International

Mitochondrial Medicine

Association


Energy
mitochondria

Mitochondrien

1856 Kolliker entdeckte rundliche Gebilde entlang der quergestreiften Muskelfibrillen

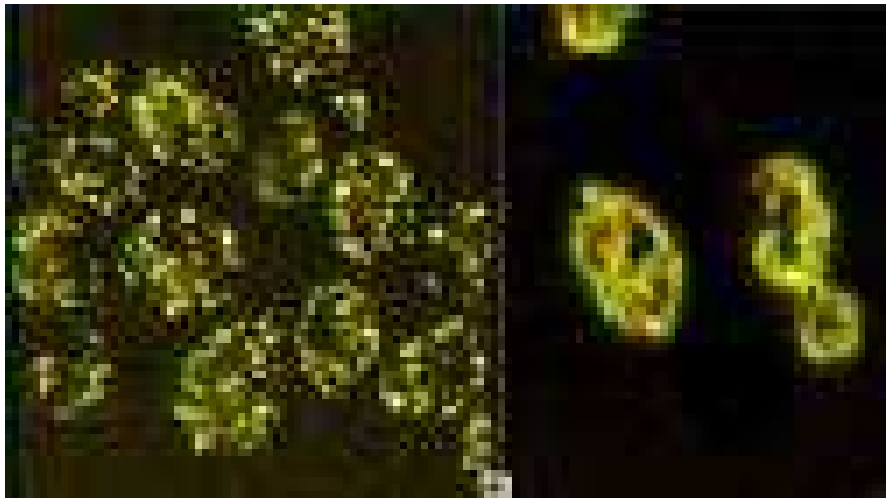
1898 Altmann: Mitochondrien stammen von Bakterien ab (äußere und innere Membran)

2 Billionen Körperzellen (2×10^{12})

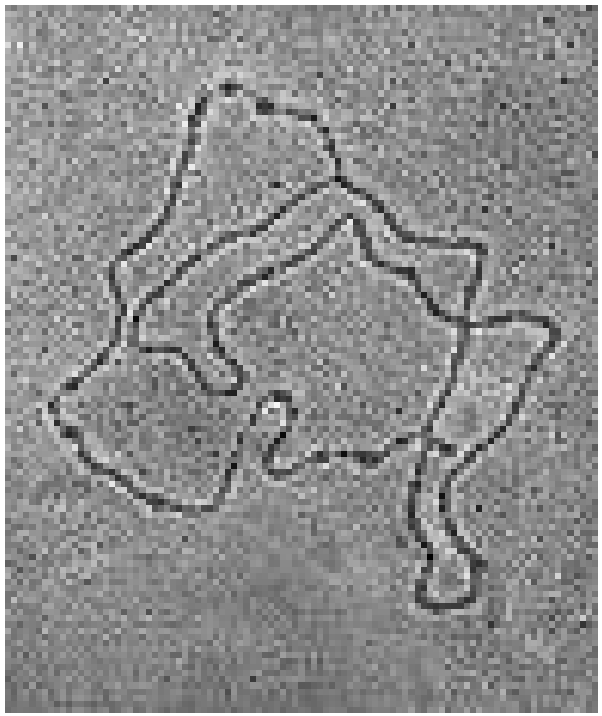
2.000 Billionen Mitochondrien: 70 kg ATP pro Tag gigantisch!

