Keynote Lecture
Walchseer Lymphological Winter Conference
11th - 12th January 2019

Lymphological expertise
from Macro - to Microcosm

Pic source: Cameron Gray in
Fritjof Capra December, 2015.
Keynote Lecture
Walchseer Lymphological Winter Conference
Structure
I

- my personal and Life principles

- Lymphological Macro Cosmos

Scientific star-hours "lymphological knowledge" from antiquity to the present in the fields of Anatomy-Pathology-Pathophysiology-Diagnostics-Conservative Therapy Methods.

- Prof. P. Hutzschenreuter: „MLD (KPE) und Science“ - Literature -

Lymphological Macro Cosmos
Bridges for research into the lymphological microcosm.

"It must be assumed that the majority of our diseases are caused by micro-edema in the connective tissue."

Quote: Prof. H. Weissleder nach Prof. H. Wittlinger in „Eine kleine Geschichte der Lymphologie“

The Endothelium: the Chief Conductor in the human organism is a "systemic effective organ".
Keynote Lecture
Walchseer Lymphological Winter Conference
Structure
II
Microcirculation

The phenomenon of chron. Inflammation in the vascular lymph system
relevant publications on the topic

The Science of Microparticles - Sophisticated Vesicles!

The World of Microcirculation Research and its Importance for MLD

PMFT (pulsed magnetic field therapy) – complementary helpful for KPE:
results of the pilot study 2015

Lymphological macro-micro-cosmos and beyond....
The soul-body axis
Good quality of life thanks to information therapy

Indian Medicine Andes/Peru
Specialist practice Bad Feilbach - Chiemgau
Head of German Acupuncture Centre
Oncology Bad Aibling
Medical Park Clinic Bad Wiessee
Lymph Clinic Wittlinger Walchsee

Specialist in Internal Medicine, Rheumatology, Cardiology - Lymphology, Naturopathy, sports medicine
Endothelial sciences

Rheumatism Clinic Bad Kreuznach
Surgery Garmisch-Partenkirchen
Dermatology Uni-Munich
Internal Medicine Uni-Munich

heart attack prevention
endothelial diagnostics
endothelial therapy
endothelial research

Biophysical influences on the Endothelium
Endothelial Acupuncture - Endothelial and Environmental Protection
Endothelium and water quality
Physical vascular therapy (information therapy)

www.info@gesundheitskonzepte.info

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www.vodderakademie.com

Wittlinger Therapiezentrum
www.wittlinger-therapiezentrum.com
Maxime of my Life:

**Fantasy** is more **important** than **knowledge**, because knowledge is **limited**.
But fantasy embraces the whole world.

Academic freedom is the freedom to learn as much as you want.
Two things tend to slow down the **progress** of medicine:
**authorities** and **systems**.

"Any material structure, including the human body, can be understood as **complex vibration system** which is caused by interference with the innumerable individual frequencies of atoms and molecules and is absolutely specific to the type and composition of the respective structure and reacts **individually to biophysical signals** " !

**Don't ever forget to laugh...!**

Dr. Vodder Akademie  Wittlinger Therapiezentrum
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How it all started.... In the Rheumaklinik Bad Kreuznach 1979 - Prof.Schilling

25-year-old female patient with the diagnosis:
Generalized soft-tissue Spine and joint ossifications, (L’Homme du Bois) of both shoulder, hip, knee and ankle joints, and predominantly polyarticular of the finger and toe joints, progressive since 15 years of age despite supportive therapy (cortisone/NSAR),
Significant improvement (!) after six-monthly
psycho-neuro-immunological therapy (mental behaviour training).

What happened here?

Regulation of endothelial cell plasticity by TGF-β
Laurens A. van Meeteren

Skeletal metamorphosis in fibrodysplasia ossificans progressiva (FOP) Frederick S. Kaplan et.al.,

Published online 2008 Nov 1. doi: 10.1007/s00774-008-0879-8

Fibrodysplasia ossificans progressiva

Best Pract Res Clin Rheumatol.
Published in final edited form as:

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www.vodderakademie.com

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**The white vessels**
The ancient Greeks knew about the lymphatic vessels and spoke of the "white" vessels in contradiction to the "red" and "blue" vessels of the bloodstream. **Hippocrates (460-377 B.C.)** already spoke of the lymphatic system as "vessels that carry white blood".

**Aristoteles (384-322 v. Chr.)**
describes vessels that carry "white blood" in humans and animals as "ductus lactei"
In biology, Aristotelian views could persist until the 18th century.
Thus William Harvey, 1578 - 1657, assumed with the discovery of the blood circulation from Aristotle's principle that nature produces nothing unnecessary, and used it to determine the nature of the blood vessels and ventricles.

**Erasistratos ( around 305 v. Chr. in Julis, auf Keos; † around 250 v. Chr.)** was a Greek doctor and naturalist, anatomist, surgeon and physiologist. As co-founder of the Alexandrian medical school, he describes "Milk vessels" in the "lamb".

**Abū Ālī al-Husain ibn Abd Allāh ibn Sīnā * around 980 † Juni 1037 –**
short Ibn Sina and Latinized Avicenna - was a Persian doctor.
He is one of the most famous personalities of his time and has shaped the history and development of medicine in particular.

**Bartolomeo Eustachi,**
(* between 1500 and 1520 † 27. August 1574*
was an Italian doctor and anatomist. In 1552 he wrote a textbook of anatomy, the *tabulae anatomicae*, in which "lymphatic vessels" are described: "*Vena alba thoracis*" in the horse. The book, which was not published until 1714, contained a remarkable collection of anatomical drawings.

