von 2 Tagen. Nach der aufwendigen Synthese beginnt für die Proteine ein reiches Arbeitsleben im Stoffwechsel. Dabei werden sie beschädigt, altern und werden abgebaut.

Nun gehört es zum „gesicherten Wissen", daß dieser Abbau den Gesetzen des Zufalls folgt. Das hieße: Einzelne Proteinmoleküle würden nach ihrer Synthese rein zufällig herausgegriffen und zerlegt - egal ob sie neu oder alt, intakt oder lädiert sind.

Individuelle Evolution

Die Evolution, die Entfaltung der Lebensvielfalt, wird durch Auslese der jeweils besser angepaßten Individuen erklärt. Nicht erklärt ist bisher die langfristige Erhaltung des Lebens im Individuum selbst. Prof. Pirlet weist auf eine integrale Eigenschaft des Evolutionsprozesses hin: Zur Erhaltung des individuellen Lebens bedarf es ebenfalls der Auslese, und zwar im Turnover der Eiweiße. Ohne diese protein-molekulare Auslese - so Pirlet - kein Leben.

Ein zufallsbestimmter Abbau wäre unökonomisch, eine unglaubliche Verschwendung mühsam akquirierter Ressourcen, nicht vereinbar mit den Gesetzen der Evolution. Nur Auslese „macht Sinn".

Neue Impulse für Ökotrophologie und Medizin

Das Neue an Pirlets Gedanken ist nicht das Stürzen eines Dogmas, sondern das Öffnen einer Tür. Denken wir weiter: Da unser Körper täglich zehnmal mehr Eiweiß umsetzt als er sich mit der Nahrung zuführt, sinkt nicht nur der Stern der „essentiellen Nährstoffe". Auch das Verhüten von „subklinischen Mängeln" tritt in den Hintergrund. Im Vordergrund steht anstelle der Menge nun die Information, zu der auch das Erkennen geschädigter Funktionselemente gehört. Die Ökotrophologie wird sich zur Signalstoff-Lehre weiterentwickeln müssen. Und, noch wichtiger: Der auslesende Charakter des Protein-Turnovers kann nicht nur das spontane Heilwerden unseres Organismus erklären. Ließe sich der rasante Umsatz therapeutisch beeinflussen oder gar steuern, wären auch schnellere Heilungen möglich - eine neue Perspektive für die Medizin.

Udo Pollmer

Liebe Leserinnen,
liebe Leser!

Die Redaktion hat sich zu diesem Sonderheft entschieden, nachdem Prof. Pirlets grundlegende Arbeit **„The Healing Power of Nature"** von internationalen Fachzeitschriften abgelehnt wurde. Wir publizieren sie in Englisch, um sie über das Internet weltweit allen interessierten Wissenschaftlern verfügbar zu machen. Eine deutsche Fassung kann beim Autor angefordert werden (Anschrift siehe S. 2).

Wir wünschen Ihnen allen, unseren Freunden, Mitgliedern und Förderern eine fröhliche Weihnachtszeit und ein rundum erfreuliches neues Jahr!

Ihr EU.L.E.N-SPIEGEL-Team

The Healing Power of Nature

Natural Selection at the Protein-Molecular Level

KARL PIRLET*

This paper is dedicated to Prof. Dr. ERNST MAYR, (Harvard University, Cambridge, USA), the Nestor of Evolution Biology, on the occasion of his 92nd birthday.

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Summary

No one can really explain the "healing power of nature", the body´s ability to heal itself. This paper presents a concept to help us understand this healing and health-preserving principle, namely by explaining this phenomenon from an evolutionary-biological and molecular-physiological point of view.

The evolution of life by means of the natural selection of individuals is the central axiom of Charles Darwin's theory of natural selection. The concept presented in this paper is concerned with preservation of individual life by means of the natural selection of physical sub-components - the proteins. The application of a principle as all-encompassing as natural selection to the protein field cannot be proven experimentally, however; rather, its validity can only be substantiated on the basis of argumentation.

A number of arguments are presented to counter the hypothesis that the break-down of uniform, structurally-intact protein groups is a stochastic, "blind", accidental process governed by first order kinetics. It is argued that supporting findings have been wrongly interpreted and that protein replacement is actually a selection process. The preferred removal of old, destructured and functionally inefficient proteins is synonymous with the selection of younger, structurally-intact, functioning proteins. In this way the cell maintains its protein stock at a high level of performance. Physiological and therapeutic influences (such as movement, heat and function intensification) accelerate the removal of aged protein molecules, and in doing so, increase their renewal and rejuvenation rate, thus enabling the cell to perform the specific tasks allocated to it by the DNA.

Only the principle of selection adequately explains the extraordinary dynamics of cellular protein turnover. Without selection at the protein-molecular level, life as we know it would not be possible. This paper purports that the much-vaunted "healing power of nature" is a selection process. Natural healing invokes this healing and health-preserving "power". In other words, natural healing is the study of nature, and as such is a truly natural science.

Everyone is familiar with the concept of the "healing power of nature", the body´s ability to heal itself, and every physician relies on it - whether consciously or subconsciously. Doctors try to stimulate and enhance the body´s ability to shake off illness, but no one really knows how this happens, and a scientific interpretation is yet to be provided. This paper presents a concept that explains the healing and health-preserving principle inherent to man from an evolutionary biological and molecular physiological point of view.

I support the body of thought known as *natural healing (Naturheilkunde)*. Not in the usual sense as a generic term for so-called natural healing methods, and definitely not as an umbrella term for alternative methods of natural treatment; rather, I use it to denote the study of the healing and health-preserving forces within us all. This is because, ultimately, it is "nature" that brings about the healing process, and not drugs, operations, massage, treatment or diet. *Medicus curat, natura sanat!* And the physician, in particular, the physician working with natural methods of treatment, expects the physiologist to explain why natural therapeutics are capable of healing and restoring man to health. As we have yet to hear a satisfactory answer, I have tried to arrive at an understanding of these physiological and molecular processes, which I present in the following.