1972 Tandler: Genom ist ringförmig

1988 Margulis: Endosymbiose: räuberischer Zielangriff



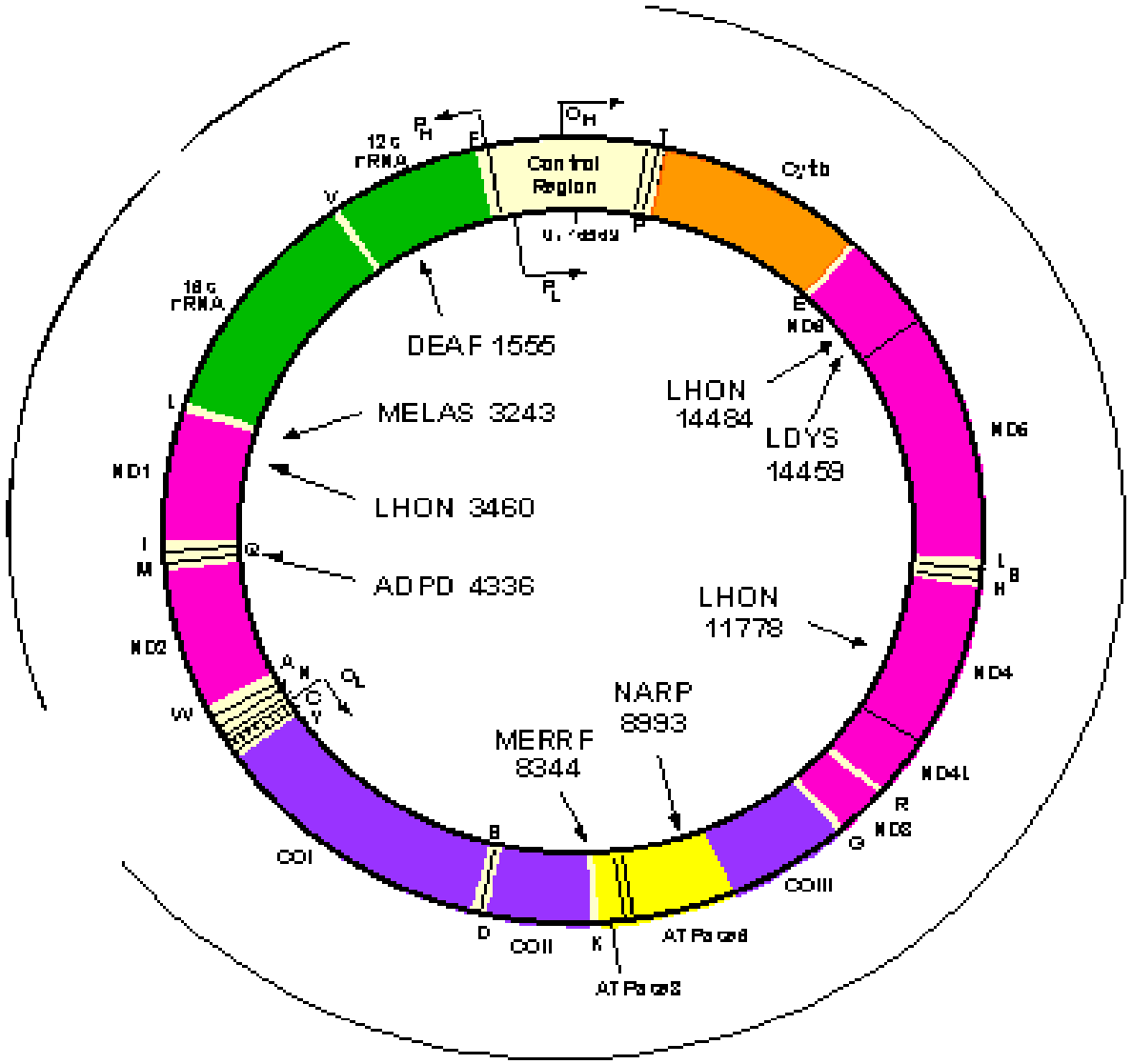
Mitochondrial DNA &
ribosomes yeast



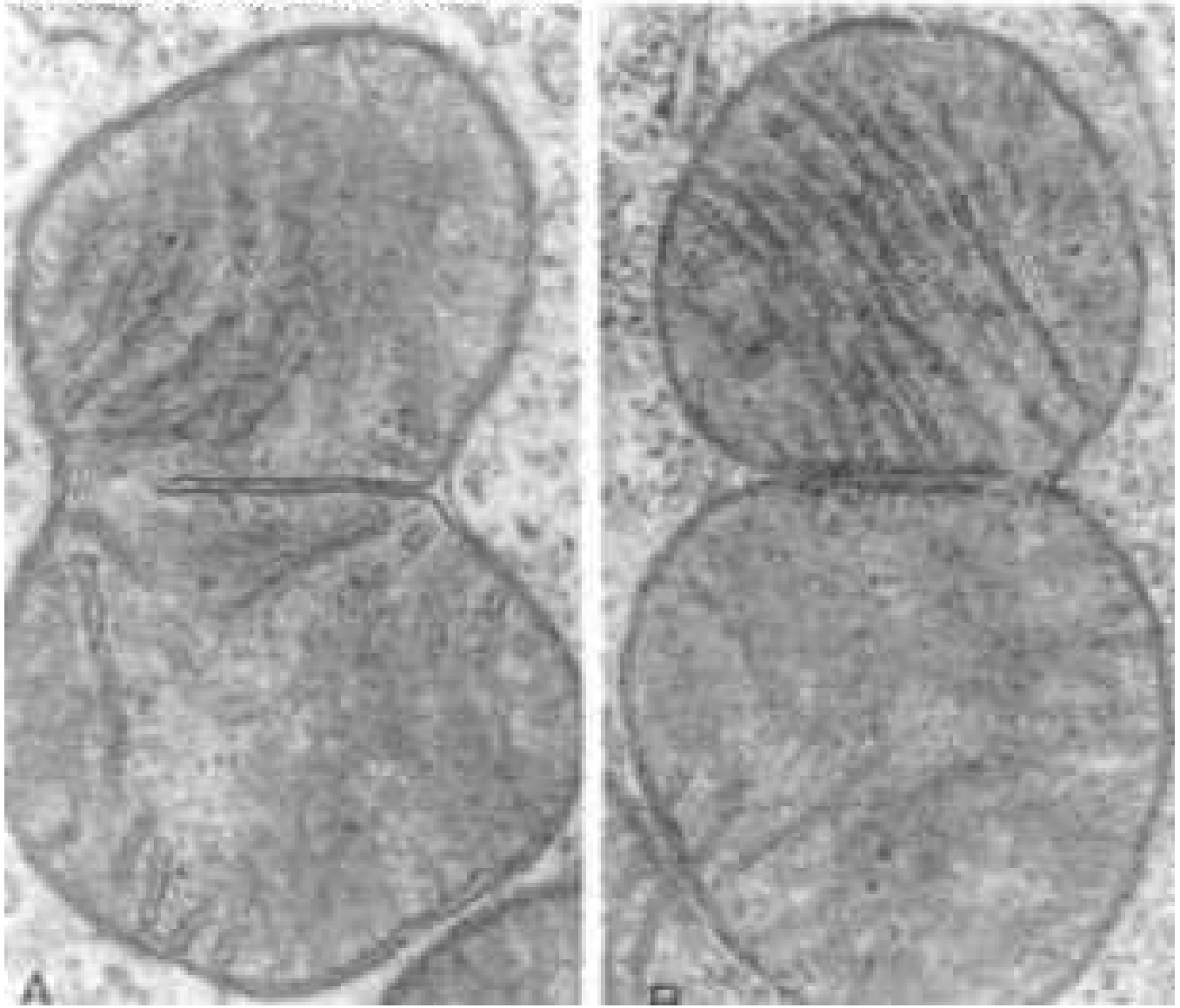
Replicating
Mitochondrial DNA

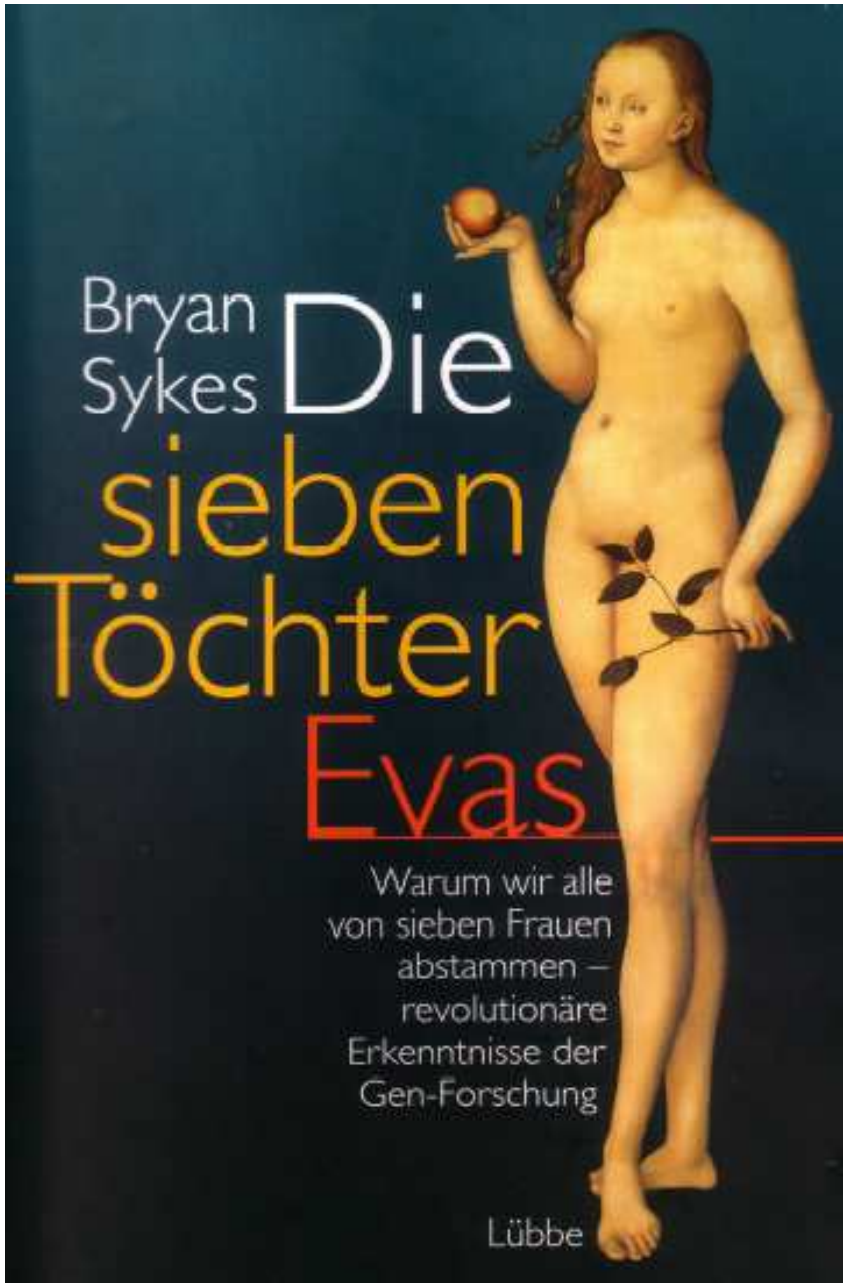
xxxxx

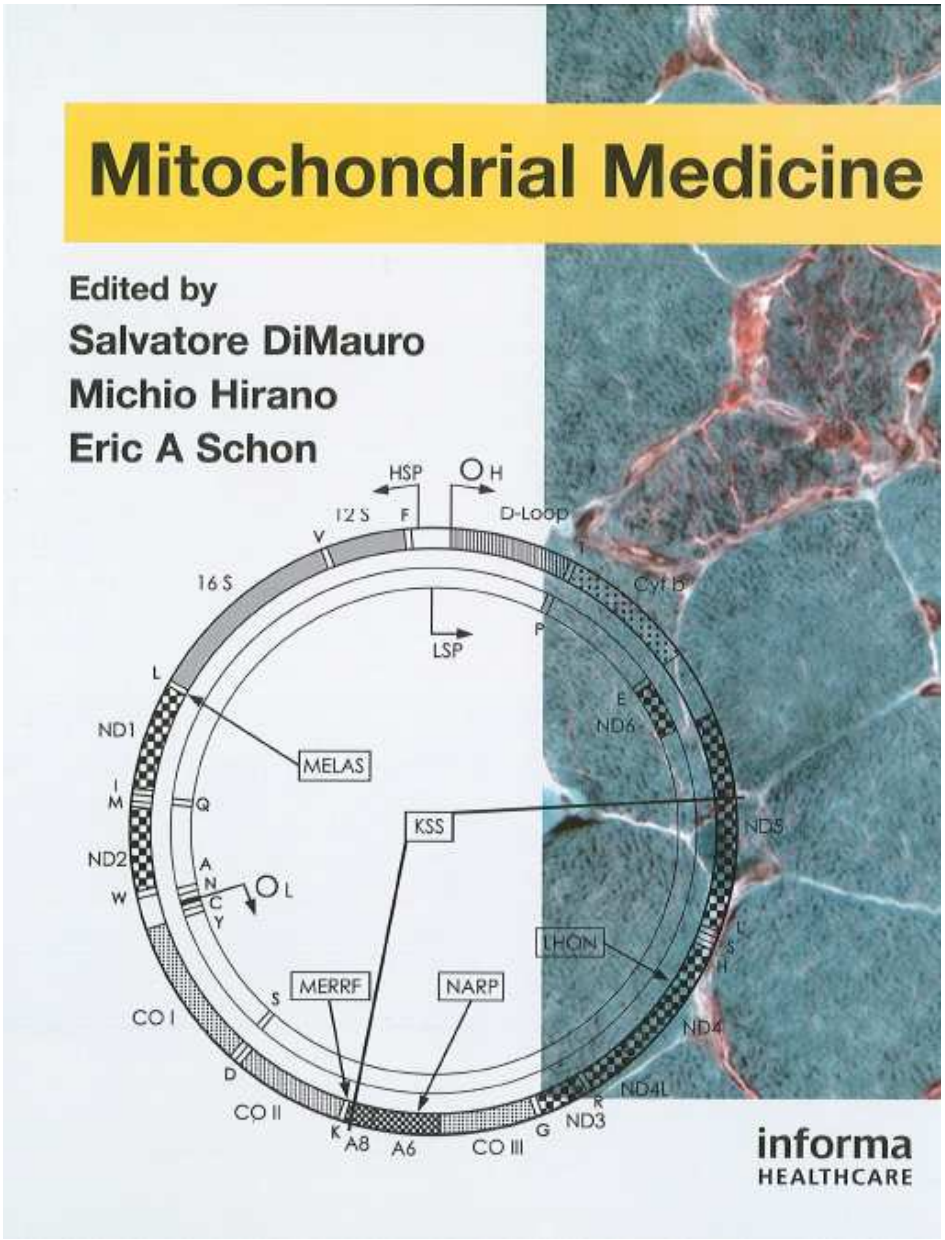
Mitochondriale DNA und mitochondriale Erkrankungen



Teilung von Mitochondrien




Bryan Sykes
Die sieben Töchter Evas
Warum wir alle von sieben Frauen abstammen – revolutionäre Erkenntnisse der Gen-Forschung
Lübbe



Mitochondrial Medicine 2006

Edited by Salvatore DiMauro, Michio Hirano and Eric A Schon

Mitochondrial dysfunction is increasingly being recognized as the basis of a wide variety of human diseases. Emphasizing translational research, this pioneering book is primarily directed to a clinical audience interested in the diverse and diagnostically challenging clinical presentations of mitochondrial diseases and their pathophysiology.

This text provides an authoritative update of our current knowledge on mitochondrial medicine, drawing together world authorities from various fields. In addition to a chapter on general therapeutic strategies, treatments presently available in the different specialties are discussed; as such, this book is essential reading for clinicians involved with the management of patients with mitochondrial diseases.

Two aspects distinguish this book from the few available works on mitochondrial diseases. First, mitochondrial textbooks have been devoted mostly – if not entirely – to neurology; while the special vulnerability of the nervous system to mitochondrial dysfunction is recognized by four chapters dedicated to the central nervous system, the peripheral nervous system and muscle, psychiatry, and neurodegenerative diseases, and there is ample discussion of other specialties, including cardiology, ophthalmology, otology, nephrology, gastroenterology, hematology-oncology, and reproductive medicine. Second, there are no chapters on basic science, which are often intimidating to clinicians: rather, the salient concepts of mitochondrial biogenesis and genetics are presented in vignettes peppered throughout the text and related to specific questions raised by the disease under discussion.

Edited by

Salvatore DiMauro MD
Lucy G Moses Professor of Neurology, Department of Neurology, Columbia University Medical Center, New York, NY, USA

Michio Hirano MD
Associate Professor of Neurology, Department of Neurology, Columbia University Medical Center, New York, NY, USA

Eric A Schon PhD
Lewis P Rowland Professor of Neurology, Department of Neurology, Professor of Genetics and Development in Neurology, Department of Genetics and Development, Columbia University Medical Center, New York, NY, USA

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www.tandf.co.uk/medicine

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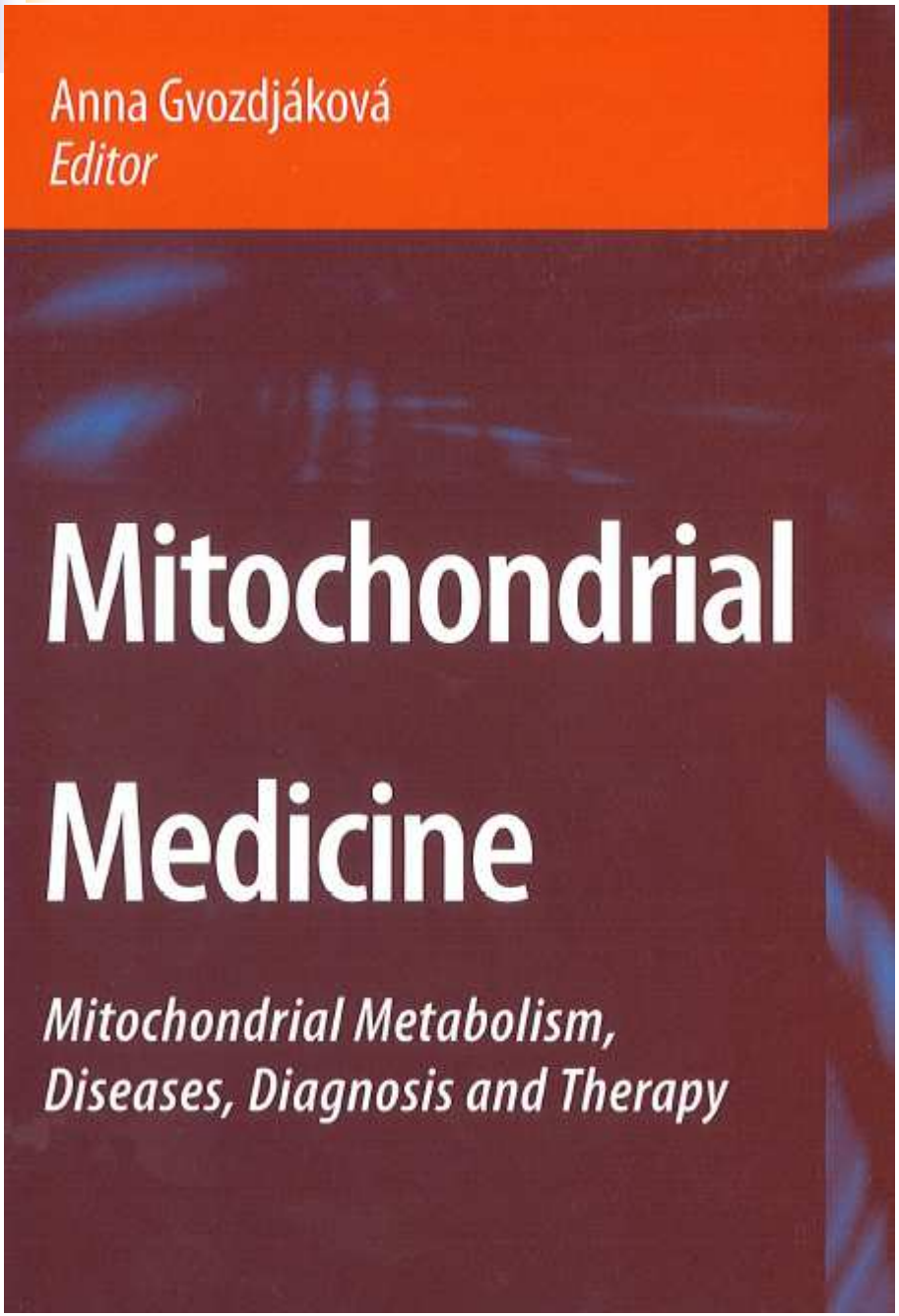


Anna Gvozdjáková
Editor

Mitochondrial Medicine

Mitochondrial Metabolism, Diseases, Diagnosis and Therapy

2008

Mitochondrial medicine is a relatively new area where several disciplines from basic science to clinical medicine converge. Mitochondrial medicine deals with diseases that are related to mitochondrial dysfunction due to a number of causes from free radical damage to genetic mutation. A primary feature of mitochondrial dysfunction is impaired cellular bioenergetics.

This book is based upon extensive data gathered over 30 years of clinical and experimental research. Internationally recognized authors share their experience and state-of-the-art knowledge in various fields of their expertise such as mitochondrial cardiology, neurology, diabetology, nephrology, immunology, rheumatology, reproductive medicine, sports medicine, and chronobiology, and guide readers through the disease process, from basic biochemical mechanisms to diagnosis to therapeutic aspects. Adjunctive therapy includes coenzyme Q_{10}, α-lipoic acid, carnitine, ω-3 and ω-6 PUFA, vitamins and polarized light.