Text-source: Eine kleine Geschichte der Lymphologie :Ch. Schuchhardt und H.Wittlinger,H.Rabe: Viavital Verlag ,Köln 2003
Scholars and scientists in the history of the lymphatics system. Journal of Anatomy. DOI: 10.1111/joa.12644
The 17th century was the golden age for the study of the lymphatic system with several discoveries:

**Caspar Asellius** (1581-1672) is considered the actual discoverer of the lymphatic system. In 1622 he discovered lymphatic vessels in dogs. He assumed that the newly discovered vessels were used to transport the resorbed food from the intestine to the liver.

**Jean Pecquet** (1622-1674) succeeded in proving that the vessels discovered by Aselli did not flow into the liver but into a bag-shaped extension in front of the lumbar spine, called Cisterna Chyli. (In French this Cisterna is called "Cisterna Pecquet"). Pecquet also described the further path of the lymph through the large thoracic duct with its opening into the left angle of the vein. Pecquet was the first to prove the connection of the lymphatic vascular system with the blood circulation.

**Paolo Mascagni** (1752-1815) published his book *Vasorum lymphaticorum corporis humani historia et iconographia* in Siena in 1787, which identified him as a specialist in the human lymphatic system and established his reputation in Europe. His drawings of these fine ramifications are still valid today. He also described quite precisely the possible causes of lymphedema.


Lymphological Macro Cosmos III

from Anatomy to Physiology

In 1650, the Swedish physician Olof Rudbeck intensively studied the lymph vessel system and recognized its importance. 1652 he discovered the lymph vessels of the intestine, the spleen and the liver. He was the first to discover that lymph flowing from the tissue via the lymph vessels to the body circulatory system.

William Hunter (\textit{*} 1718 \textit{†} 1783) describes the entire lymphatic system of the body - this not only affects the belly area, but the whole body in the sense of a "large and general system".

William Hewson (1739-1774) knowing about the work of William Hunter he worked on physiological problems of "lymph formation"

Carl Ludwig (\textit{*} 1816 \textit{†} 1895) : succeeded in the first cannulation of the lymph vessels - Berliner Blau for the depiction of lymphatic vessel. Increase in blood capillary pressure leads to increased fluid filtration and evacuation via the lymph vessel system.

Cecil Kent Drinker (1887-1956) :
He was the first to prove that blood proteins are able to leave the bloodstream and that these plasma components are only reabsorbed by the lymphatic vessels.

Text-sources:
Heinz Schrör: \textit{Carl Ludwig. Begründer der messenden Experimentalphysiologie 1816–1895} (Große Naturforscher 33), Stuttgart 1967
Lymphatics, lymph, and lymphoid tissue; their physiological and clinical significance, Cambridge, Mass., Harvard University Press, 1941.
Wikipedia

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Due to improving technical possibilities offered through imaging, it was possible to improve diagnostics and as a result to improve therapy methods.

**Alexander von Winiwarter** reports in 1892 about the treatment possibilities of Lymphedema with massages, bandages and mobility exercises.

**Estrid & Dr. phil. Emil Vodder** in Paris at the Beauty and Health Exhibition in 1936, manual lymph drainage was introduced as a universal therapy.

**In the 1930s**, Emil Vodder described a gentle, effective treatment of edema that stimulates lymph transport by increasing lymph vessel activity. In 1985 he was awarded the Rohrbach Medal by the Physical Therapy Association in recognition of his life's work. This award was also associated with the confirmation of a professional association that Emil Vodder is the creator and eponym of his method: **Manual lymphatic drainage according to Dr. Vodder**.

**Der Arzt J. Asdonk** got to know the "**manual lymphatic drainage**" according to Emil Vodder in 1963. He introduced the subsequent compression bandage into the treatment scheme in order to maintain the volume reduction achieved by manual lymph drainage. In the meantime, this so-called complex physical decongestion therapy (KPE) has established itself worldwide as the most effective treatment for lymphedema. In 1967, the "Gesellschaft für manuelle Lymphdrainage nach Dr. Vodder" was founded in Essen. From this society the **German Society for Lymphology** was founded in 1976 with the participation of Eberhard Kuhnke, Gregl, Földi and Hohlbaum. Especially the cooperation with E. Kuhnke and Földi brought a lot of dynamism to the still young lymphology at that time, because they developed the theoretical basics of this therapy.

**Prof. Hildegard Wittlinger** - The spirit of the house “Wittlinger”

Massage therapist Specialist teacher for manual lymphatic drainage according to Dr. Vodder/KPE

Co-founder of the "Gesellschaft für Manuelle Lymphdrainage according to Dr. Vodder", book author "Manuelle Lymphdrainage nach Dr. Vodder"

**Frau Prof. Wittlinger** travels to lectures and courses in many European countries and also overseas, mainly to the USA and Canada, where she introduced the Vodder Method in Manual Lymph Drainage to interested therapists.

Due to its intensive teaching, the Dr. Vodder School Austria has gained a worldwide reputation.
Lymphology as a life mission:

Prof. Prof. h.c. Dr. med. Michael Földi with his wife Dr. med. E. Földi, as an internist, lymphologist and international capacity, has had a significant influence on lymphology in Germany and worldwide.

Prof. H. Weissleder: Former President of the German Society of Lymphology. Expert in lymphological imaging: Example: Diagnostics of the lymphatic system over time: direct lymphography, fluorescence micro-lymphography, capillary scintigraphy, sonography, computer tomography, Magnetic resonance tomography and MRI lymphography - Possibilities and limitations of the individual examination procedures - LymphForsch 16 (2) 2011

Dr. med. Ch. Schuchardt: Internist, haematologist and internal oncologist - medical director of several schools for manual lymphatic drainage in Asdonk/Földi (Switzerland, Germany, Canada). Regular lectures at home and abroad. Former President of the German Society of Lymphology.