Acknowledgments

I owe special thanks to Lothar JAENICKE, Professor of Biochemistry at the University of Cologne, for his friendly cooperation and the constructive criticism and encouragement he has provided me over the years, and to Hugo FASOLD, Full Professor of Biochemistry at the University of Frankfurt, who confirmed to me many years ago that the catabolism of proteins is selective in character. I also owe thanks to Ernst MAYR, Professor at Harvard University, for kindly corresponding with me on the topic of this paper. He initially expressed misgivings about my ideas, but eventually came round to agree that the principle of natural selection is not only responsible for genetic evolution but also for protein-molecular turnover and for every conscious decision taken by man.

The Preservation and Evolution of Life

Charles Darwin´s fundamental message is that the *evolution of life* in populations unfolds by the natural selection of their individual members. I complement this thought by adding that the *preservation of individual life* (i.e. the preservation of individual health) unfolds by the *natural selection of proteins*. It is the power of nature which sustains health, day for day, year for year. When disruption occurs, it is the power of nature which reestablishes the status quo, often with medical assistance, but often without. For lack of any better definition, medicine refers to the *self-healing power of nature, the phenomenon of health preservation*. This leads to the basic question of how this is achieved. This has never been asked before so bluntly in the world of physiological studies or orthodox medicine, and has therefore never been answered. Physiology is the study of the nature of the *physis* - it describes the flows and processes at the cellular and molecular level in the organ and functional systems. However, systemic or molecular physiology has yet to provide an *explanation of health and healing*.

This is because *to describe is not to explain.* We use experiments to describe what we observe, depicting our findings in curves and tables, publications and text books. Explaining is entirely different: it means making interrelationships synoptically understandable. Explaining is always an intellectual act, and the *explanation* of natural phenomena is the concern of this paper.

Let us first take a look at the *facts*, of which there are a great many. All lead to one and same principle, and shall therefore be quoted in the following. The cells - the basic components of the body, which are ultimately responsible for our existence - are turbulent, highly active places. The proteins, the active elements of the cells, are built up and broken down with almost unbelievable dynamism, namely at a rate of about 500 quadrillion protein molecules per second.

> Molecular biologists have asked for theoretical proof of this figure, which I provide as follows. Making a very conservative estimate, the body has 25 trillion cells (not including some 25 trillion erythrocytes), whereby each cell has 5 billion protein molecules. Assuming that the average life-span of enzyme and structural protein molecules amounts to three days, this results in a turnover rate of
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> 5 x 109 x 2.5 x 1013 / 2.5 x 105 = 5 x 1017, or
>
> 500,000,000,000,000,000 protein molecules/second.

It might be more, it might be less. Those acquainted with the details of protein production and activity will be surprised by figures of this magnitude, since they imply that about as many protein molecules are created every second as seconds have elapsed since the Big Bang. All cellular proteins are renewed within a few days. Moreover, cells that only form once in a lifetime, as in the brain, muscles and heart, exchange and replace their protein building blocks more than 10,000 times[1], and more than 50% of the chemical energy generated by a cell is used solely for protein turnover[2]. Molecular biology has no explanation for these dynamics.

Let us move on to an analogous thought. Evolution, the development of life over billions of years, is a fact. We are all aware of the diversity of life in macro communities, a bewildering process of conflict, cooperation, congregation, working with, for and against each other, the "live or die" aspect of nature. Many of the molecular-genetic and molecular-chemical details of this diversity have been described in depth and are consequently well-known today, but we cannot *explain* the development of this diversity of life without returning to Charles Darwin´s theory of *natural selection as the basic principle.* The environment, isolation, progeny, mutation, recombination and hence variation are simply the prerequisites of natural selection. In other words, we have our theory of selection, and we think we can explain the evolution of life on this planet.

The single entity - the individual being - is also subservient to the process of evolution. The individual matures, multiplies, rears its offspring and passes on the selected genetic material in the genotype to following generations. During the life-span available to perform this task, i.e. 40 to 50 years in the case of man, nature gives us the ability or the opportunity to stay fit and healthy in order to fulfill this task. This raises the following question: Is the process by which the systems work with and for one another, i.e. the interaction of physiological systems, such as the circulation, the metabolic/material balance, the immune system, the DNA repair systems and protein repair systems, explanation enough? Can the sole existence of these genetically programmed and programmable systems guarantee a stable order in the body over 40 to 50 years? Or is all this - as in evolution - based on some principle which also explains health and healing?

In 1968, I developed the following answer on the basis of clinical and therapeutic observations and molecular biological data: *the healing and health-preserving power of nature consists of a selection process at the protein-molecular level*[4; 5; 6]. Today, some 30 years later, we have so many facts at our disposal that they can barely be taken in, but nevertheless, many of them appear to confirm the above hypothesis. Since it is my hope to make this theory understandable to the medical profession, which may not be familiar with certain molecularphysiological data, they shall be outlined in the following. Practical medicine is in need of the help of molecular physiology, and I gladly welcome criticism and comments.

Protein Kinetics - Chance or Selection

Life is characterized by two basic phenomena: the fact that it develops over long time periods within populations, and the fact that it is sustained for short time periods in individuals. The preservation of life and health in an individual is a prerequisite for the development of life within populations. The individual must remain healthy to be in a position to produce and rear healthy offspring, amongst whom the selection process then takes place, thus ensuring the survival of the strongest, fittest and the best-adapted to the ambient environment. It is the *preservation of life and health* in the individual which provides the foundation for evolution in the first place.

An axiom of selection theory states that *adaptation is selection*. And selection means differentiating and then selecting. Differentiation takes place on the basis of certain structure-dependent characteristics, depending on whether the individual is adapted or unadapted, young or old and healthy or sick. This selection principle is recognizable throughout the whole of the evolutionary process, and, as I believe, in areas of cellular and molecular activity. When nature performs basic tasks such as the continuous break-down and rebuilding of proteins, it cannot afford to work blindly or on the basis of chance. Only infrequent "accidents" such as the doubling up of the DNA helix that occurrs in the division of cells, can be put down to "chance", as also applies to accidents occurring during other enzymatic processes, such as transcription and ribosomal synthesis. Chance is also at work in the damage created by oxygen radicals and toxic substances. Indeed, being a mono-molecular process, every single denaturating accident exhibits a stochastic characteristic pattern and is random in nature. What is astonishing, however, is the ability of cells to *purposefully* rectify such damage. Disrupted sites on the DNA helix and on proteins are recognized and repaired, whilst intact sites and proteins are left untouched, bracketed off so to speak, and thus selected, so to speak, for survival. One could almost say that *a strategic process of molecular healing and health preservation is at work.*