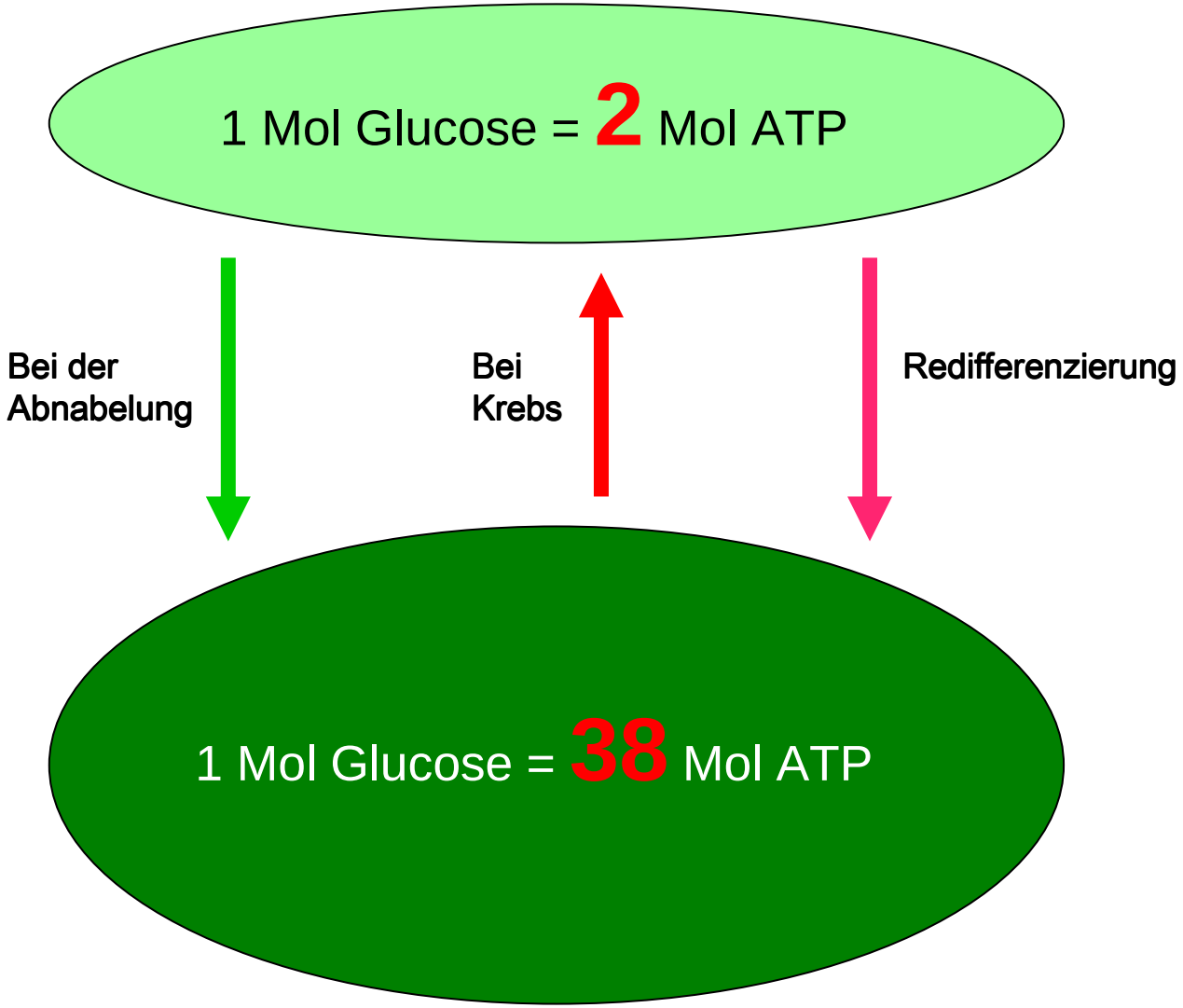
Mitochondrial Medicine is also dedicated to Dr. Frederick L. Crane, discoverer of Coenzyme Q_{10} in 1957, and to the Celebration of 50th year of Coenzyme Q_{10} discovery.

This book is intended for general medical practitioners, for specialists such as cardiologists, neurologists, and diabetologists, biochemists, nutritionists, pharmacists, and also for graduate students.

ISBN 978-1-4020-6713-6

Evolution und Energie

Gärung



Oxidation

Mitochondriale Erkrankungen

vererbt

- Neuropathien (Gehirnatraphie, Epilepsie)
- Myopathien (Muskeldystrophie, Herzmuskelerkrankungen, kardiale Reizleitungsstörungen)
- Veränderungen Sinnesorgane (Blindheit, Taubheit)

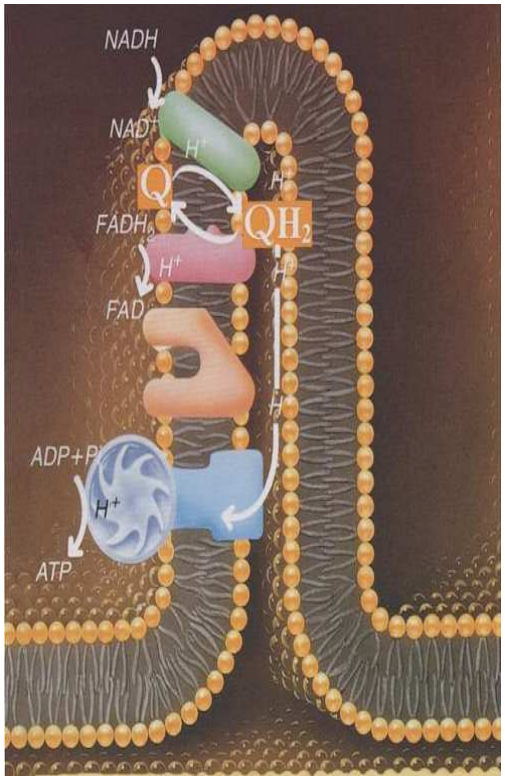
Erbkrankheiten (KSS, CPEO, MELAS, MERF)

xxxxx

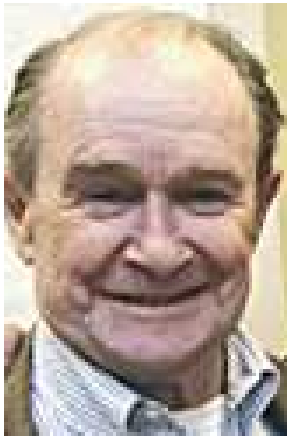
erworben

- Störungen des mitochondrialen Energiestoffwechsels

(Bioenergetisches Defizit)



Prof. Rolf Luft



Schwedischer Endokrinologe (1914-2007)

war der Erste, der mitochondriale Mutationen in Zusammenhang mit Krankheiten brachte (1962).

Entscheidend für den Durchbruch einer Krankheit ist der **Schwellenwert**, bei dem Symptome auftreten, die im Zusammenhang mit dem Energiebedarf eines spezifischen Organgewebes stehen.

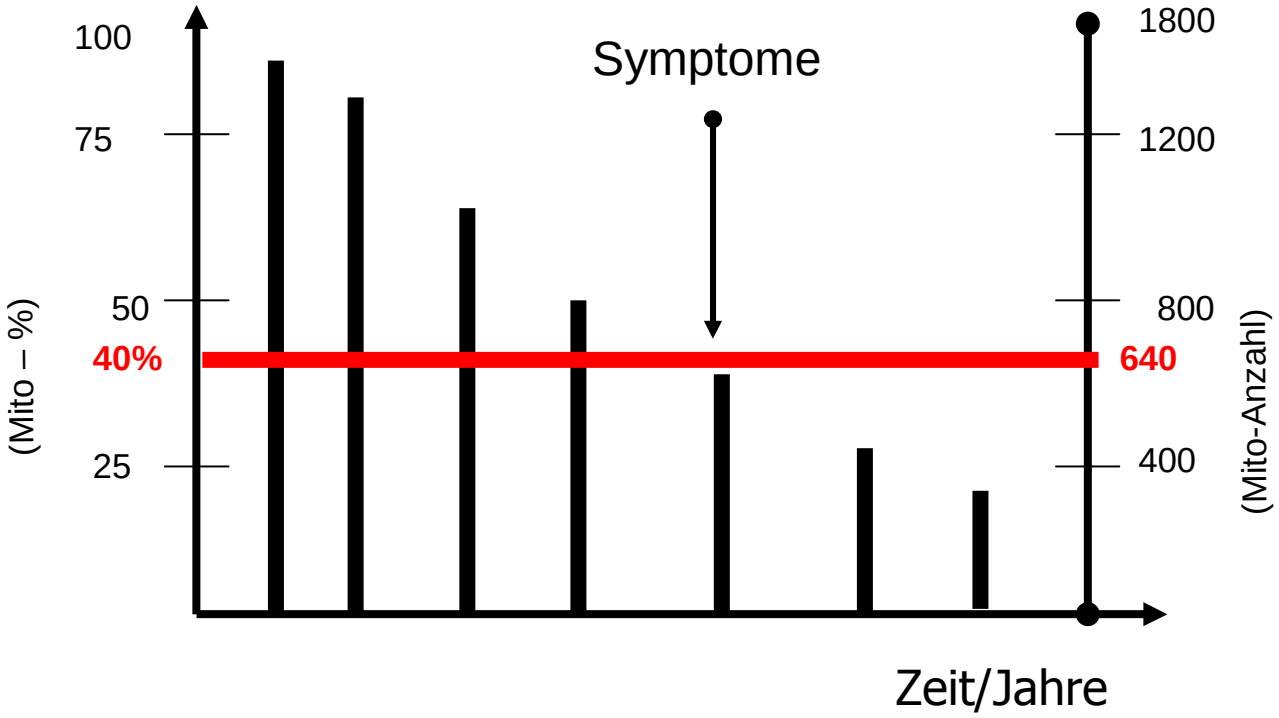
Abb.: www.ki.se/essaer200ar

Der chronisch kranke Patient

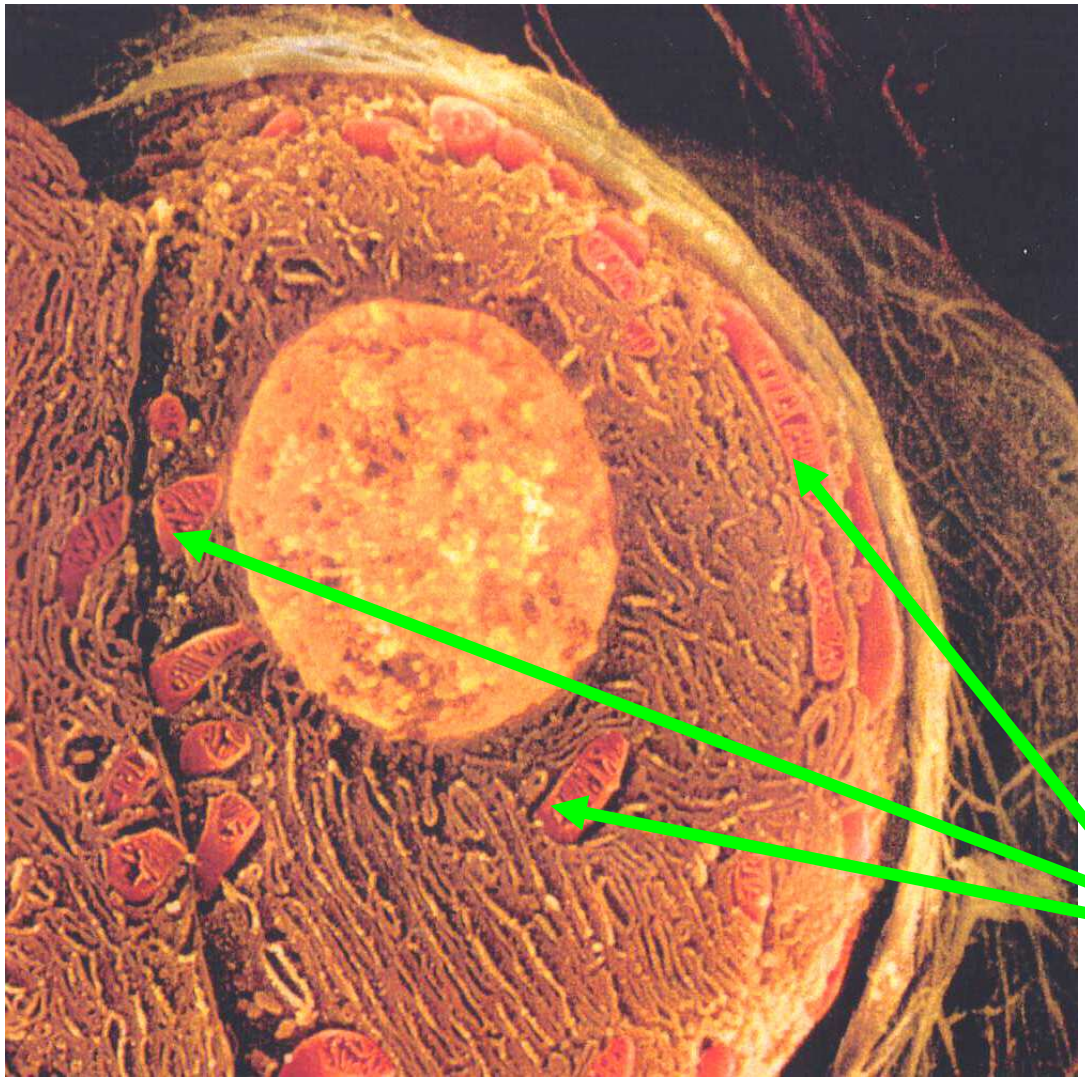
läuft Gefahr, seine Mitochondrien irreversibel zu schädigen.

Sind etwa **60% der Mitochondrien** geschädigt, so treten die typischen Symptome einer chronischen Krankheit auf.
Überschreitet ein Q10-Defizit **25%**, so kommt es zu morphologischen Mitochondrialen Veränderungen, zu empfindlichen Störungen und Funktionsverlusten **aller** Körperfunktionen.