Ao. Univ. Prof. Dr. E. Brenner
Clinical-functional anatomy University of Innsbruck

Prof. Dr. Dr. med. habil. R. Baumeister
Consultant for Lymphology and Reconstructive Microsurgery

Dr. med. W. J. Brauer - Radiology: currently: Possibilities and limits of sonographic lymph node diagnostics: how to do it, LymphForsch 22(2)2018

Dr. F. J. Schingale
Medical director of the Lympho-Opt-Klinik
Specialist in liposuction.

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Prof. P. Hutzschenreuter: „MLD (KPE) and Science“ - literature-extract -

**Lymph formation and lymph transport in experimental lymphedema.**
Hutzschenreuter P., Brümmer H.
Aktuelle Beiträge zur Manuelle Lymphdrainage. 1992; 3: 8-11

**Spontaneous anastomosis of lymph collectors after lymphadenectomy - an experimental study.**
Hutzschenreuter P., Brümmer H
Aktuelle Beiträge zur Manuellen Lymphdrainage: 1992, 3: 24-33

**Scar and lymphatic drainage.**
Hutzschenreuter P., Brümmer H.
Aktuelle Beiträge zur Manuellen Lymphdrainage: 1992, 3: 88/89

**The vegetative nervous system in patients and practitioners treated with manual lymph drainage according to Dr. Vodder.**
Hutzschenreuter P., Wittlinger H., Hermann H., Silberschneider K., Kitzbichler M.
Aktuelle Beiträge zur Manuellen Lymphdrainage. 2000; 7: 109

**The effect of manual lymphatic drainage on arterial occlusive diseases in the pAVK IIa stage.**
Hutzschenreuter P., Ehlers R.
Aktuelle Beiträge zur Manuellen Lymphdrainage. 1992; 3: 85-87

**Change of the microcirculation during the manual lymph drainage technique according to Dr. Vodder.**
Hutzschenreuter P., Brümmer H., Kurz I., Wittlinger D.
Aktuelle Beiträge zur Manuellen Lymphdrainage. 1992; 3: 44-52

**Manual lymphatic drainage and smooth musculature.**
Hutzschenreuter P.
Aktuelle Beiträge zur Manuellen Lymphdrainage. 1994; 4: 32-34

**Microcirculation in AVK and diabetes mellitus.**
Hutzschenreuter P.
Aktuelle Beiträge zur Manuellen Lymphdrainage. Band 6, Heidelberg: Karl F. Haug Verlag, 1998

**The effect of lymph drainage on vasomotion.**
Hutzschenreuter P., Brümmer H.
Aktuelle Beiträge zur Manuelle Lymphdrainage. 1992; 3: 19-20
Lymphological Micro Cosmos
The Endothelium

What is the Endothelium?
**Definition: Endothelium**

Single-layer cell structure which covers the inner vessel wall of arteries, capillaries, lymph vessels and veins.

The endothelium operates as a biological network system (biological sensor and signal generator) in response to all internal and external influences. and is responsible for the energy supply to approx. 80 trillion cells!
The Endothelium - the "chief conductor" - is a systemic organ!

THE ENDOTHELIUM

Covering an area of 6-8000 square meters
Weight: 1.5 Kg.

Biological Sensor:
Expression of endothelial receptors:
Growth-factors: IGF, FGF, VEGF, ICAM, VCAM, P-Selektin, Cytokine, bacterielle Toxine, Neuropeptide, CRH

Biological signal transmitter:
Production of vasoactive peptides and hormones

Vasodilators: NO, Prostacyclin, EDHF, Bradykinin, Adrenomedullin, C natriuret. Peptid, ADP...

Vasoconstrictors: Endothelin-1, Angiotensin II, Thromboxan A2, Prostaglandine, Hydrogen peroxide, Freie Radikale.....

Major Tasks of the Endothelium:
Regulation of homeostasis and haemostasis / thrombosis, immunomodulation, vasorelaxation and constriction, vascular growth - vascular tightness - remodeling - apoptosis...!
The Endothelium - the “Chief Conductor" - is a systemic organ!

From conception to death, the Endothel is THE coordination center of all "Life-creating, sustaining, and terminating mechanisms."

It is a key factor for development and differentiation of the entire vascular and lymphatic system:

- VEGF and Notch Signaling in Angiogenesis
- Pericytes in Vascular Development and Function
- Development and Differentiation of the Lymphatic Vascular System

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What is the importance of keeping my Endothelium in good health?
A "well-kept" Endothelium gives statistically 14.2 years of life!

NEJM 2012;366:321: Cardiovascular Lifetime Risk Pooling Project
### Molecular reaction fields of the Endothelium