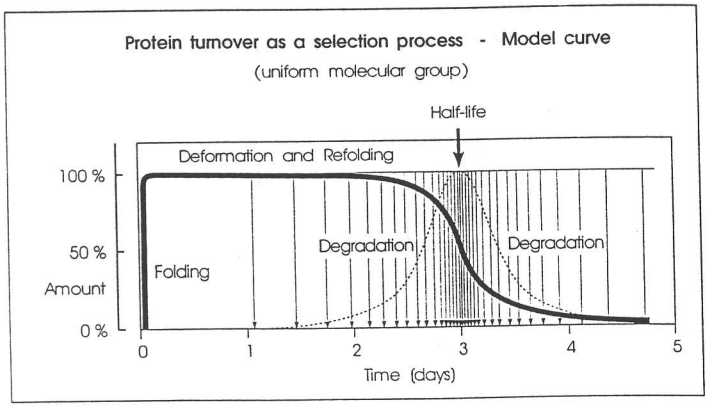
In 1986 I drew a kind of "model graph" (fig. 1) showing the life curve of a *uniform, structurally-intact protein cohort* to illustrate these thoughts. This curve is similar to or the same as the curve for human populations[7], laboratory animals[8], cell cultures[9], erythrocytes and hemoglobin molecules[10] and rhodopsin molecules[11]. After a certain life- and work-span, reflected in the graph by the flattened section of the curve, the aged, structurally damaged, irreparable and malfunctioning proteins are dis-assembled and rejected (as shown in the downward arrows). In other words, newly created, structurally healthy and fully-functioning proteins are *selected* for survival.

In conversations with Hugo Fasold in Frankfurt and Lothar Jaenicke in Cologne (cf. Acknowledgments), these catabolic characteristics have been confirmed to me by two biochemists. Fasold, for example, stated that the exponential curves, as shown in fig. 2, are not correct, explaining that newly-folded proteins are stable and fully functional for long periods, and that it is only later on that proteins are unfolded and destructured at an increasing rate, which confirms the curve in fig. 1. After acquainting themselves briefly with my theory, other biochemists[12; 13] regarded my description as wrong, stating that Poole, Leighton and De Duve had ascertained something different in 1969, namely a kinetics of catabolism, as depicted in fig. 2. The molecular geneticist Nierhaus (cf. Acknowledgments) had the opinion that the denaturation and break-down of proteins displayed a time characteristic that corresponds to the disintegration of radioactive isotopes (fig. 2).

I have long concerned myself with the experimental animal studies conducted by Poole et al 14, which are typical of studies of similar type[11; 12; 13]. Their theory is that *the break-down of a uniform, structurally-intact protein cohort takes place in a stochastic, random manner*, and they regard the elimination of ^{3}H-leucine as a measure of the kinetics of catalase break-down in liver cell peroxisomes, and as being in accordance with kinetics of the first order. Now, if one attempts to assess and interpret this dynamic process of protein construction and destruction as a physician, this chance-determined concept of kinetics (fig. 2) is of very little help since random kinetics only correspond to the elimination characteristics of small molecules, medicine, toxic substances, stains, pigments, the final products of metabolism, and other substances.

The words chance, random, and coincidence enjoy pride of place in the biology of evolution in reference to

Fig. 1: Schematic representation of a postulated „life curve" of a uniform, initially structurally-intact group of 100 protein molecules, unfolded within 10 minutes and remaining stable in structure and functionally intact for a period of two days. This was followed by deformation and refolding, and then by irreparable destruction and degradation in initially increasing and ultimately decreasing numbers (arrows). The concept of this work has been published in Pirlet[4-6].



the many "chance accidents" that happen in the *cells of the germ line*, i.e. mutations in the nucleic acid of the genetic code, thus creating the variations necessary for natural selection. On the other hand, "chance accidents" taking place in the proteins and nucleic acids of the *somatic or mature cells* (if they are not repaired) only result in reduced functioning and premature aging of the cell. Thus evolutionary biology can speak of chance *and* selection working hand in hand. In a descriptive, statistical, time-related observation of protein kinetics, however, the question chance *or* selection has to be raised. In other words, is the break-down of protein a random or selective process, and does protein break-down take place in accordance with the curve in fig. 2[14] or in fig. 1 (as this paper purports).

Arguments Against the Concept of Chance

This question can only be explained by using molecular biological to argue the case. Even Darwin developed his theory of natural selection on the basis of deduction and argumentation, not having a single piece of conclusive evidence to prove its validity (Ernst Mayr[15]). This is how evolutionary biology has had to continue to the present day Karl Popper[16]. However, the proof that has been gathered in the form of circumstantial evidence and argumentation is overwhelming.

On the other hand Poole et al.[14] discovered an elimination characteristic of the first order (fig. 2). Their conclusion, which is still frequently quoted today, is the concept of protein molecular turnover, and states that the break-down of a uniform protein cohort takes place according to a stochastic, random process. According to this concept, the catabolistic systems (involving ubiquitine and proteasome, for example) randomly pick on a single protein molecule at some time in its long period of life and activity between folding and unfolding, and break it down - irrespective of whether the protein molecule is new, structurally sound and fully-functioning, or old, structurally damaged and no longer capable of function. This at least is Poole´s, Leighton´s and De Duve´s interpretation of the exponential curve[14].

My objection in this respect is that if the break-down of proteins were a stochastic, random process, it would gravely reduce the performance capacity of the cell since too many newly-formed and fully-functioning proteins would be selected for rejection immediately after folding. There would be no differentiation, no means of selecting between structurally-intact and structurally-damaged proteins. And in the case of our example (fig. 2), the cell would have to survive another 10 - 20 days with old, malfunctioning molecules.