Abnahme der intakten Mitochondrien



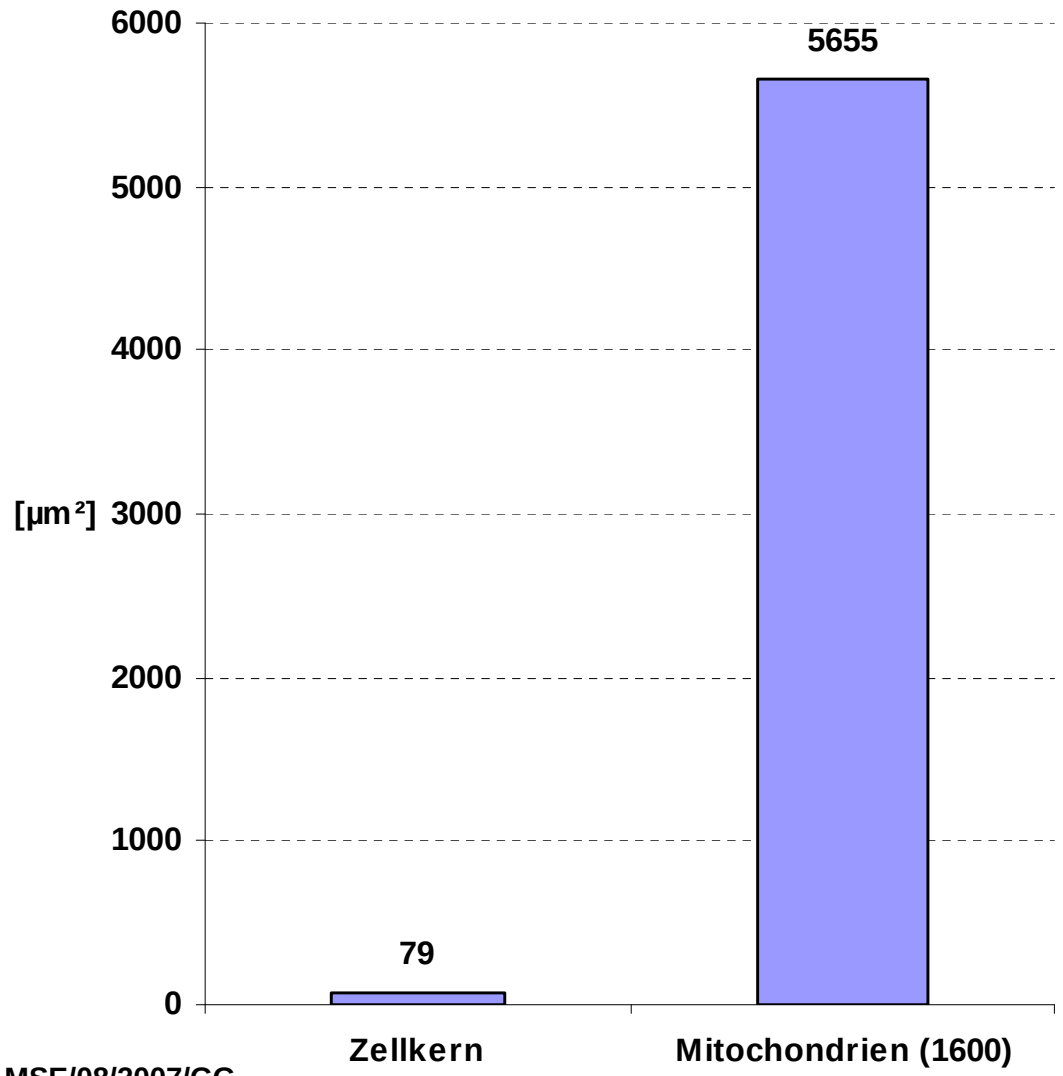
Mitochondriotrope Substanzen können prophylaktisch das Unterschreiten der kritischen Schwelle verhindern und/ oder therapeutisch die Unterbrechung des Elektronenflusses überbrücken.



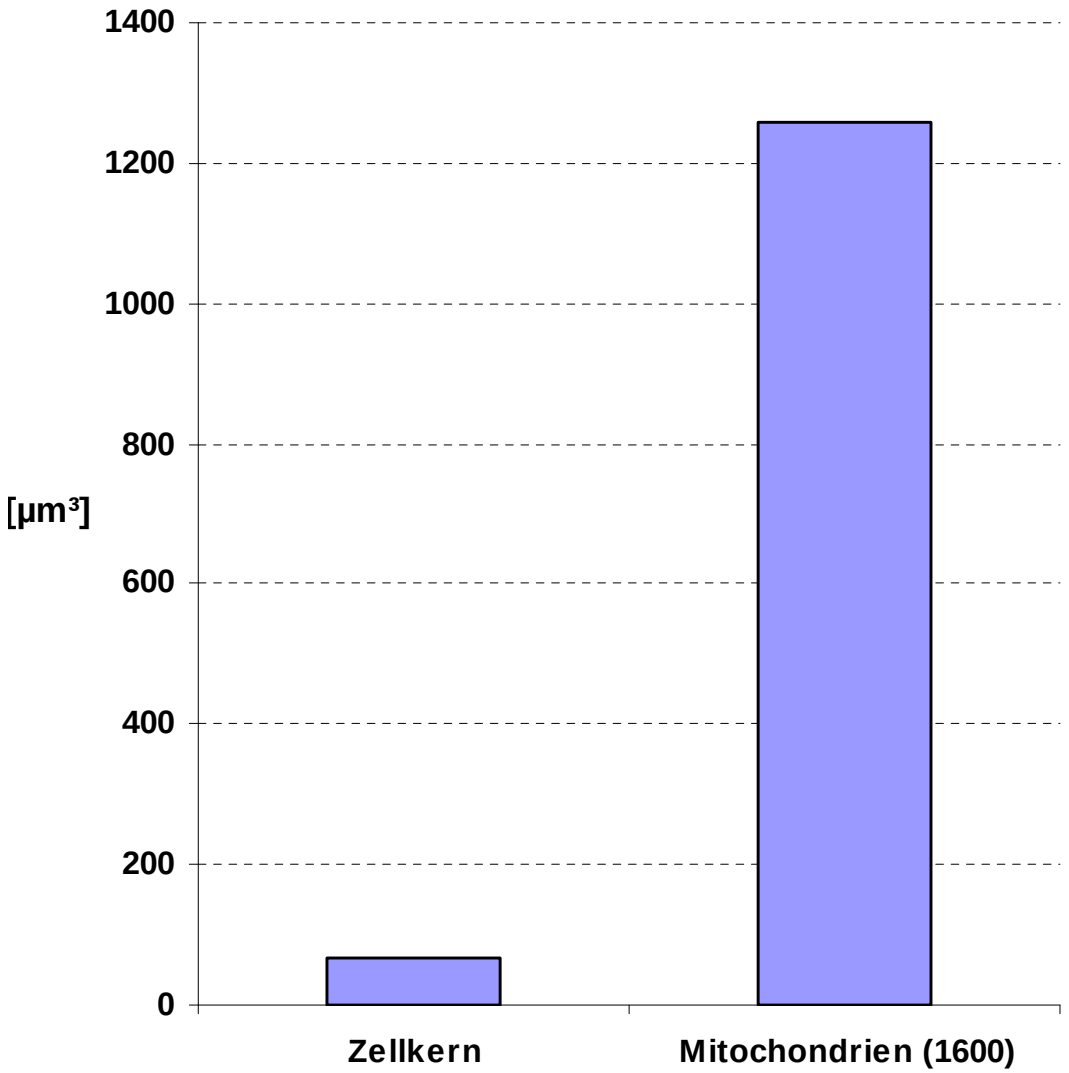
Zellkern wurde abgeschält, um alle inneren Strukturen sehen zu können. Die Drüsenzelle enthält eine Vielzahl von Mitochondrien (15 000fache Vergrößerung).

Größenverhältnisse

OBERFLÄCHE IM VERGLEICH



VOLUMEN IM VERGLEICH



MSE/08/2007/GG

Ribosomen ∞ Mitochondrien

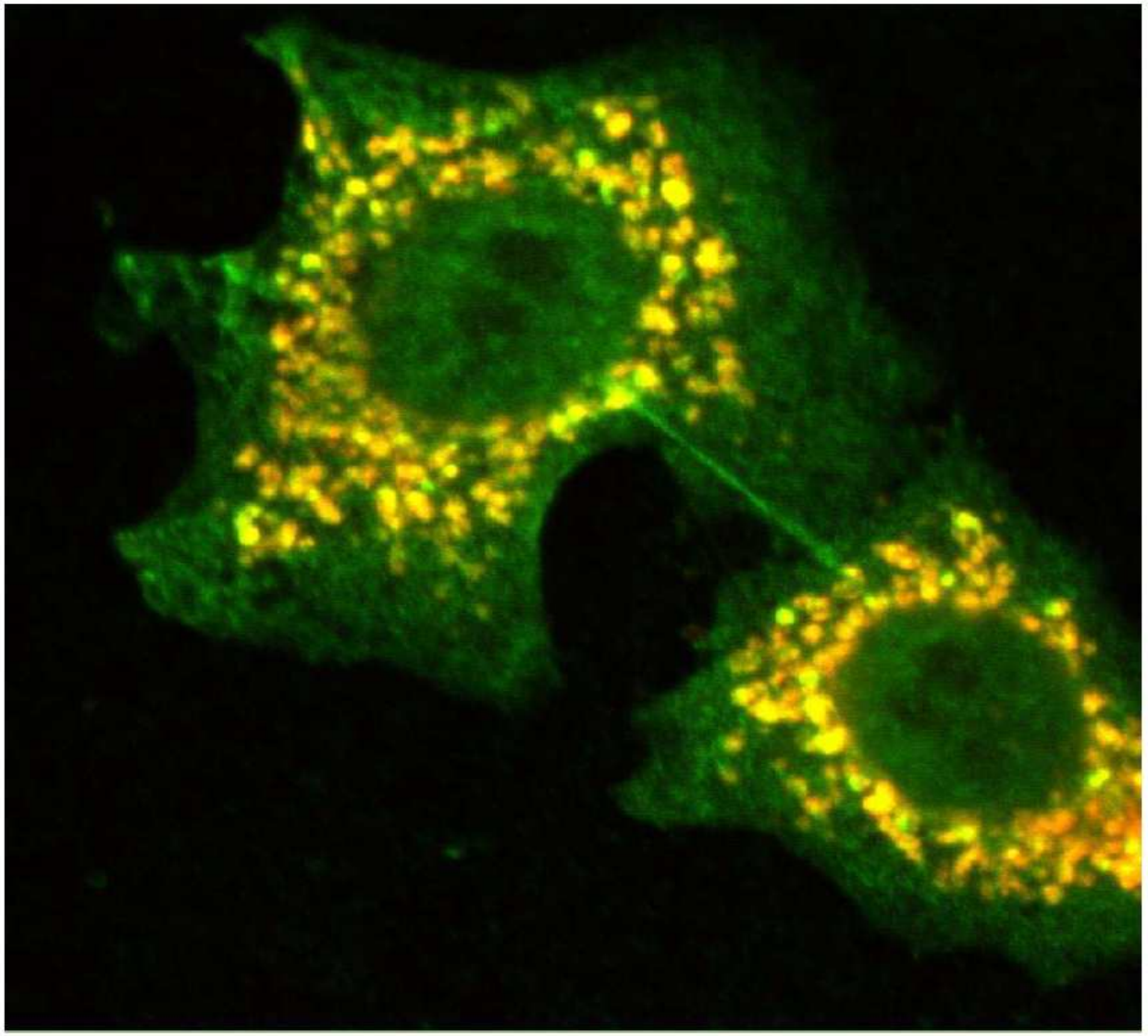
Ribosomen sind für die Protein-Synthese notwendig.

Die Voraussetzung für die Bildung von Ribosomen liefern die Mitochondrien. Diese synthetisieren ein hierfür notwendiges **Eisen-Schwefel-Protein**: Rli1

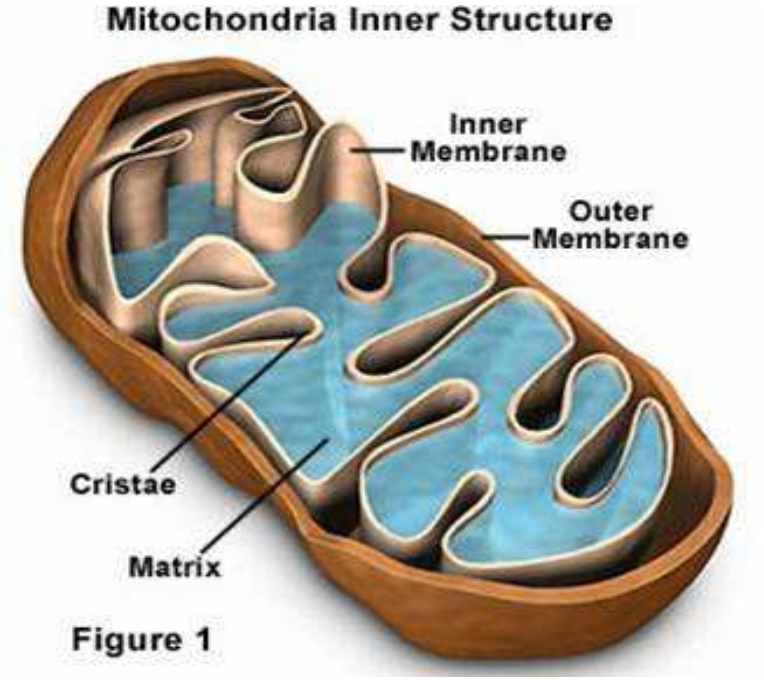
Störungen dieser Maschinerie führen zu neurodegenerativen Krankheiten.