<table>
<thead>
<tr>
<th>Group</th>
<th>Function</th>
<th>Receptor/Cytocine/Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptors of the immune system</td>
<td>Cell adhesion and cell migration</td>
<td>ICAM-1 = Intercellular Adhesion molecule-1 (CD54)</td>
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<tr>
<td></td>
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<td>ICAM-2 = Intercellular Adhesion molecule-2 (CD102)</td>
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<td></td>
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<td>VCAM-1 = Vascular Cell Adhesion Molecule-1 (CD 106)</td>
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<td>E-Selectin = Endothelial Selectin (ELAM-1) (CD 62E)</td>
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<td>P-Selectin = Platelet Selectin(CD 62P)</td>
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<td>PECAM-1 = PlateletEndothelial Cell Adhesion Molecule-1 (CD31)</td>
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<td>VEGF=VascularEndothelial Growth Factor</td>
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<td>LFA-3 = Lymphocyte Function Antigen -3 (CD 58)</td>
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<td>Endoglin = TGF-β binding protein = Transforming Growth Factor β</td>
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<td>Antigen-presentation</td>
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<td>MHC – 1 = Major Histocompatibility Complex Class I</td>
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<td>MHC – 2 = Major Histocompatibility Complex Class II</td>
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<tr>
<td>Coagulation-active substances</td>
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<td>Tissue Factor (Thromboplatin) v.Willebrand Factor</td>
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<td></td>
<td></td>
<td>PAF = Platelet Activating Factor (CDw 109) Kinogen</td>
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<td></td>
<td></td>
<td>TFPI = Tissue Factor Pathway Inhibitor (Fxa-Inhibition)</td>
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<td></td>
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<td>PSBP= Endothelial Cell Derived Protein S Binding</td>
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<tr>
<td></td>
<td></td>
<td>tPA = Tissue Plasminogen Activator</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PAI-1= Plasminogen Activator Inhibitor</td>
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<tr>
<td></td>
<td></td>
<td>HS = Heparansulfat (AT III binding)</td>
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<tr>
<td></td>
<td></td>
<td>PG I-2 = Prostaglandin I-2 Inhibitor</td>
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<tr>
<td></td>
<td></td>
<td>NO = Nitric Oxide</td>
</tr>
<tr>
<td>vasoactive substances</td>
<td>Dilatation</td>
<td>Endothelin -1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ACE= Angiotensin Converting Enzym</td>
</tr>
<tr>
<td></td>
<td>Constriction</td>
<td>IL-1, IL-6, IL-8, MCP 1u3, G-CSF,GM-CSF, TGFβ,</td>
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<tr>
<td></td>
<td></td>
<td>TNF-R-I (p55),TNF-R-II (p75),IL-1R, IL-3R,IL-6R</td>
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<tr>
<td></td>
<td></td>
<td>PG=proteoglycan,Fibronectin,Elastase, Collagenase</td>
</tr>
<tr>
<td>Cytokine /chemokine/Receptors</td>
<td>TNF -alpha</td>
<td>PIEZO 1</td>
</tr>
</tbody>
</table>
What is „NO“ ? !
NITRIC OXID

is the most important protector of the ENDOTHELIUM towards the vascular inflammatory process!

EVERYWHERE!!
NO is a gas......

...which exists in the vessels and in the vascular bed in the form of a NO vapour and provides the adequate energy supply for the cells .... !
NO regulates the blood pressure!
NO regulates ....

the nerve signal transmission.
the learning process! ...
the memory!
NO regulates.... ...... the cell supply via the

blood distribution adjusted to the need

in the field of microcirculation!
NO regulates and influences ....

our entire immune system!
NO-deficiency: The reduced bioavailability of NO - the body's own "anti-rust agent" - plays a significant role in atherogenesis and in the dynamics of ageing processes. The protection of NO is synonymous with arteriosclerosis prophylaxis.

Lüscher et al. / Zürich
Ignarro et al.
Drexler H.
Endothelial medicine: Why does the endothelium get sick?

Imbalance between aggressive factors (inflammatory stress) and the endothelial protection factor NO.

- nicotine consumption, reactive oxygen species (ROS)
- Physical / Chemical stress/ Water quality!
- Environmental stress / pesticides / nutritional stress
- Lifestyle / Family Amnesty
- Sports inactivity / osteoporosis body weight
- Chronic inflammation !!!! / Rheumatism
- Elevated blood pressure
- Fat metabolism disturbance/food additives !!
- Diabetes mellitus
- emotional and mental stress, noise pollution!!!
- Depression, anxiety, panic Depressive episodes or chronic
- Depression are precursors of disease on the the way to coronary heart disease
Stress !!

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In this study, 293 patients received a combined PET / CT scan to document the activity and inflammation of their arteries in the brain, bone marrow and spleen.

High activity of their amygdalae resulted in a 60% higher risk. (P <0.0001) for myocardial infarction, angina, heart failure, stroke and peripheral arterial disease.

During stress, signals are apparently sent from here to the bone marrow and other body regions to increase the production of white blood cells and other inflammatory substances.

Brain scans of volunteers showed increased activity of the amygdala.

(Photos: REUTERS)
Endothelfunction and Shear/Stress!

Functional endothelial barrier
- Cell survival and low turn over
- Anti-inflammatory, anti-coagulant
- Low oxidative stress

Loosened endothelial barrier
- Cell death and high turn over
- Epigenetic modifications
- High oxidative stress and inflammation
- Neo-angiogenesis, hemorrhage, leukocyte extravasation

Shear
Strain

Intima
Media
Adventitia

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Shear stress dependent vascular inflammatory activity at nuclear level

Endothelial dysfunction

Endothelial cells exposed to low oscillating shear stress (OSS) show proinflammatory response due to the increased expression of proinflammatory genes (VCAM-1, BMP4, MMPs)!

Endothelial cells exposed to fast harmonic flow, high shear stress (HSS), react anti-inflammatory due to the expression/production of anti-inflammatory genes = atheroprotective genes (Klf2, Klf4, eNOS).

Conclusion:
"Reduced vascular inflammation" through sporting + mental activity / good water quality / trained stress management ...positive lifestyle (!) ....... (Avoid naggers and "know-it-alls"!)

Stress influences the quality of endothelial flow profiles and deteriorates thus pre-existing endothelial dysfunction disorders!

Endothelial diseases are "curable"!