> This argument can be demonstrated by other means. Let us take the example of a car-manufacturing plant producing 1,000 cars per week. These cars are designed to have a long service life, whereby their mean life expectancy is assumed to consist of ten years, or 150,000 miles, and once sold, are regularly sent in for inspection and repair. Once too many parts start to go wrong, the cars will no longer be worth repairing and will be scrapped and recycled. In other words, the life curve of these cars corresponds to the curve in fig. 1. The same applies to the countless technical systems created, used and improved on by man, all according to the principle of (natural) selection.
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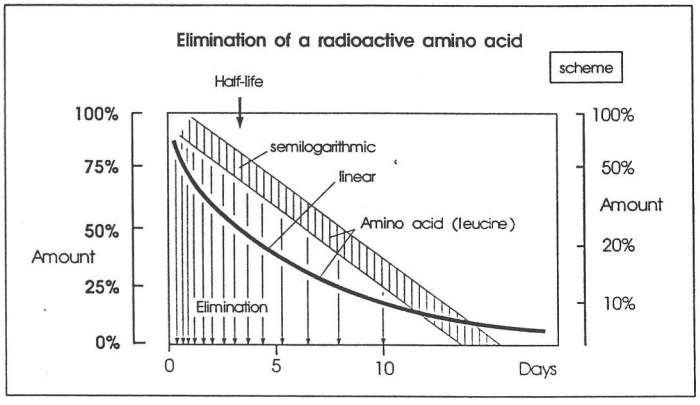
> In other words, the 1,000 cars are not taken off the road in a random, stochastic manner. After all, this would mean that the same percentage of cars per time period - for example 10 percent a year - would be taken off the road annually. This in turn would mean that "healthy" roadworthy cars, almost half of those produced in the first place, would be scrapped in the first five years. This, however, is not how things are done, rather, we "select" roadworthy cars for continued existence by taking the others off the road.

In my opinion, a random form of kinetics does not makes sense when one considers the amazing effort that each cell invests into building billions of protein molecules within a few days by means of transcription, ribosomal synthesis and folding. The continuous process of synthesis requires 250 different types of proteins and 50 different types of RNA, most of which are packaged together in ribosomes. As a statistical average, each type of protein and RNA molecule is present in numbers in the order of 100,000 to 1,000,000 per cell, and each has the sole purpose of providing the cell metabolism with the proteins and, in particular, the enzymes - the active elements of the cell - responsible for everything taking place in and outside the cell. They are the so-called "molecules of life"[17],"the most sophisticated, the most finely devised molecules known"[18]. Are we expected to believe that they are catabolized at random, as shown in the arrows in fig. 2. Biological common

Fig. 2: Random elimination of radioactively-labelled leucine from rat liver peroxisomes. The semi-log plot shows a straight line with scattered individual values (according to Poole[14]). The linear plot shows an exponential curve. The initially higher elimination of leucine molecules is indicated schematically (arrows).



sense forces us to say that this cannot be the case. This raises the question if the findings of Poole et al. could be interpreted incorrectly.

The logarithmic division of the ordinates in fig. 2 produces a straight line, as demonstrated in the elimination of small molecules, while a linear division of the ordinates produces an exponential curve. This is a more intelligible depiction in that the downward arrows illustrate the abrupt catabolism of proteins, which takes place immediately after folding. In the early fifties, I investigated the elimination of pharmacological substances and plotted the results with similar straight lines and curves. The question is thus whether Poole et al. only determined the elimination of ^{3}H-leucine, as I shall attempt to prove as follows.

To this end I have drawn up fig. 3 to demonstrate what happens to a radioactive amino acid on the intracellular level. In this case, ^{3}H-leucine is introduced intraperitoneally and is integrated into all proteins of the test animal, as in the liver cells in the catalase molecules of the peroxisomes, for example, after resorption. This is known as pulse marking, although without the subsequent flushing out of the tracer - which would have been essential. Long-lived proteins (top) and short-lived proteins (bottom) both take up leucine. However, before the first long-lived protein is catabolized, numerous short-lived proteins have previously returned their leucine to the cytosol, i.e. to the leucine pool from which the ribosomes withdraw the leucine needed for the construction of new short-lived and new long-lived proteins. Furthermore, the leucine released later on as a result of the break-down of long-lived proteins is integrated into new long-lived protein molecules; in other words, there is a great deal of leucine recycling. As a result, the type of protein under test will be detected by these tracer amino acids long after the catabolism of the original proteins has taken place. In fact it will be detectable for 10 to 20 days until the tracer amino acids have been washed or metabolized out of the cell. This explains how elimination straight lines and elimination curves come about, thus demonstrating first order kinetics (cf. fig. 2).

> The recycling of ^{3}H-leucine could have been partially prevented by applying a surplus of non-marked substance after injecting the marked substance, i.e. by attempting to "wash out" the ^{3}H-leucine in a process known as pulse and chase. If this had been done, the elimination curve would have dropped more steeply after about two days - at a shorter half-life value - and would have taken on a similar time structure as shown in fig. 1. This questions the methodic approach taken by Poole at al. and explains the detailed portrayal of the recycling process in this chapter and in fig. 3.

Another aspect is that an adult human synthesizes around 400 - 500 g protein daily. This is ten times the amount of protein ingested per day, and is another indication that more than 90% of the amino acids released during protein catabolism are recycled, i.e. are repeatedly reprocessed into proteins during ribosomal synthesis. The curves and straight lines as depicted in fig. 2 are therefore not a pertinent measure for the half-life of a particular protein population, and are by no means evidence of the fact that protein catabolism is random in character.