Roland Lill, Marburg

HORMONREZEPTOREN IN MITOCHONDRIEN

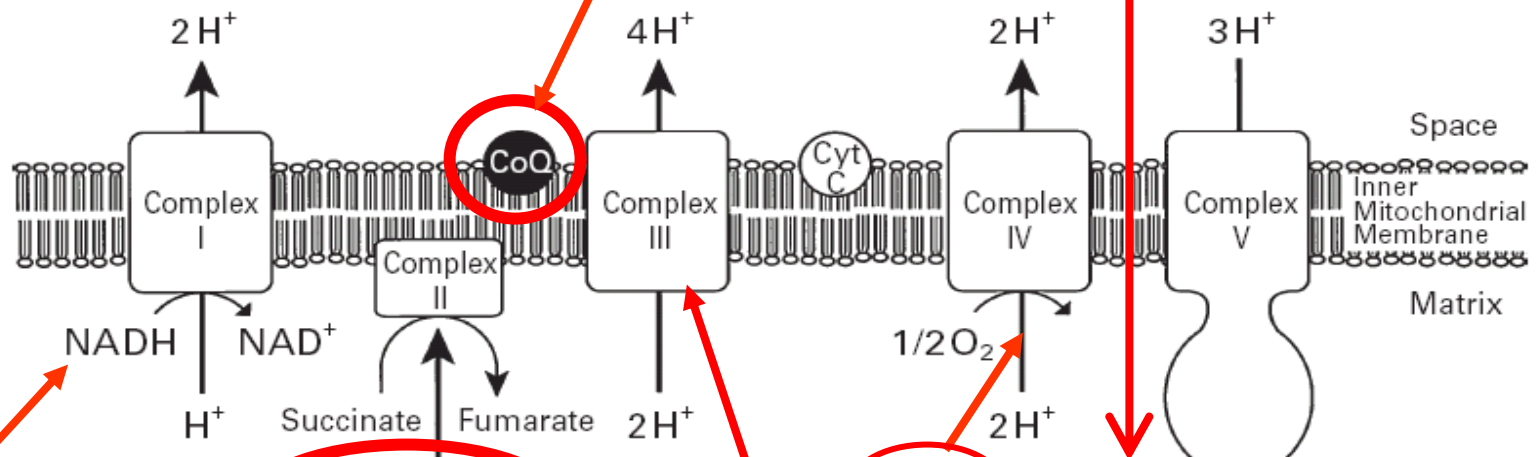


European Journal of Cell Biology, 2000,79



Magnesium

UBIQUINON



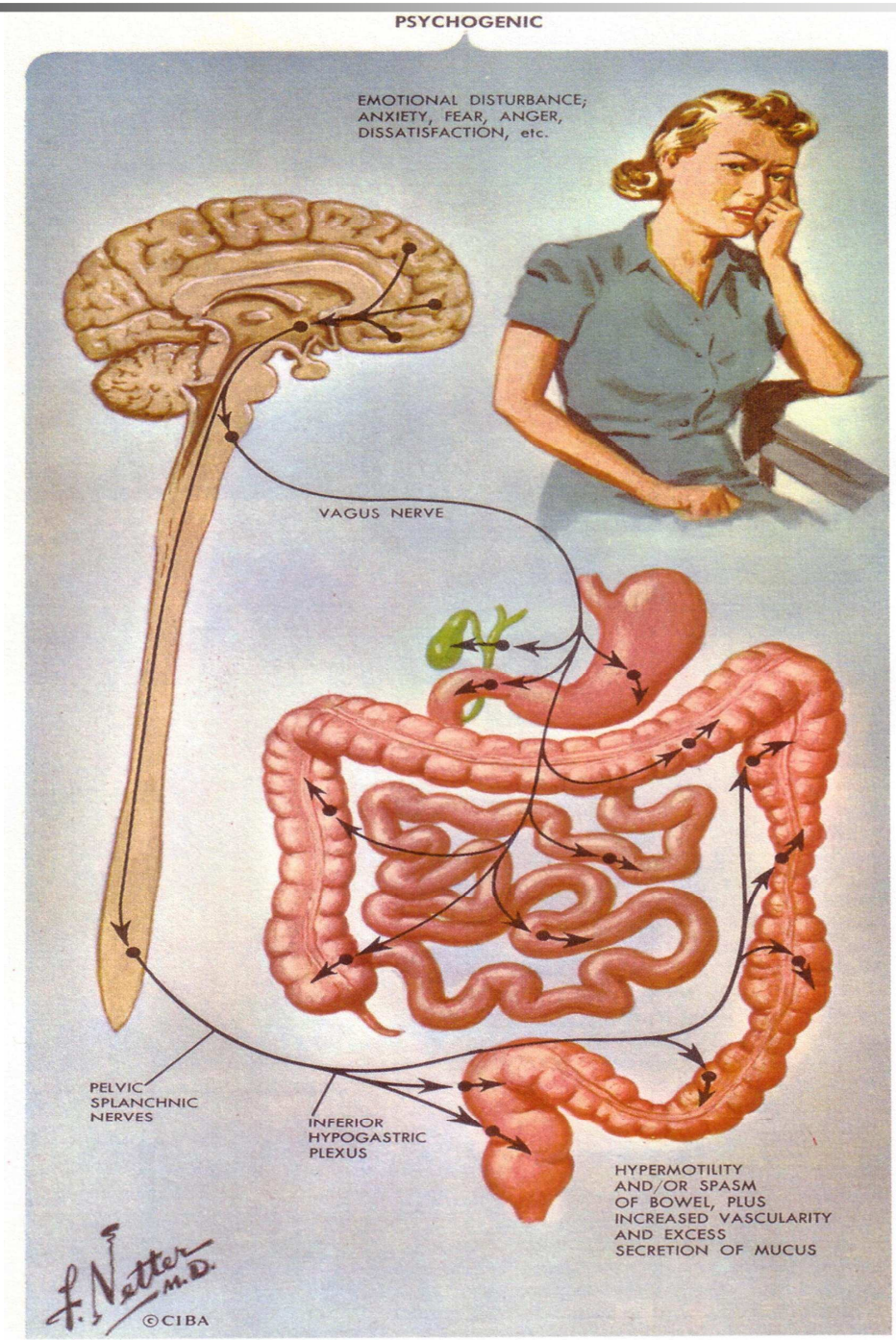
NIACINAMID

RIBOFLAVIN

Vitamin B6

Cu

Mg^{2+}

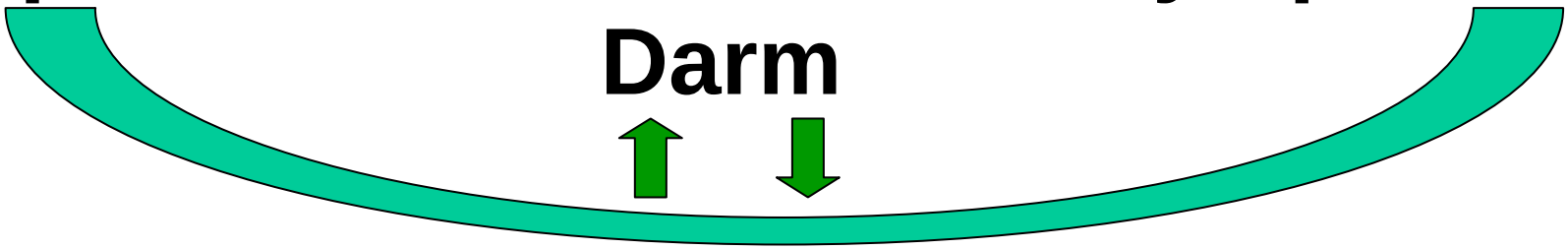

PSYCHOGENIC
EMOTIONAL DISTURBANCE;
ANXIETY, FEAR, ANGER,
DISSATISFACTION, etc.
VAGUS NERVE
PELVIC
SPLANCHNIC
NERVES
INFERIOR
HYPOGASTRIC
PLEXUS
HYPERMOTILITY
AND/OR SPASM
OF BOWEL, PLUS
INCREASED VASCULARITY
AND EXCESS
SECRETION OF MUCUS
F. Netter M.D.
©CIBA

Mitochondriale Medizin

Energie

Entzündung [$O_2^{\bullet -}$ + NO = $ONOO^{\bullet -}$]

Sympathikus **Parasympathikus**



Nebenniere ⬅ **Hypothalamus** ➡ **Hypophyse**

Mitochondrien

Mitotrope Substanzen

Der Verlust an intakten Mitochondrien und das Nachlassen der mitochondrialen Energiebildung führt zum Nachlassen von:

- Ausdauer (Muskelkraft)
- Konzentrationsfähigkeit
- Gedächtnis (Demenz / Alzheimer)
- Sehkraft (AMD)
- Riechvermögen
- Hörvermögen
- Knochenbelastbarkeit
- Hautelastizität

METOX-Konzept

Das Schachbrett der mitochondrialen Medizin

Herz • Herzinsuffizienz • Arrhythmien • Herzstillstand	**Immunsystem** • Immunschwäche • Immunstimulation • Neuro-Immuno-Achse	**Gehör** • Tinnitus • Hörsturz	**Auge** • Altersblindheit • AMD
Gingiva • Parodontitis • Gingivitis • Kiefer-OP	**Krebs** • Vorsorge • OP-Vorbereitung • NW-Management	**ADHD** • Autismus • Konzentrations-Störungen	**Nervenschutz** • Parkinson / PSP • Demenz • Alzheimer • Geruchsstörung
Schmerz • Migräne • Neurop. Schmerz • Juckreiz	**Lunge** • Asthma • COPD • Apnoe	**Niere/Blase** • Dialyse • Apherese • Inkontinenz	**Haut** • Alter, Wunden • Neurodermitis • Psoriasis

Mitochondriale Medizin

aktuelle Diagnostik

- Maternaler Erbgang: mtDNA-Untersuchungen aus Blutzellen
  5 – 10 ml EDTA-Vollblut
- Muskel-mtDNA Analyse: 30 – 100 mg Gewebe tieffrieren
- Metabolitveränderungen: organische Säuren im Urin,
  Amino- und Fettsäuren im Serum
- Spiroergometrie
- PET-Messung
- Internet-Dienste: OMIM, Mitomap, MITOP, MITONET
- Common deletion: betrifft 1/3 des gesamten mt-Genoms:
  etwa 5000 bp.

Stufenkonzept Mitochondropathie oxidativer und nitrosativer Stress

Stufe 1 (Screening)

Citrullin im Urin	20 ml zweiter Morgenurin

Stufe 2 (Basisdiagnostik bei Mitochondriopathie)

Großes Blutbild, Coenzym Q10	1 EDTA
GOT, GPT, γGT, LDH	3 Serum
Kreatinin, Blutzucker, Harnsäure	2* NaF
Cholesterin, Triglyzeride, HDL, LDL	
TSH	
Antioxidative Kapazität	
Lipidperoxidation	
Laktat	
Pyruvat	
MDA, CRP	

Stufenkonzept Mitochondropathie oxidativer und nitrosativer Stress

Stufe 3a (Mikronährstoffe Basis)

Na, K, Ca, Mg, Cu, Fe und Zn im Vollblut	2 EDTA
Vitamin B6	2 Serum
Vitamin B12	2 Heparin
Folsäure	
Vitamin C	
Coenzym Q10 (oxidiert/reduziert)	- 80℃

Stufe 3b (Ergänzende Mikronährstoffe)

Aminosäurestatus	2 EDTA
Vitamine E	2 EDTA gefroren
β-Carotin	2 Serum
Glutathion reduziert	1 Heparin
Selen	