**RESEARCH ARTICLE**
Shear-sensitive microRNA-34a modulates flow-dependent regulation of endothelial inflammation (Huvec)
Wendong Fan, Rong Fang, Xiaoyuan Wu, Jia Liu, Mingzhe Feng, Gang Dai, Guojun Chen, Guifu Wu
J Cell Sci 2015 128: 70-80

“In the present study, we report that mechanosensitive miR-34a modulates the flow-dependent regulation of endothelial inflammation, partially through sirtuin 1 (SIRT1) and its downstream nuclear factor κB (NF-κB) signaling pathway.”
Diagnostik der Endotheldysfunktion:

Inflammatorischer Stress gilt heute als Hauptvermittler beschleunigter Alterungsprozesse.

**Risikomarker:**
- ox.LDL / LOX-1, Pb,Hg,Fe,Cu
- PAI-1, Vitaminmangel, spez. B-Gruppe, Selen, Homocystein...
- IL-1, NT-proBNP,
- Prostaglandin E2
- VCAM-1 / sP-Selektin / ICAM-1
- NFkB / IL-6 / TNFα
- Leucotrien B4
- MCP-1, ADMA
- Myeloperoxidase
- CRP, CD-40-Ligand
- Platelete aggregation
- Lipoprotein a, EBV, CMV,
- Herpes -Virus

**Quellen:**
- Cardivasc Res. 2003 Jan; 57(1): 238-43
- Atherosclerosis. 2002 May;162(1):179-85
- Murad Atmaca et al. :Serum folate and homocysteine levels in patients with obsessive-compulsive disorder; Psychiatry Neurosciences 59 (5), 616-620; Firat University, School of Medicine, Elazig, Turkey:
- Circulation:Vol.117, 2008:Extreme Lipoprotein A Levels and Risk of Myocardial Infarction...“The Copenhagen City Heart Study"
The Mikrocirculation!

The Human Microcirculation: Regulation of Flow and Beyond.
Gutterman DD et al.

J Am Heart Assoc. 2016 Nov 4;
"Small Blood Vessels: Big Health Problems?，“
Scientific Recommendations of the National Institutes of Health Workshop.
Microcirculation
the functionally most important part of human blood circulation.

Microcirculation includes:

The blood and its components, blood vessels with diameter \( d < 100 - 200\mu m \) (arterioles, capillaries, venules),

Initial lymphatic vessels/pre-collectors

Interstitial space
(area between cells and vessels)
The world of microcirculation research and its significance for MLD

Blood Vessels.

Distribution of blood vessels in the body

- Arteries ca. 11.5%
- Veins ca. 14.5%
- Mikrocirculation ca. 74.0%
The world of microcirculation research and its significance for MLD
Microcirculation: area and expansion

Area ca. 7,000 qm
Expansion: 100,000 km
Zur Mikrozirkulation gehören:

Das Blut und seine Bestandteile, Blutgefäße mit Durchmesser
(d) < 100 - 200µm
(Arteriolen, Kapillaren, Venolen), das Endothel!

Initiale Lymphgefäße, LEC.

Interstitieller Raum
(Bereich zwischen Zellen und Gefäßen)

Microcirculation the functionally most important
Blood circulation.
What is the problem??
Vasomotion

Rhythmic vascular diameter changes due to local tonus changes of the smooth musculature independent of heart rhythm, neuronal or humoral regulation in the microvascular regions.

„The" triggers improvements in microcirculation

Informational dynamics of vasomotion in microvascular networks: a review
R. K. Pradhan1, V. S. Chakravarthy2
Conditions Linked to Microvascular Dysfunction:

**Ischemic Cardiomyopathy**: Am Heart J. 2003 Sep; 146(3):549-54.


**Obstructive Sleep Apnea**: Am J Respir Crit Care Med. 2010 Dec 15; 182(12):1540-5.


**Schizophrenia**: Transl Psychiatry. 2015;5:e616.


**Chagas Disease**


**Cerebral Vasospasm**: Biomed Res Int. 2014; 2014():253746.


**Systemic Sclerosis**

**Hypertension**: Aging Cell, 2017 Mar 14

Lymphedema: a systemic inflammatory process!

Lymphedema is a progressive disease caused by congenital anomalies, obstructions, injuries, or infections of the lymphatic system, usually due to lymph vessel injury damage during cancer treatment with risk factors such as extensive lymph node dissection and adjuvant chemo/radiotherapy. (1)

If a lymphatic injury is present, the fluid flow is interrupted, leading to fluid accumulation, increased lymph flow, vasodilatation, valvular dysfunction and reflux. Changes in normal tissue function due to inflammation, tissue remodeling, lymphatic hyperplasia and adipocyte deposition subsequently occur and lead to lymphoedema phenotype.

"A histological feature of lymphedema is the infiltration of inflammatory cells and recent studies with animal models and clinical biopsy specimens have shown that this response plays a key role in the pathology of lymphedema.(2)

An increased liquid flow itself can serve as an early signal for inflammation. The TGF-β1 is an autocrine upregulation of the transforming growth factor β1 - (TGF-β1) with differentiation into myofibroblasts and increased collagen production when lateral lymph vessels are not able, to compensate for the initial lymphatic damage, the resulting persistence of fluid accumulation in the interstitial space contributes to a sustained positive feedback loop of inflammation that ultimately leads to pathological changes in lymphedema.(3)

1) Dtsch Arztebl 2017; 114(5): [14]; Das Lymphödem
Inflammatory Manifestations of Lymphedema

3) A driving force for change: Interstitial flow as a morphoregulator.
Inflammatory Manifestations of Lymphedema

Both experimental and clinical studies over several decades have identified inflammation as a critical component in the pathophysiology of lymphedema. A histological feature of lymphedema is the infiltration of inflammatory cells and recent studies with animal models and clinical biopsy samples have shown that this response plays a key role in the pathology of the disease.