> Not a single biochemical or molecular biological textbook refers to the experimental studies performed by the de Duve group, and no statements are to be found on this "concept of protein molecular turnover", either. Admittedly, Bohley recently described "the fate of proteins in cells"[13], but only with regard to the development and break-down processes taking place within seconds or minutes. Nothing is said about the "fate" of the proteins in the thousand times longer period between folding and unfolding, yet it is precisely this period during which the proteins perform their actual task that is of interest to the clinical physician while being the main concern of this paper.
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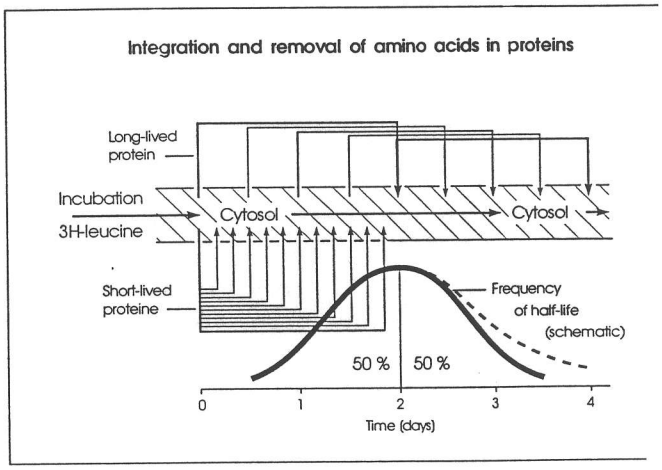
> Frequent attempts have been made to describe the characteristics of protein break-down in human and animal cells[11; 13; 19], but none take important cellular physiological conditions into consideration. The same criticism as I have expressed with regard to the theories evolved by Poole et al.[14] applies accordingly. Despite washing, it is impossible to avoid the recycling of an applied test substance. The examination methods employed are sometimes so artificial and non-physiological that the findings cannot possibly be applied to smoothly functioning cells. Admittedly, the individual laboratory data may be correct and capable of interpretation within the respective experimental conditions, but they do not supply applicable information on the break-down kinetics of proteins in the human organism.

As yet, I have been unable to find confirmation of the study results and theories of Poole et al.[14; 20] by means of another, incontestable methodology, and in the va-

Fig. 3: Diagram showing the integration and removal of radioactive amino acids in short-lived and long-lived cell proteins.



rious conversations I have conducted with experts in the field, "opinions" and "assumptions" were expressed, but no explanations. *In my opinion, no experimental evidence exists that proves that uniform, structurally-intact protein groups in living cells are catabolized according to the principle of chance.*

A Case for the Selection Model

The alternative to the above is to seek explanations on the basis of established molecular biological facts, some of which shall be *repeated* (as in the case of Poole´s work) *in order to present them from a different angle and piece them into a new picture.* The following ten points help clarify the arguments in favor of the selection model and a kinetics of catabolism as shown in fig.1.

4.1 Average life expectancy, i.e. the half-life of a particular protein group, is determined during ribosomal synthesis. All the members of a given group have the same sequence of amino acids and the same amino terminal groups. The average life-span of these proteins is pre-programmed, in a manner of speaking; indeed, one could almost talk of protein clones. Lifetime differences in each respective protein group result from the differing intensity of oxidative or age-related damage to individual molecules. If one were to plot the life span of 100 identical structurally-intact molecules (all folded within only a few minutes), the result would be a life curve similar to that in fig. 1. In my view, this is an extremely crucial argument. The long term preservation of structure and function, however, is also assured by the high initial stability of the proteins and by the continuous repair work performed by the chaperones (sections 4.3 and 4.6).

During ribosomal synthesis, however, the polypeptide chains sometimes receive the wrong amino acids. These polypeptides are useless as they cannot be folded into tertiary structures, and are quickly and purposefully catabolized in a stochastic manner as the exponential curve on the left of fig. 1 demonstrates. Molecular biologists talk in this respect of the "infant death" of proteins[13]. The vast majority of polypeptide chains, however, are folded into stable, structurally sound and fully-functioning proteins, and it is the fate of these intact protein groups that is the concern of this paper.

4.2 Proteins demonstrate a high degree of flexibility. The peptide loops *rotate* around their longitudinal axis billions of times per second at an angle of 20 to 50 degrees[21], enzyme proteins *pulsate* depending on their alternating frequency at anything from 100 to 100,000 times per second, with conformation changes in the picometer and nanometer range, and they also *vibrate* millions of times per second under the thermodynamic bombardment of ATP and other small molecules in the cytosol[18]. Each molecule has to cope with and coordinate this range of movement[21]. If the peptide loops are damaged by oxygen radicals or by outer valency binding to foreign molecules, the coordination is disrupted. The bonds in the core sections of the protein molecules loosen and *the damage increases,* bringing about an increasing loss of stability. In combination with the effect of ubiquitine this results in the abrupt, lightning-fast break-down of the protein molecule, as confirmed to me by[22; 23] and Fasold (cf. Acknowledgments), and depicted in fig. 1.

4.3 Proteins are subjection to a constant process of alteration. For example, they are increasingly destabilized by high-frequency rotation, pulsation and vibration (cf. 4.2) and are deformed by oxygen radicals, toxic substances and the toxic products of the body´s own metabolism, as occurring during inflammatory processes. A repair system consisting of the chaperones[23; 24] brings the proteins "back into order" *in vivo*, i.e. in the cells, thus preserving their functionality. This repair work is another argument that speaks out against the strict exponential kinetics as depicted in fig. 2. This is because the restoration of structure and function can only be expected in the case of young, stable proteins but hardly in that of aged, destabilized and more or less denaturated proteins, thus providing a further argument in favor of the postulated flattened section of the curve in fig. 1.

Despite much criticism, I shall not refrain from referring to the "repair of proteins". *Reparare* means to reconstitute, replace, renew and rejuvenate. In the DNA helix, the correct sequence of bases is crucial. If the helix is damaged, the piece is "replaced or renewed" in a process referred to as DNA repair. In the case of proteins, it is the right conformation which is vital. If a protein molecule is deformed (by heat, expansion, toxins, etc.), the correct conformation is "reestablished" by stress proteins, heat-shock proteins or chaperones (for an overview, cf.[25]). Chaperones hold proteins together, and bend and form the proteins back into shape; i.e. they literally "rejuvenate" them. I regard chaperones as performing "repair appropriate to the protein molecule", similar to DNA repair, but would not go so far as to talk of repair proteins. On the other hand, the proteins are not "protective" either, in that they do not protect the protein from heat, stress and other factors. Rather, they remove the effects caused by these factors; in other words, they repair.

4.4 In recent years, many papers have stated that *only or mainly* molecules which are deformed, irreparably damaged and past all use are catabolized[12; 13; 18], whereby "mainly" refers to 50 percent or perhaps 60 to 80 percent of the proteins. As Sies puts it, they are "taken out of circulation"[26; 27].

The latest edition (1995) of the standard work *Molecular Biology of the Cell* (Alberts et al.) talks of "selective

proteolysis" and "selective protein turnover", whereby "selective" is understood as referring to the purposeful sorting, exclusion and removal of denatured and non-adapted proteins. In this respect the "selected" proteins are the ones "chosen" to survive. In other words, the process entails one of making room for the chosen proteins, and it is in this regard that the evolutionary biologist understands the term selection.