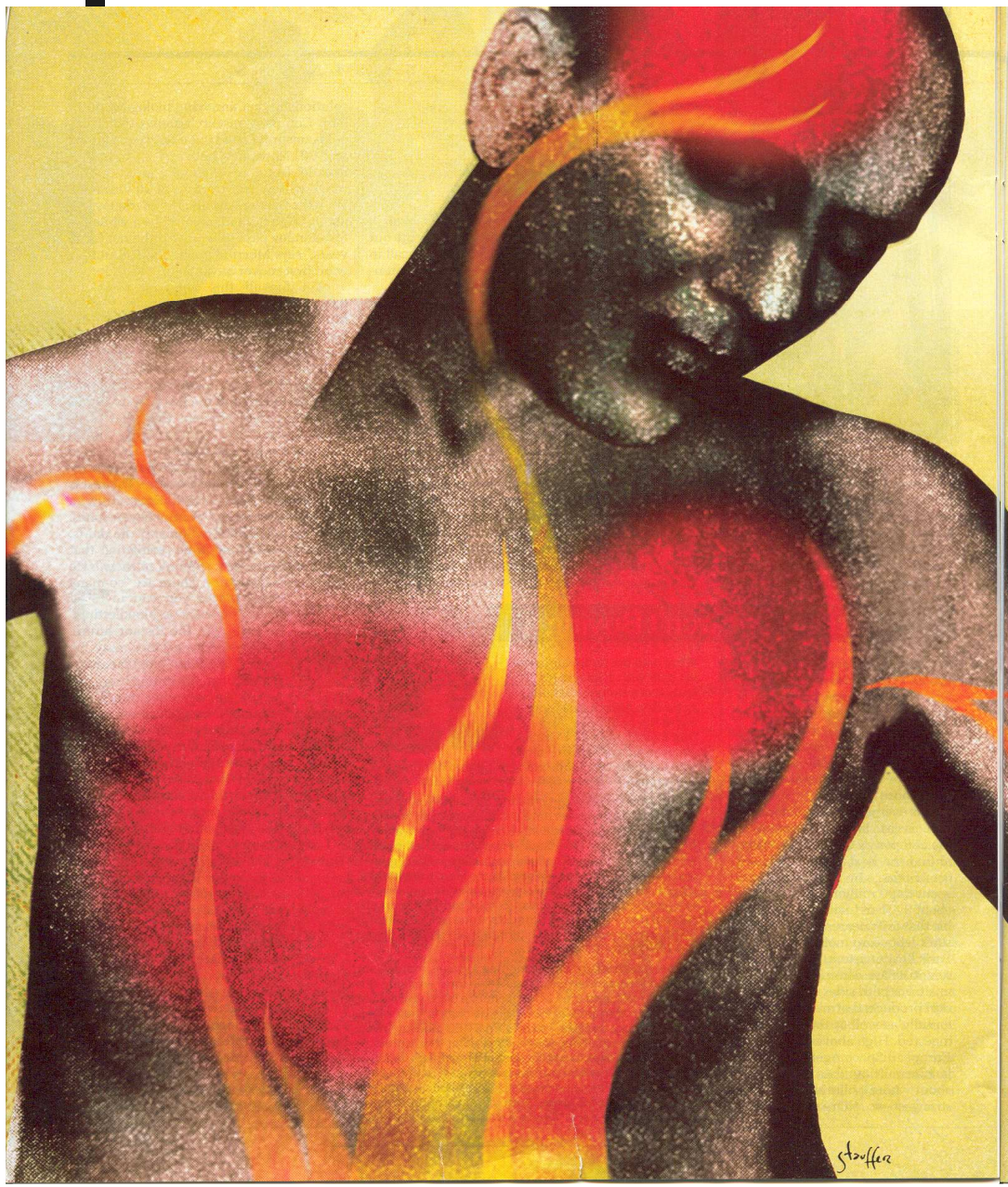
Stufe 4 (Nachweis der Folgen)

Nitrotyrosin
Mitochondrienpotenzial (→ noch nicht verfügbar)

Das „Feuer“ in uns!

Zur Abwehr von Infektionen reagiert das Immunsystem mit akuten Entzündungsreaktionen. Chronische inflammatorische Prozesse können jedoch unspezifisch zu Herzattacken, Darmkrebs, Parkinson, Alzheimer oder anderen degenerativen Erkrankungen führen.

Die Mitochondriale Medizin versucht, eine Antwort darauf zu geben.



The FIRES Within

Inflammation is the body's first defense against infection, but when it goes awry, it can lead to heart attacks, colon cancer, Alzheimer's and a host of other diseases

Illustration for TIME by Brian Stauffer

By CHRISTINE GORMAN and ALICE PARK

WHAT DOES A STUBBED TOE OR a splinter in a finger have to do with your risk of developing Alzheimer's disease, suffering a heart attack or succumbing to colon cancer? More than you might think. As scientists delve deeper into the fundamental causes of those and other illnesses, they are starting to see links to an age-old immunological defense mechanism called inflammation—the same biological process that turns the tissue around a splinter red and causes swelling in an injured toe. If they are right—and the evidence is starting to look pretty good—it could radically change doctors' concept of what makes us sick. It could also prove a bonanza to pharmaceutical companies looking for new ways to keep us well.

Most of the time, inflammation is a lifesaver that enables our bodies to fend off various disease-causing bacteria, viruses and parasites. The instant any of these potentially deadly microbes slips into the body, inflammation marshals a defensive attack that lays waste to both invader and any tissue it may have infected. Then just as quickly, the process subsides and healing begins.

Every once in a while, however, the whole feverish production doesn't shut down on cue. Sometimes the problem is a genetic predisposition; other times something like smoking or high blood pressure keeps the process going. In any event, inflammation becomes chronic rather than transitory. When that occurs, the body turns on itself—like an ornery child who can't resist picking a scab—with aftereffects that seem to underlie a wide variety of diseases.

Suddenly, inflammation has become one of the hottest areas of medical research. Hardly a week goes by without the publication of yet another study uncovering a new way that chronic inflammation does harm to the body. It destabilizes cholesterol

NEURO-IMMUN-ACHSE

NEURALROHR

ENTERALES NERVENSYSTEM (DARM) – HYPOTHALAMUS

(chronische) ENTZÜNDUNGEN

PHYSISCHE + PSYCHISCHE BELASTUNG

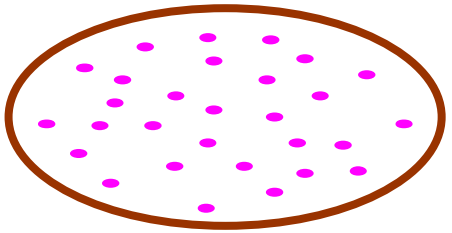
ÜBERGEWICHT (MET. SYNDROM)

UMWELTGIFTE

MEDIKAMENTE

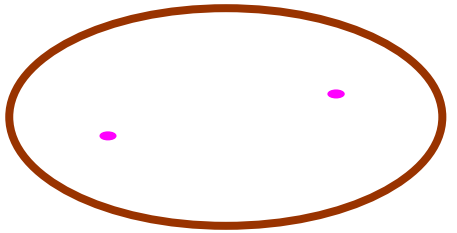
BESTRAHLUNG

INTAKTE ZELLE



ZELLE MIT MITOCHONDRIEN → ENERGIE (+++)

TOTE ZELLE

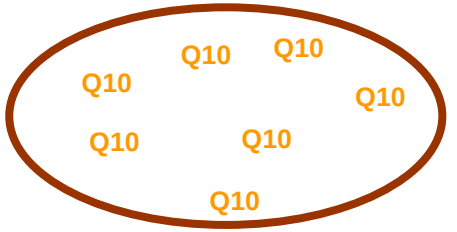


†

ZELLE OHNE MITOCHONDRIEN → KEINE ENERGIE (-)

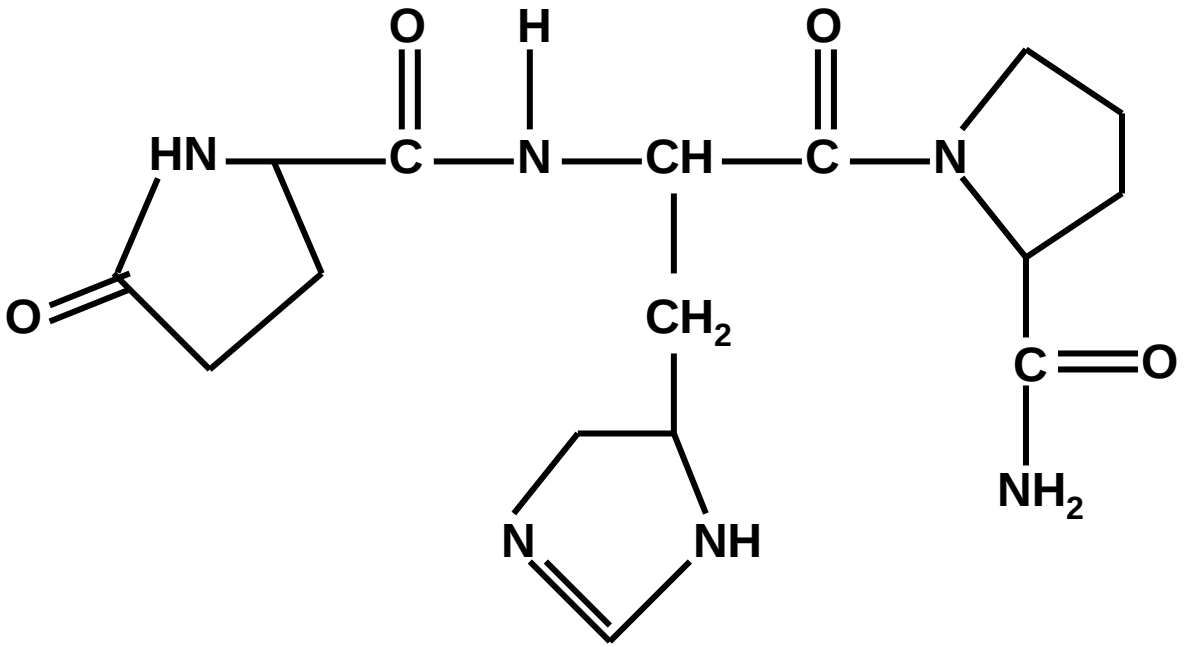
ZUGABE VON Q10

ÜBERLEBENDE ZELLE



ZELLE OHNE MITOCHONDRIEN + Q10 → WIEDER ENERGIE (+)

Thyrotropin-“releasing“-Hormon TRH



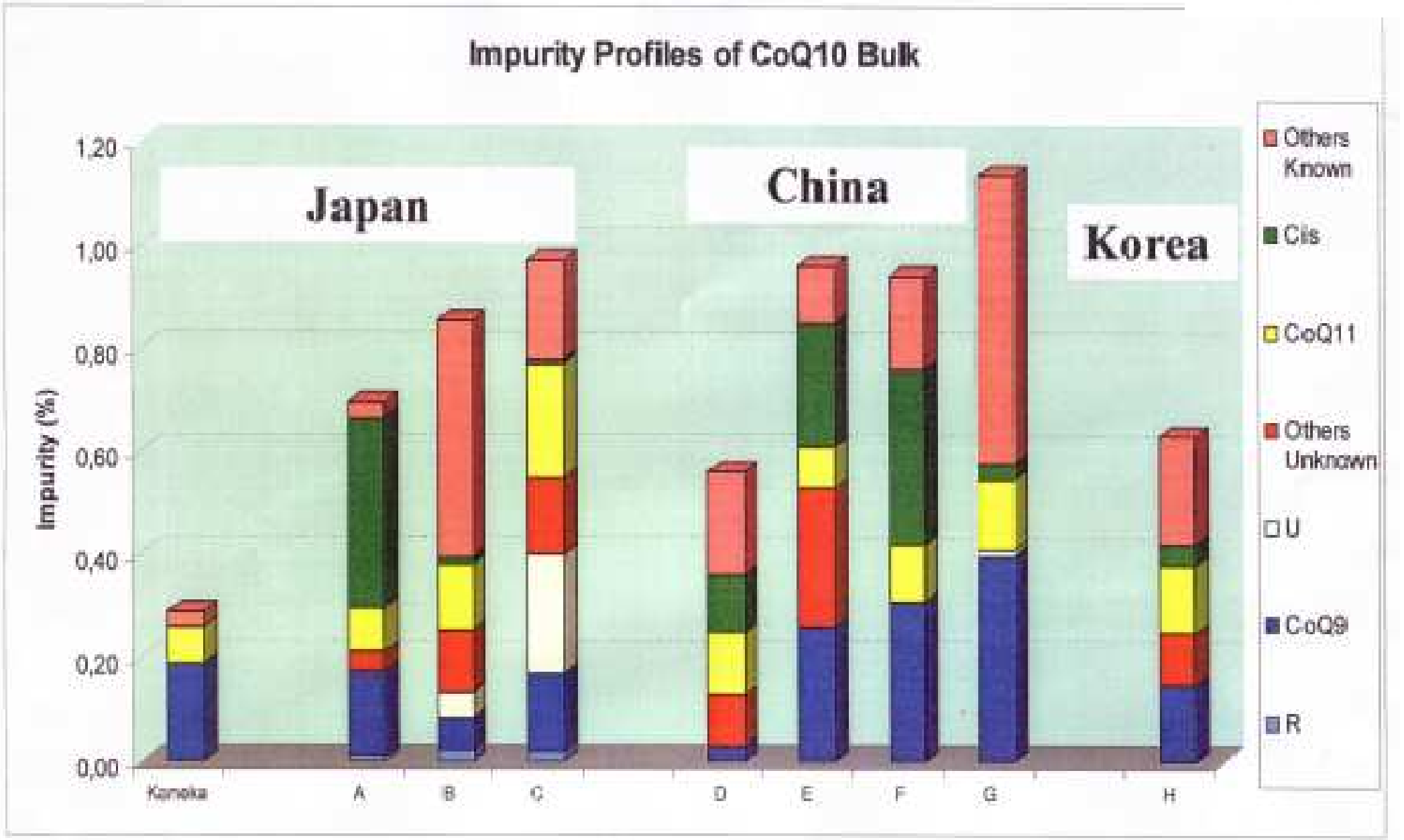
Mitochondriotrope
oder
Mitotrope Substanzen