A: This leads to lymph congestion, lymph vessel dilatation, tail swelling, inflammation, fat deposition and fibrosis, which accurately simulates the histological characteristics of postoperative lymphedema in humans.

B: With the help of near infrared imaging, it was determined that the removal of the lymph node with the corresponding fat pad leads to vascular ruptures, skin reflux and lymph drainage through collateral vessels, similar to breast cancer surgery after ALND (Axillary LymphNode Dissection).

C: A new mouse model in which lymphatic endothelial cells (LECs) are not surgically removed, resulting in progressive lymphedema. Using Cre-Lox technology, the human diphtheria toxin receptor (DTR) is coupled to a lymph specific promoter known as Fms-related tyrosine kinase 4 (FLT4), which enables ablation of LECs from the entire lymphatic network through DTR activation.
Lymphological Micro - Cosmos

The lymph-peri lymph system is a "systemically active organ." Lymphangiogenesis is a recognized hallmark of inflammatory processes in tissues and organs.

No region of the body is impenetrable to the flames of inflammation.

Inflammation-associated lymphangiogenesis (IAL): the basic drainage task of lymphatic vessels is a complex balance of locally processed and transported antigens as well as interstitial cytokine and immune cell signaling. "Inflammatory progression (IAL) is present in acute and chronic tissue pathologies throughout the body. Lymphatic vessels play physiological roles relevant to all medical fields as important regulators of fluid balance, immune cell trafficking, and immune identity. (1)

Importance of IAL in tissue inflammation pathologies: Examples:

Dermal inflammation and lymphangiogenesis

Lymphangiogenesis in intestinal inflammation

Adipose tissue, the metabolic syndrome, and lymphatic function (3)

Recently, more active roles for LECs in immune regulation have been receiving more attention.

LECs have the ability to - themselves take up and process antigens,
- alter immune cell phenotype and function
- serve as a site of immune cell interaction
- secrete cytokines that propagate immune responses both locally and in the downstream node. (2)

1) Lymphangiogenesis: fuel, smoke, or extinguisher of inflammation’s fire

2) Emerging roles of lymphatic endothelium in regulating adaptive immunity.

3) Mechanisms of obesity and related pathologies: the macro- and microcirculation of adipose tissue.

Picture from 1)
Lymyphedema: a systemic inflammatory process!

III

In a study of affected patients undergoing CDT, for example, Foldi et al. noted that the expression of pro-inflammatory genes such as that for CD14, interferon-gamma (IFN-γ) receptor, tumor necrosis factor-alpha (TNF-α), integrin alpha 4 beta 1 (α4β1; also known as Very Late Antigen-4 or VLA-4), tumor necrosis factor receptor p55 (TNFR1), and CD44 were increased prior to and significantly decreased after the first phase of treatment.

Effect of complex decongestive physiotherapy on gene expression for the inflammatory response in peripheral lymphedema.
Foldi E¹, Sauerwald A, Hennig B

IL-6 regulates adipose deposition and homeostasis in lymphedema

Current evidence suggests that a variety of key players, including T helper cells, Tregs, macrophages, and dendritic cells, play complex roles in the pathology of the disease by elaborating inflammatory cytokines and regulating the development of collateral lymphatic vessels.

Inflammatory Manifestations of Lymphedema

Dr. Vodder Akademie
www.vodderakademie.com

Wittlinger Therapiezentrum
www.wittlinger-therapiezentrum.com
Lymphedema: a systemic inflammatory process!

Toll-like receptor deficiency worsens inflammation and lymphedema after lymphatic injury


“In conclusion, we have shown that TLR function plays an important role in homeostatic responses to lymphatic fluid stasis. These molecules (endogenous danger signals: extracellular matrix breakdown products (hyaluronan fragments), heat shock proteins (HSPs), members of the S100 family of proteins, and nuclear proteins, such as high-mobility group box-1 (HMGB1)..... regulate a variety of effects like lymphangiogenesis, fat deposition, inflammation, and tissue fibrosis. These molecules are known to activate TLR 2, 4, and 9, suggesting that these pathways play important roles in the regulation of tissue responses to lymphatic fluid stasis and inflammation processes.”
# Lymphedema: a systemic inflammatory process!

## IV

Summary of selected cytokines and growth factors involved in lymphedema

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-γ</td>
<td>Impairs lymphangiogenesis&lt;br&gt;Activates macrophages</td>
</tr>
<tr>
<td>IL-1</td>
<td>Induces DC migration</td>
</tr>
<tr>
<td>IL-13</td>
<td>Impairs lymphangiogenesis&lt;br&gt;Promotes M2 macrophage activation</td>
</tr>
<tr>
<td>IL-4</td>
<td>Impairs lymphangiogenesis&lt;br&gt;Promotes M2 macrophage activation</td>
</tr>
<tr>
<td>IL-6</td>
<td>Regulates chronic inflammation&lt;br&gt;Decreases adipose deposition</td>
</tr>
<tr>
<td>TGF-β1</td>
<td>Mediates soft-tissue fibrosis&lt;br&gt;Negatively regulates lymphatic vessel regeneration</td>
</tr>
<tr>
<td>VEGF-C</td>
<td>Promotes lymphangiogenesis</td>
</tr>
</tbody>
</table>
Lymphological Micro - Cosmos

The phenomenon of chronic inflammation in the vascular lymph system

Relevant publications on the topic (selection)

Mast cells and histamine are triggering the NF-κB-mediated reactions of adult and aged perilymphatic mesenteric tissues to acute inflammation.