This is also the place to mention what is known as pre-programmed cell death, or *apoptosis*. Is apoptosis a form of „selective cytolysis"? After all, cells and cell populations are degraded because they are old, damaged or no longer required (as in the case of lymphocytes). This therefore raises the question as to whether apoptosis should also be regarded as a form of (expedient) selection in the sence put forward by Darwin.

The cell, although it is not wholly understood how, recognizes structural defects on protein molecules. As a result, ubiquitine proteins are attached to the proteins, and cell deconfiguration builds up as a result, whereby some protein molecules are unfolded and broken down by protease enzymes, while other proteins, and protein complexes, are subjected to lyosomal catabolism. None of the above accounts indicate *undifferentiated random catabolism.* The graphic depiction of a kinetics of catabolism of this type would produce a life-curve equal to that of fig. 1, but not the random curve plotted in fig. 2.

4.5 In 1989, the Nobelist Christian de Duve wrote that the cell digests its own building blocks - the proteins - and that these "autophagic processes keep the cell young and make it adaptable. Thanks to this continuous turnover, which constantly replaces old cell components with new ones, the cell approaches the ideal of eternal youth." It is precisely this concept that I am trying to put across in this paper. *Adaptation equals selection*, whether at the protein-molecular level or elsewhere. Aging, as de Duve points out, requires the passing of time, and it is only over time that damage is able to build up. In the case of proteins, functional capacity declines as the protein molecule reaches old age, is recognized as such and removed from circulation. Structurally-intact, fully-functioning proteins are formed on a continual basis, but they are *not immediately catabolized*; rather, they are "selected" by the withdrawal of old, dysfunctional proteins. *Selection, and not chance, is the principle that lies behind this dynamic turnover.*

According to evolutionary biology notions, particularly with regard to the concept put forward by the Nobelist Manfred Eigen[28; 29], selection was the decisive principle of the early biomolecular realm four billion years ago in that nucleic acids, the carriers of genetic information, and their active partners, the proteins (the so-called ribenzymes), displayed differences with regard to performance and stability. The factors variation and selection were and still are the motors of cell development, complete with its optimized and complicated interplay of the nucleic acids, which carry information, and the proteins, which perform the tasks involved. Evolution is impossible without genetic selection, but it is also impossible without selection on the protein-molecular level.

4.6 In publications, text books and personal discussions (as with Fasold, cf. Acknowledgments) biochemists and molecular biologists repeatedly refer to the premise that protein molecules are *extremely stable* once they are folded into correct tertiary structures[1; 3; 18; 30; 31; 32]. Indeed, de Duve has written that "the tissue of life" (in reference to proteins) "mainly consists of very resistant molecules, which are as stable as polystyrene or polyvinyl chloride; biological break-down cannot be entrusted to some random, spontaneous process." In this view, we are not dealing with the immediate, random break-down of newly-folded proteins, and thus not with kinetics of the first order. This would mean, however, that denaturated proteins, namely the ones destabilized at a later point (!), are preferred for break-down. This in turn indicates a form of kinetics as found among human and animal populations, cell cultures and in erythrocyte, hemoglobin and rhodopsin (Section 2).

The well-known studies conducted by the recently deceased Nobelist Christian Anfinsen prove that protein molecules display a great deal of stabilizing power in that proteins broken down and denaturated by mechanical, thermal and chemical alteration return of their own accord to their old conformations and activities in a physiological milieu. In other words, protein molecules display an amazing drive with regard to optimal structure, performance and stability. This demonstrates the fundamental difference between the "finely devised" molecules of life, and "quasi dead" small molecules (catabolites, medicine, radioisotopes). Moreover, small molecules are discarded without exception according to a stochastic pattern - in other words, according to the kinetics of the first order as illustrated in fig. 2.

Recent work[22; 23; 33] shows that protein molecules are not as "PVC-stable" as previously assumed. Although it is true that proteins maintain their structure, and hence their functions, for hours and days, they live at the *margin of this stability zone.* Disturbing influences weaken the internal bonding of the protein molecules, leading step by step to destabilization and in some cases to break-down. Physiological influences, as exerted by improving and optimizing intracellular trophic conditions (as described by Anfinsen), are sufficient, however, to re-stabilize unstable protein molecules. This "flexible endurance" of the proteins at the limit of instability has apparently been interpreted to date as "stability", but the fact of the matter is that proteins age nevertheless, although damage is repaired or tolera-

ted for a certain time. Depending on the amino acid sequences involved, half-lives or average life-spans of hours and days are achieved in this way. This "labile stability" appears to be a precondition of the fact that suitable physiological influences, such as tension, pressure, deformation, heat, stimulation, functional intensification and irritation (and influences of this kind applied in the course of medical treatment), lead to the ultimate destabilization and preferential break-down of mainly aged and damaged protein molecules, thus resulting in the "selection" of young, structurally-intact proteins (fig. 1).

The birth and death, or folding and unfolding, of a protein molecule[18], takes only seconds, possibly minutes. Hours and days (2,000 to 3,000 minutes as a statistical average) lie between these two events in which the proteins fulfill their special tasks, depending on whether they are programmed as enzyme, canal or receptor proteins. During this time span, the functional power of the proteins determines the performance of the cell and keeps it in good working order. This leads to the conclusion that nature aspires to achieve a maximum of protein-molecular performance in each and every cell, namely by a combined strategy of maintaining the initial stability of the proteins, repairing them and, above all, by precisely selecting structurally-intact and hence fully-functioning proteins for survival.