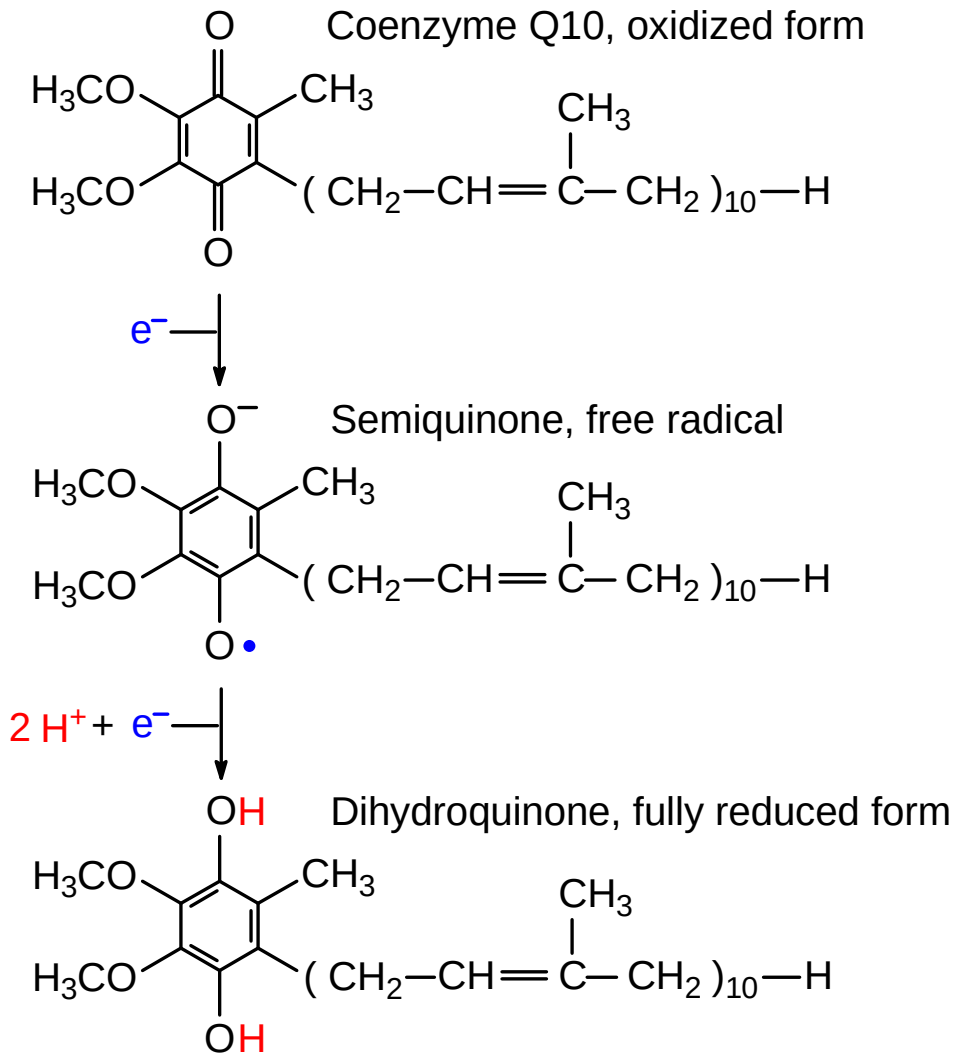
Energie		**Membran**	**Antioxidantien Entgiftung**		**Spurenelemente**
Ubiquinol	***MigränoMit®***	**Phospolipide**	**SOD**	***EVOLENZ®***	**Zink; Mangan**
Vit. B2		**ω-3 Fettsäuren**	**GPx (GSH)**		**Selen; Kupfer**
Vit. B3(NADH)		**Tocopherole**	**KAT**		**Chrom**
Vit. B1			**Vitamin C**		
Magnesium			**Ubiquinol / -on**		
Carnitin (Vitamin C)			**Vitamin E**		
Glutamin			**Carnitin**		
Liponsäure			**Vitamin B12**		
Kreatin					
Taurin					

Anforderungsprofil für mitotrope Substanzen

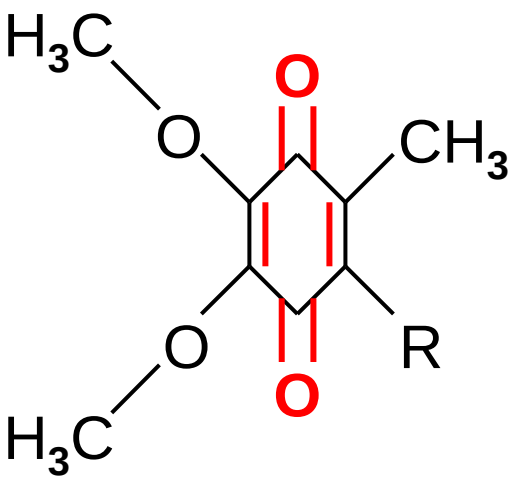
Sie müssen so dosiert sein, dass sie die Mitos erreichen !

- Ausgangsmaterial
  (Bäckerhefe, Bakterien, Pflanzen, Synthese)
- Reinheitsgrad
- Pharmakologie
- Toxikologie
- Humankinetik
- Kinische Studien


Impurity Profiles of CoQ10 Bulk
Japan
China
Korea
Impurity (%)
1,20
1,00
0,80
0,60
0,40
0,20
0,00
Kaneka
A
B
C
D
E
F
G
H
Others Known
Cis
CoQ11
Others Unknown
U
CoQ9
R

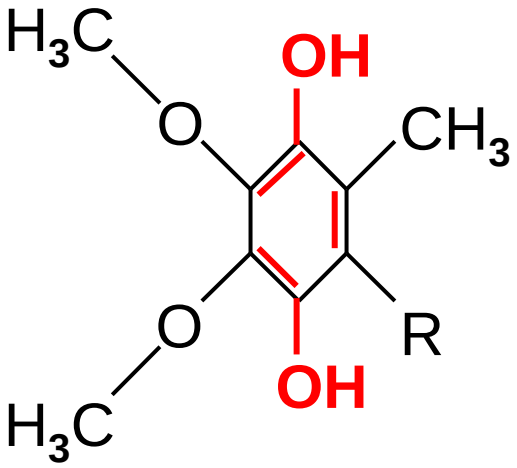


Oxidized, partially and fully reduced state of coenzyme Q10



+ 2 H

- 2 H

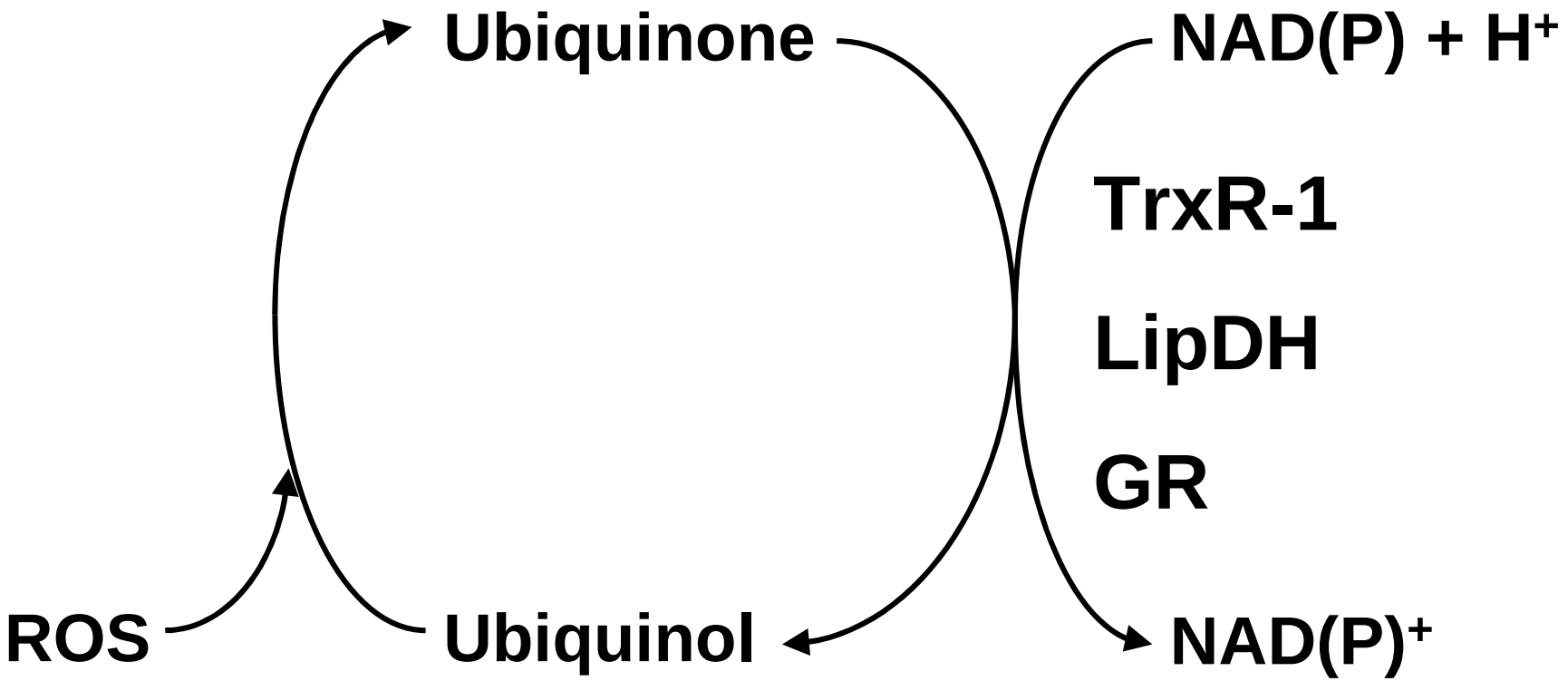


oxidierte Form
Ubiquinon = Coenzym Q10

$R = (\quad)_{10}$

reduzierte Form
Ubiquinol = Ubihydroquinon

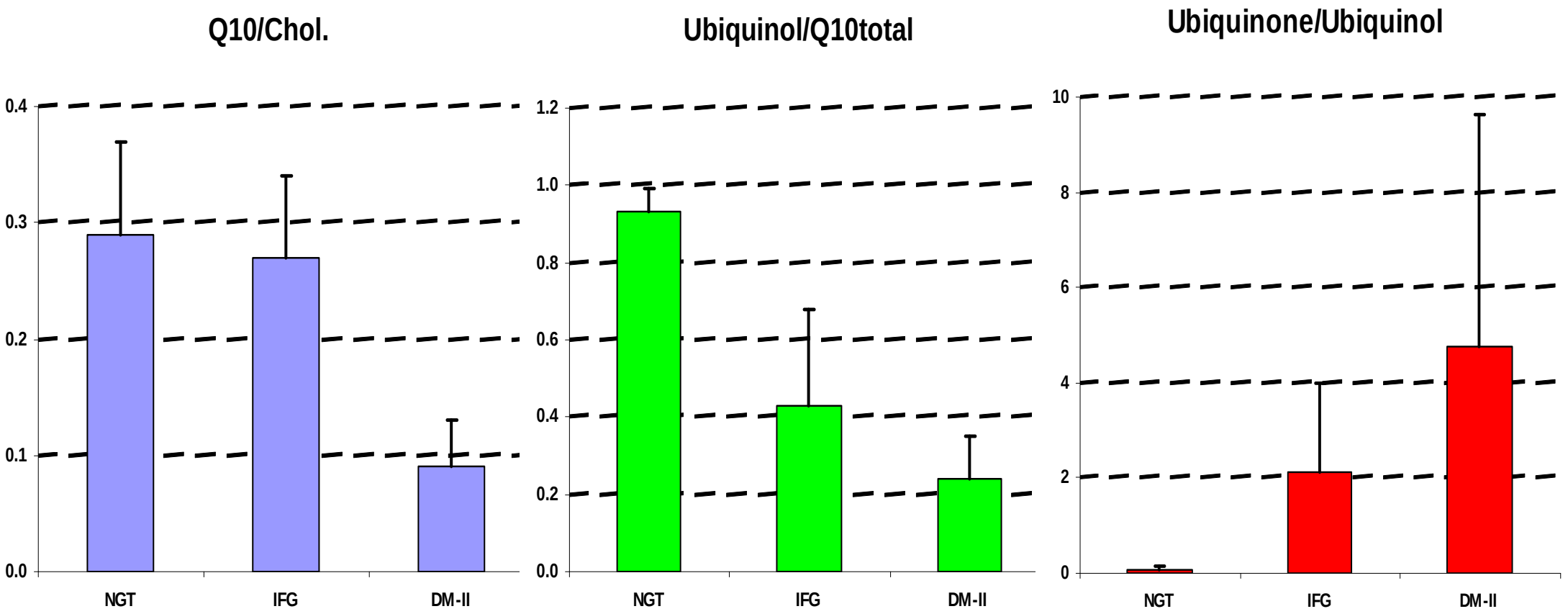
Regeneration of the antioxidant ubiquinol