Lymphatic endothelial cells, lymphedematous lymphangiogenesis, and molecular control of edema formation.

Inflammatory Manifestations of Lymphedema

Physiological Perspective on Therapies of Lymphatic Vessels
Lymphological Micro - Cosmos

The phenomenon of chron. Inflammation in the vascular lymph system

Relevant publications on the topic (selection)

New member of endothelial arsenal against inflammation

Inflammatory responses and inflammation-associated diseases in organs.
Fu et al. found that inflammatory genes were associated with a greater number of symptoms due to Lymphedema:

**IL-4 rs2070874** was significantly associated with phenotype of impaired limb mobility and fluid accumulation.

Phenotype of fluid accumulation was significantly associated with **IL6 rs1 800795, IL4 rs2243250 and IL4 rs2070874**.

Phenotype of discomfort was significantly associated with **VEGF-C rs3775203 and IL13 rs1800925**.
**Science of „Microparticles“ – Sophisticated Vesicles !**

Microparticles are small (0.1-1 µm) large lipid-rich vesicles that are caused by various mechanisms such as mechanical stress (Diehl, Nagy et al. 2008), apoptosis (Barry, Pratico et al. 1997), (Mallat, Hugel et al. 1999) and cell activation (Beaudoin and Grondin 1991) of plasma membranes of multiple cells. They probably have many (patho)-physiological functions e.g. in the area of haemostasis and in the development and progression of diseases such as atherosclerosis and malignancies (Barry and FitzGerald 1999), (Diamant, Tushuizen et al. A subgroup of microparticles are endothelial microparticles (EMP) that originate from activated, destroyed and/or apoptotic endothelial cells and thus represent a marker for vascular damage”.

Excerpt from : Cellular Internalization of Microparticles Dissertation On the acquisition of the Doctorate of Medicine at the Medical Faculty of the Ludwig-Maximilians-Universität Zu München Submitted by Géraldine Müller-Stoy from Munich 2013
Extract from: Inaugural dissertation for the award of a doctorate in medicine from the High Medical Faculty of the Ruhr University Bochum presented by Lisa Marie Niedballa from Seeheim-Jugenheim

**RESEARCH ARTICLE**

Shear-sensitive microRNA-34a modulates flow-dependent regulation of endothelial inflammation

J Cell Sci 2015 128: 70-80

Role of flow-sensitive microRNAs in endothelial dysfunction and atherosclerosis – “Mechanosensitive Athero-miRs”


“Emerging evidence indicates that alteration of flow conditions regulate expression of miRNAs in endothelial cells both in vitro and in vivo”.

The key signaling pathways that are targeted by these mechano-miRs include the endothelial cell cycle, inflammation, apoptosis, and nitric oxide signaling.
Science of „Microparticles“ – Sophisticated Vesicles!

The majority of the microparticles present in healthy blood originate from thrombocytes. Other cells of the entire vascular system, such as erythrocytes, granulocytes, monocytes, lymphocytes and endothelial cells are capable of forming microparticles. (Van Wijk, VanBavel et al. 2003), (Morel, Hugel et al. 2004). The fragments of the membrane with intracytoplasmic material are released into the extracellular space.

Recent reports identified particles containing micro RNAs that exert protective effects on downstream targets. “Microvesicles appear to be more than just biomarkers of vascular injury. They serve as important para/endocrine mediators in cell-to-cell communication“. “Given its large volume, the microcirculation probably serves as the major source of endothelial microvesicles in the circulation”.

Circulating microvesicles from patients with cardiovascular disease impair endothelial function in vessels from healthy animals!! Circulation. 2001 Nov 27; 104(22):2649-52.

The mechano-miRs that are implicated in atherosclerosis are termed as “mechanosensitive atero-miRs” and are potential therapeutic targets to prevent or treat atherosclerosis. Arterioscler Thromb Vasc Biol. 2014 Oct; 34(10): 2206–2216.
Endothelial microparticles are jointly responsible for the Development of "endothelial dysfunction" and determinable as diagnostic marker.

Clin Chem. 2013 Aug;59(8):1166-74..
Evolving role of microparticles in the pathophysiology of endothelial dysfunction.

Microparticles include membrane and cytoplasmic Cell parts: RNA, microRNA, lipids, but also "functional Endothelial NO-Synthase" !!
MP´s are biomarkers for vascular damage and inflammation!

Size: 100 nm-1µm
Role of flow-sensitive microRNAs in endothelial dysfunction and atherosclerosis –
“Mechanosensitive Athero-miRs” Sandeep Kumar, Chan Woo Kim, Rachel D. Simmons, and Hanjoong Jo
Arterioscler Thromb Vasc Biol, 2014 October

Recent publications have identified particles containing micro-RNAs that have protective effects on downstream targets. Microvesicles serve as important endocrine mediators in cell-to-cell communication. In view of its large volume, microvesicles probably serve as the main source of endothelial microvesicles in the circulatory system.

Circulating microvesicles of patients with cardiovascular disease interfere the healthy endothelial function in vessels of animals! Circulation 2001, Nov 27
The world of microcirculation research and its significance for MLD

The lymph flow can be influenced by internal and external stimuli.

Sympaticolysis during MLD increases vasomotion and lymphatic volume

Improved Vasomotion = Altered Shear Stress = Reduced Inflammation

Professional MLD/KPE is the "Manual Therapeutic Agent" in the field of Microcirculation improvement!