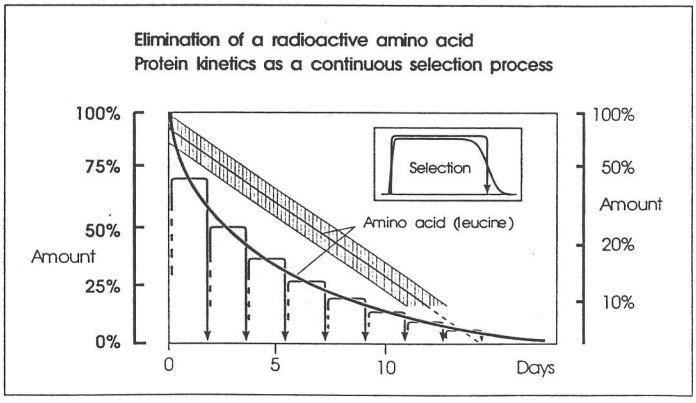
4.7 The *aspect of economy* is also worth touching on at this point. Over the course of billions of years, nature has learned to use no more than four letters to specify the way in which in every cell, 20 amino acids are linked in special sequences to form 10,000 different types of proteins, namely by means of transcription, followed by translation, ribosomal synthesis and folding. After synthesis, continuous efforts are undertaken by the cell to repair any damage to these proteins. In addition, each cell possesses the fascinating ability to employ reversible phosphorylization to tell each individual enzyme molecule again and again whether to remain passive or become active. Biochemists who believe in kinetics of the first order and the abrupt initial catabolism of these proteins, concede that this random break-down "is very uneconomical", but since it has been proved experimentally, do not question it. The "concept" of random protein catabolism (in the period between folding and unfolding) has been adopted universally, and thus only the half-lives are determined.

My response is to point out that economy is the highest quality in natural orders, and that if we do not recognize this economy for what it is, we simply do not understand what is going on. Either the measurements are incorrect, or we have not reasoned out the interrelationships involved. Nature always penalizes uneconomical systems by discarding them[34]. *Natural selection expresses this economy.* After all, selection means economical use of these "molecules of life", this evolutionary tools.

4.8 Of course, one could argue that this is simply a case of *opinion versus opinion,* so it is reiterated that the exponential curve and the straight line in fig. 2 demonstrate nothing of the break-down of proteins over time, but simply show that a sequence of amino acids is discarded or metabolized. No single argument or experimental finding supports the idea that protein catabolism is stochastic and random in character. There are, however, many arguments in favor of the selection model of protein turnover, as demonstrated above. If it is accepted that the exponential curve in fig. 2 is the elimination curve of an amino acid (such as leucine), it follows that this exponential curve concurs with my plot of a selection curve (in fig. 1), as fig. 4 tries to show. Selection kinetics can be simplified, as the rectangle at the top right of this illustration demonstrates. Every minute and day, new cohorts of a certain protein are first synthesized, and then catabolized after a period of two days. The cohorts synthesized at a later date only have a small fraction of the initially applied amino acid at their disposal, and shrink in size. Therefore, the elimination kinetics of the amino acids and the selection kinetics of the proteins are in no respect contradictory.

4.9 To put forward an *evolutionary biological line of thinking,* the geneticist Theodosius Dobzhansky[35] once said that "nothing in biology makes sense if it is not viewed in the light of evolution". Medicine and molecular physiology are biological sciences, and it is the diversity of the environment and the major *long-term changes* in the circumstances of life that make evolution possible in the first place.

Fig. 4: Diagram showing elimination of an applied amino acid and protein selection from a uniform protein group (for more information, see text).



Changes in food sources, climate and many other factors make populations adapt by favoring the best-adapted individuals. This "environmental pressure" or "adaptation pressure" can be sufficiently powerful to initiate significant evolutionary steps. This type of continuous selection, which imparts direction and leads to further development, is referred to as *evolutionary selection.* However, if the average conditions of life do not change for long periods (one of many possibilities), the affected populations will not undergo major developmental steps, but nevertheless, the process of continuous selection ensures the preservation of the population or species. In this respect we speak of a stabilizing or *preservational form of natural selection* (Ernst Mayr 1979).

The *preservation of the individual* is analogous to these processes, albeit over a relatively short period. Again, the necessary selection is apparent in sub-units and components, but not in organs or cells, but in the protein turnover of every cell, including the cells that are formed only once in a lifetime, such as brain, heart and muscle cells. Evolutionary steps are not possible in mature organisms and somatic cells; rather, they are restricted to the structural and functional aspects of the program which is laid down in the zygote and transferred to every descendant cell. In the short lifetime of an individual it is *these short-term changes*, the "oscillating effects" of the environment, that accelerate the removal of aged proteins and embody the pressure to select structurally-intact proteins. These effects impinge on us continuously and cannot be avoided.

In general these effects consist of all function-intensifying and stimulating influences, such as nutrition, weather, heat, cold, movement, pressure, tension, light, all forms of neural, spiritual and intellectual activation, and every cellular and molecular emergency situation. These factors result in strong and enduring conformational changes in the protein molecules (abrupt protein stress, and heat shock are known phenomena in molecular biology). Damaged, aged or denaturated proteins are not capable of withstanding these induced conformational changes, and are catabolized as a result. In contrast, *stable and structurally-intact, i.e. fully-functioning, proteins are selected by this process.* These are the influences under which, for millions of years, individual life has been able to maintain itself for a limited time span, and it is these influences that physicians working with natural treatment methods use in a purposeful and measured manner to re-establish and preserve health. Such *natural healing methods* include dietetic treatment, climatic therapy, hydrotherapy, thermotherapy, kinetotherapy, psychotherapy and non-specific stimulation therapy.

4.10 *Medical and therapeutic aspects.* In the light of the above, it is likely that the physician will arrive at the following insights and conclusions, namely that it is selection, *the pressure and power of selection at the protein-molecular level*, that enables the preservation of life and health, and healing in accordance with natures intention. Assuming this to be the case, the body has a daily fundamental need for function-intensifying and stimulating influences. All subsystems in the body need to be used according to their nature, and indeed demand that increasing claims be made on their functional capacity. This includes the acceleration of protein turnover as a principle of selection, and this molecular selection and renewal process is the key to good health and healing. If a stochastic process were at work here (as Poole and colleagues claim), physiotherapeutic and dietetic measures would not have a healing or health-preserving effect.

It is solely this concept of selection that provides an explanation of how dietetic therapies, physiotherapies and natural healing methods work; indeed, we no longer need to refer to nebulous concepts such as the "power of self healing" or "self-regulation". It is to be hoped that these insights into evolutionary biological and molecular physiological interactions will give orthodox medicine reason to consider the body of thought behind naturopathy. *Natural healing is a natural science,* the science of man as a manifestation of nature, and natural therapeutics are a form of treatment appropriate to man as a natural being.