TrxR-1 = Thioredoxin reductase
LipDH = Lipoamide dehydrogenase
GR = Glutathione reductase

Nordman T. et al. (2003); BioFactors 18; 45-50

Mitochondrial oxidative burden in diabetes patients



NGT = mormal glucose tolerance / IFG = impaired fasting glucose / DM-II = Type 2 diabetes

Lim SC et al. (2006); Diabet Med; Dec 23(12): 1344-1349

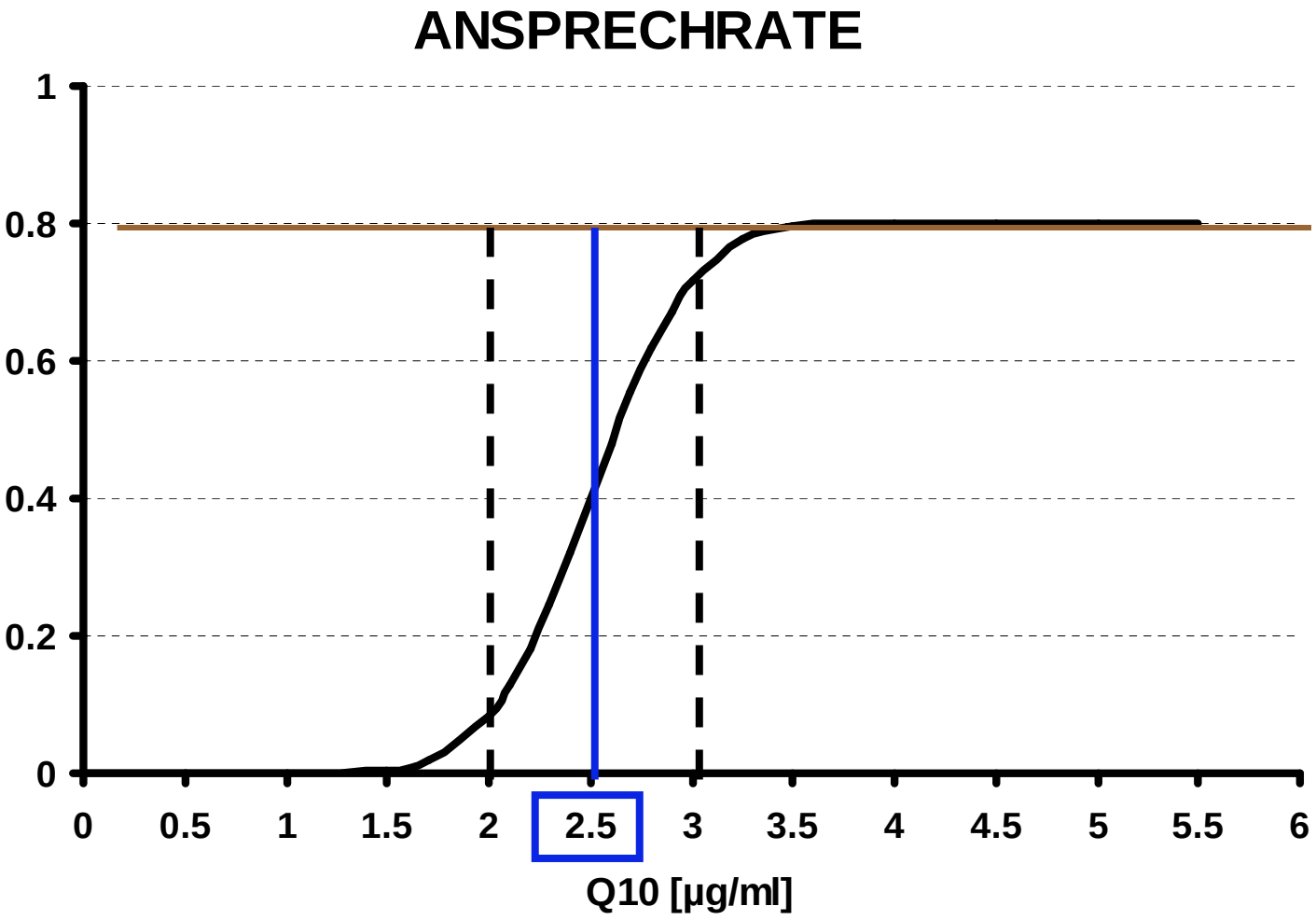
Regeneration von extramitochondrialem Ubiquinol

Die antioxidative Kapazität von Ubiquinol hängt ab von dessen Regenerierbarkeit aus oxidiertem Ubiquinon Q10 durch folgende drei **Flavoenzyme:**

- **Lipoamide-Dehydrogenase** **Zink ! - abhängig**
- **Thioredoxin-Reductase** **Selen ! - abhängig**
- **Glutathion-Reductase** **Zink ! - abhängig**

Oxidativer Stress und insbesondere **Entzündungsprozesse (CRP)** verschieben das Q10/ Quinol Verhältnis von normal 10/90 auf hohe Werte bis zu 90/10.

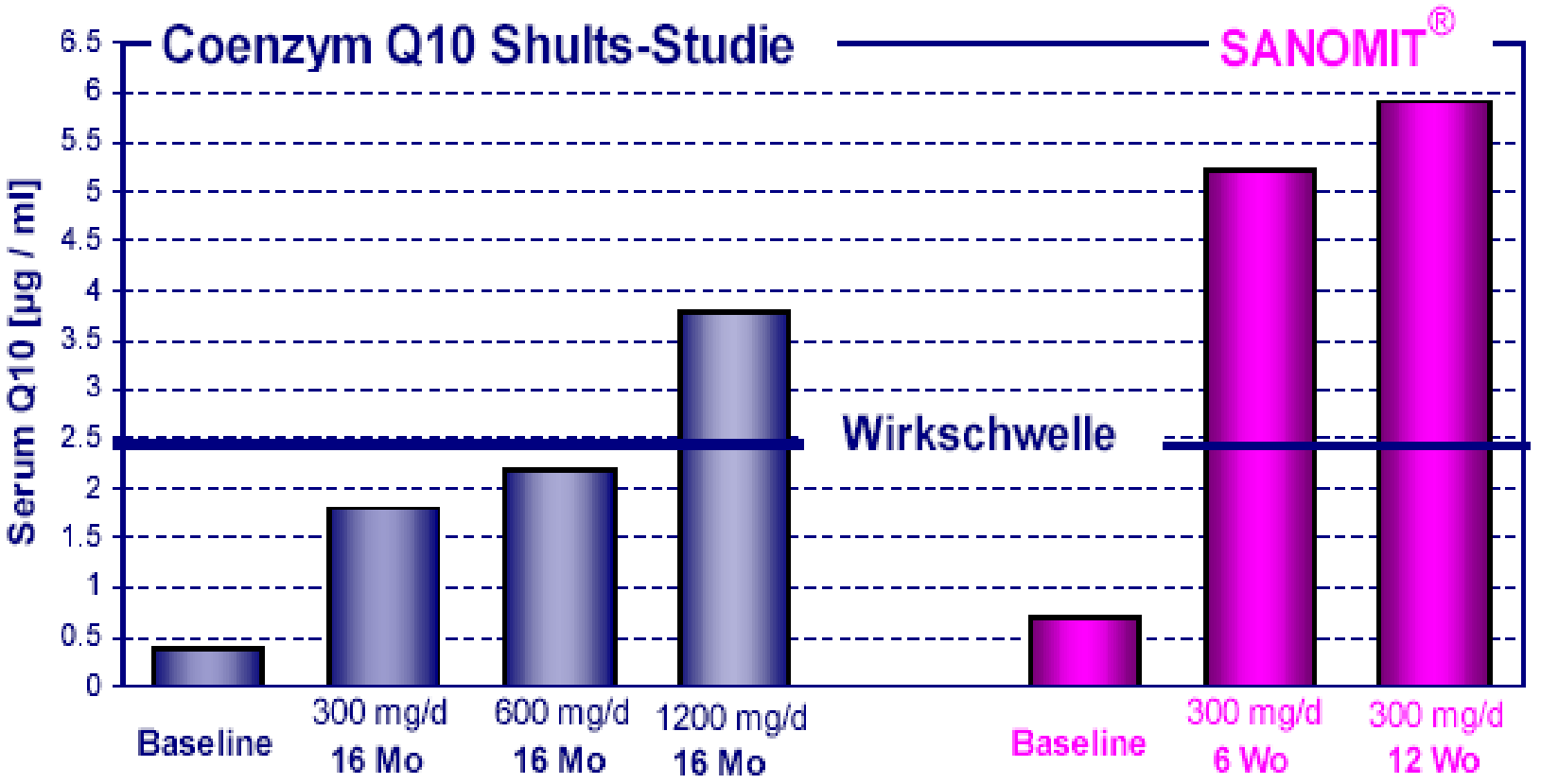
Die drei Q-10 Regenerierungsenzyme helfen, das Verhältnis von Q-10 und Quinol bei etwa 10/90 zu halten. Voraussetzung für deren Wirksamkeit ist der Einbau von Selen oder Zink.



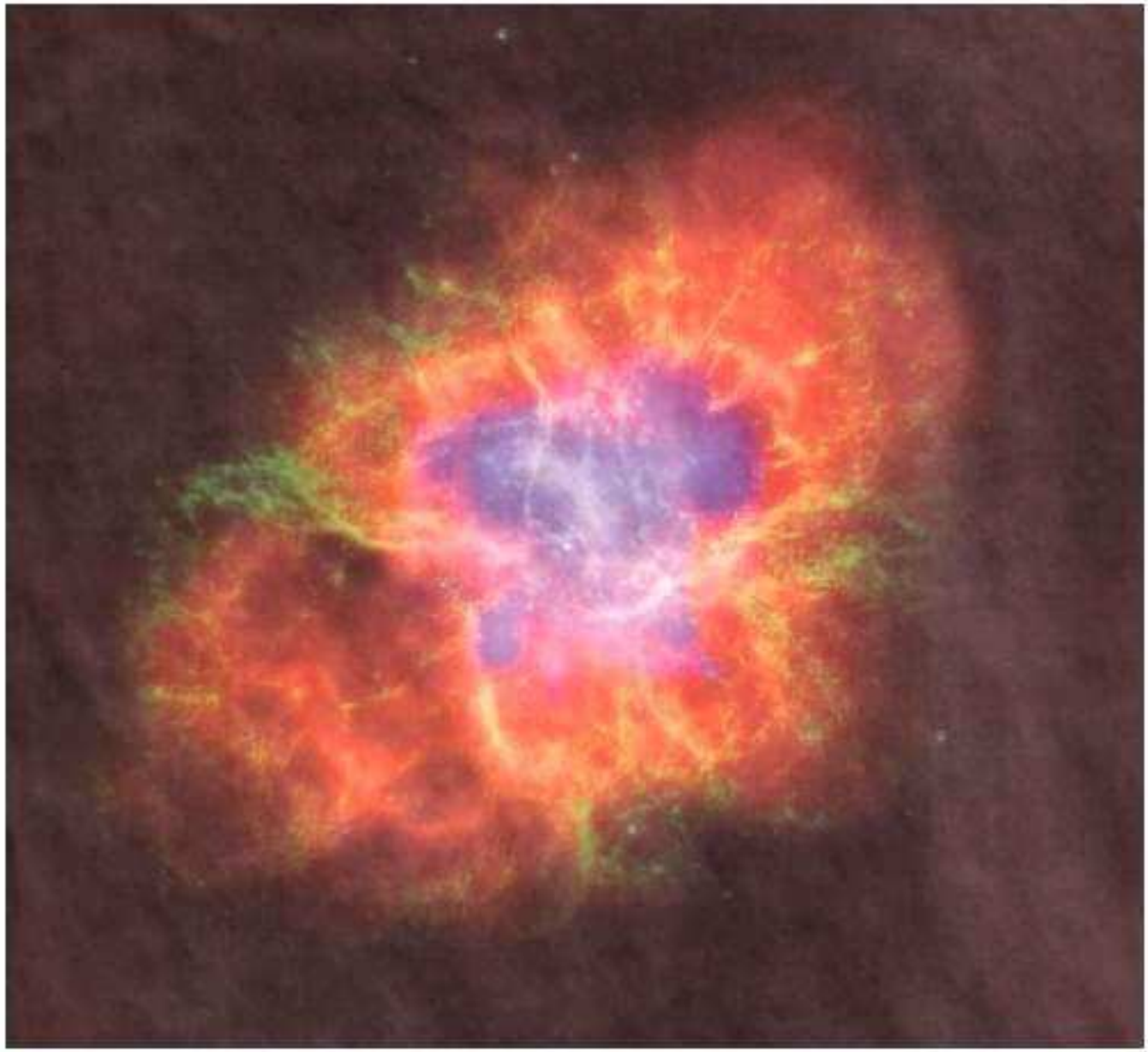
Minimaler wirksamer Q 10 - Blutspiegel bei Krankheiten

2,5 µg/ml

VERGLEICH PARKINSON STUDIEN
Shults et al. vs. Reichmann et al.
Q10-Serum-Spiegel nach Behandlung mit Q10



Explodierende Mitochondriale Medizin



Mitochondriale Forschung – Schritt in die Zukunft