Physical improvements achieved through this usually result in the additional optimization of "emotional factors" (trust, hope, joy, self-acceptance) an improvement of the systemic inflammation process and immune strengthening!
Microcirculation optimization through "Pulsed electromagnetic field therapy (PEMFT)"

Dr. Vodder Akademie
www.vodderakademie.com

Wittlinger Therapiezentrum
www.wittlinger-therapiezentrum.com
Improvement of microcirculation in the lymphatic area through PMFT: Microcirculation in the focus of research

Abbildung 341
Meßdaten zum Merkmal „Strömungsfluß der initialen Lympe Ql“ (Mittelwerte) im subkutanen Targetgewebe in einem 60-tägigen Behandlungszeitraum bei einer Stichprobe aus geriatrischen Diabetikern mit Polyangioneuropathie, die zusätzlich zur kliniküblichen Therapie komplementär mit einem bestimmten elektromagnetischen Wechselfeld mit Vasomotionsstimulation behandelt wurde (Verum), im Vergleich mit einer Stichprobe, bei der keine komplementäre Behandlung stattfand (Kontrolle).

Klopp et.al.: „Mikrozirkulation im Fokus der Forschung“
Mediquant Verlag 2008
Lymphatic smooth muscle: the motor unit of lymph drainage

Pierre-Yves von der Weid, David C. Zawieja

Embedded into the wall of collecting lymphatic vessels and trunks, the *lymphatic smooth muscles* are cardinal to the functions of the lymphatic system. Their intrinsic contractile property — *the intrinsic lymph pump* — is sensitive towards physical signaling....!

.... rhythmical and phasic contractions of the vessels, represent the principal mechanism by which lymph flow is generated.
Evidence-Based Use of Pulsed Electromagnetic Field Therapy in Clinical Plastic Surgery

Berish Strauch, MD, Charles Herman, MD, Richard Dabb, MD, Louis J. Ignarro, PhD, Arthur A. Pilla, PhD

Microcirculation improvement in the vascular/lymphatic system through PEMF therapy:

**Diabet Foot Ankle.** 2013; 4: 10.3402/dfa.v4i0.22081.
Gaurav Thakral, MD, et al.: Electrical stimulation to accelerate wound healing

Coupling of pulsed electromagnetic fields (PEMF) therapy to molecular grounds of the cell.
Funk RH.¹

**Br J Pharmacol.** 2005 Mar;144(5):605-16.
Vasomotion: cellular background for the oscillator and for the synchronization of smooth muscle cells.
Aalkjaer C, Nilsson H

**Microcirculation: the focus of research; Introduction to biomechanical, physiological and pathophysiological basics and selected treatment options**

Lympathic smooth muscle: the motor unit of lymph drainage
Pierre-Yves von der Weid⁴, David C. Zawieja⁵

Different ways of PEMF-coupling to molecular biology of the cell:
Pilotstudy 2015:
Pawelke - Wittlinger – PMFT

Is there a specific effect of a specific PMFT signal in regard to oedema reduction and inflammatory parameters in addition to the established KPE therapy as part of a 3-week intensive therapy?

YES, clearly with all examined parameters!

R. Pawelke: unpublished data 2015
Clinical follow-up study - Pawelke/Wittlinger 2015
outcomes

In 10 consecutively admitted patients with prim./sek. Leg lymphedema
the signal configuration BEMER (P3) was additionally tested twice a day for 20 minutes in addition to the
standardized therapy program.

All patients showed a significant reduction of oedema!

without PEMF signal (previous stay !) : edema reduction between 3.09 % - 9.07 % on average of 6.68 %.
with PEMF signal : oedema reduction between 5.73 % - 12.41 % on average of 8.96 %

A comparison of the two groups showed an increase in oedema improvement with an additional
Use of the PEMF signal configuration on an average of 37.23 %!

Summed edema improvement of both comparison groups:
WITHOUT PEMF therapy (previous stay) : 4,070 ml, average 678 ml.
WITH PEMF therapy : 5,332 ml ,average 892 ml.

The collected laboratory data showed relevant changes in "inflammatory parameters".
tendency proinflammat.parameter(TNF-alpha ,CRP increased ,) -and tendency anti-inflammatory
(FGF reduced, VEGF,PDGFbb increased , MCP-1 reduced IL-6, IL-8 reduced) !

The score "general condition" - subjective patient information (0-10) showed improvements in the course of the study
from scale value + 1 (7 to 8) to scale value +7 (2 to 9) -- on average improvement by 4.8 scale values
Lymphological macro-micro-cosmos and beyond....
The soul-body axis!

In view of the scientific data in the field of "Shear Stress" and "Microparticle Research", the fantastic seeming solution and dissolution of the "soul-body dualism" to be realized by the communication network of "microparticles"!

As a bridge between the individual spiritual world and the Human morphology down to the cellular and subcellular level.

Wouldn't it be wonderful, in the microcosm to get closer to the mystery of life? The many still open questions of the micro-cosmos, the instant cell-cell communication between approx. 80 trillion cells, in reaction and in cooperation with the "Emotional feeling and processing" and the "Emotional being and consciousness" are in the future Call and order in the sense of sustainable prevention and therapy!
What protects and affects the endothelium, the blood/lymph flow conditions, the immune system, the world of microparticles?

Loving…

Laughing…

Dancing…

Joy, friends and good atmosphere…!
Lymphological macro-micro-cosmos and beyond....
The soul-body axis !

This field of research, especially the knowledge of the mode of action of the "lymphological endothelial microcosm" gives it the significance of a "Systemic Organ" and "Lymphology"
a more important medical interdisciplinary in the future, even a Pacemaker function in successful treatment systemically effective endothelial diseases.

In this sense....
... on to scientifically fruitful new shores .......  Thank you for your time!