Conclusion

To come to a close, it must be admitted that I have painted a simple picture, using a palette made up of well-known facts. This section is therefore mainly intended for readers without a background in molecular biology, and in particular for physicians. After all, anyone wishing to form a founded judgment on the concept outlined in this paper must first become acquainted with all the pros and cons of the argumentation.

All the work performed by the organism, such as the work of the organs and regulatory systems, and every single type of communication between cells and organs, be it endocrinic, paracrinic or neural, indeed, even the production of extracellular structures, is done by cells. Two macromolecules, namely nucleic acids and proteins, are the powerhouses of the cells in that they determine cell structure and function. The functional and regulatory quality of larger superordinate sy-

stems (such as the heart, liver, kidneys, nervous system, immune system and others) depends on these two molecules. Nucleic acids in the form of the DNA double helix contain the program. This program is scanned, but the DNA helix itself remains passive, and if damaged, is repaired with incredible precision.

Proteins are the active elements of every cell. Young, newly-formed proteins are stable, and although they are continuously destructured and deconfigured, a repair system restores them to their original shape and working order. However, not all damage can be repaired, and an aging process sets in, with the result that the proteins become unstable and their activity declines. Days or hours later, they are catabolized and replaced by structurally sound, fully-functioning proteins, all in a continuous process of repair, a constant whirlwind of dismantling and reconstruction. Selection - *the selection of young, structurally-intact and fully-functioning proteins* - is the superordinate principle of this activity. Improved molecular quality of the cell is associated with improved functional quality, which is how nature maintains the special capabilities of every single cell at a high level. This applies equally to brain, cardiomuscular, liver, mesenchyma and even immune cells. In this way, *each individual cell is enabled to perform the tasks specified by its DNA information headquarters*, and is thus able to play its role in the cell system. The same applies conversely, and is so obvious to be almost banal: An organic or regulation system depends on the molecular integrity of its elements, i.e. on the functional quality of every cell, thus presenting physiological research and experimentation with the task of explaining how various factors (nutrition, movement, warmth) are able to influence this protein-molecular process of selection.

A short digression will now be made to discuss the spontaneous and natural healing of pathological states. Every cell in the body contains the complete genetic program of the zygotes resulting from the union of sperm and ovum. The development of the differing forms and functions of molecules, cells and organs, indeed, of a whole life in all its individuality, is laid down in this stem cell, as effectively demonstrated by the phenomenon of identical twins.

The genetic program also determines how cells and organs react in cases of injury, bacterial assault, additional strain, wound healing, inflammatory resistance, adaptive tissue changes, and other pathological and healing states. The way in which these tasks are performed by a functional system depends on the protein-molecular equipment of the cells involved.

One of the special concerns of physicians engaged in the practice of natural methods of treatment is to ensure - with the patients help - that the cell systems are in optimal molecular condition. This is done by ensuring the adequate supply of all required nutrients, the avoidance of exogenic, intestinal and intermediary intoxication, and by guiding selective molecular turnover in every organ and cell by means of physiologically appropriate natural forms of treatment. Apart from dietetics, these involves rest, movement, heat, cold, and guidance on an emotional, mental and spiritual level.

To return to the question addressed at the beginning of the paper, how does nature keep man healthy? How does it eliminate structural and functional disruption? Once again it is answered: by dynamically replacing the basic molecular building blocks, the proteins, or to be more specific, by *solely or mainly* replacing old, denatured proteins that no longer serve a specific task in the cell. *Selection is the principle* which keeps us healthy and helps us regain health when we are ill. The much-praised "healing power of nature" is nothing other than a protein-molecular selection process. One is tempted to say that we are predestined by nature to be healthy, for we are "reborn" daily to new health and vigor. Death is unavoidable, however, because not all damage sustained by the DNA helix - the central information source - can be rectified. In other words, we age to the stage where we eventually die.

The concept of life stands on two pillars, namely the preservation of life (and health) in individuals, and the evolution of life in populations. If health preservation had no time limit, evolution would not take place. No matter which phenomenon of life is concerned, *nature follows the principle of selection*. The enormous dynamics of protein anabolism and catabolism can only be explained by the process of natural selection. Without selection at a protein-molecular level, life as we know it would not exist.

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Nachruf

Hasko Grünberg, 1. Vorsitzender des EU.L.E. und Gründungsmitglied, lebt nicht mehr.

Hasko Grünberg starb auf der Autobahn bei Stuttgart, am 21. November 1997, zusammen mit zwei weiteren Menschen, die schuldlos in einen absurden, unnötigen und grausamen Unfall verwickelt wurden. Mit ihm ist ein Freund von uns gegangen, der es auch in diesen Zeiten verdient hat, Mensch genannt zu werden. Wir werden immer und gerne an ihn denken.

Hasko Grünberg war ein kommunikativer Mensch, einer, der Verbindungen knüpfen konnte, der vieles und Sinnreiches dadurch bewegte, daß er die richtigen Menschen zur rechten Zeit am richtigen Platz zusammenbrachte. Seine weltweiten Erfahrungen und Geschäftsbeziehungen von Südafrika bis Japan sowie seine bescheidene Art ermöglichten es ihm, Weitblick und Perspektive mit dem maßvollen Blick auf das Mögliche, Machbare zu verbinden.

In der Gründungsphase des EU.L.E. und in seiner Tätigkeit als Vorstand seither war ihm einiges zu verdanken, was aus unserer Gemeinschaft nicht mehr wegzudenken ist. Seine Verbindungen eröffneten uns viele der Perspektiven, die wir heute verfolgen.

Hasko Grünberg war ein zurückhaltender Mensch. Er trennte berufliches und privates Leben, er war immer Freund und gesuchter Ansprechpartner, wenn es um wichtige Entscheidungen ging. Sein Rat war wohl abgewogen, sachlich und präzise. Die grausame Tatsache, daß Hasko Grünberg im Zenit seines Lebens und Arbeitens durch diesen unverschuldeten Unfall von uns genommen wurde, wird uns stets daran erinnern, daß wir selbst verletzlich und sterblich sind.

für das EU.L.E.: Fritz Schlecht • Udo Pollmer • Ulrike Gonder