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Focus

Environmental dentistry

- **Interactions between periodontal and systemic diseases**
- **The immunopathogenesis of periodontitis**
- **Link between chronic inflammatory dental diseases and mental health symptoms**
- **Dental materials**
- **Multidimensional systemic diagnosis of root-filled tooth**

Multi-dimensional systemic diagnosis of root-filled tooth

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Biogenic amines (mercaptan/thioether/hydrogen sulphide) originating from endodontically treated teeth may show chronic-subtoxic and immunological systemic effects. These impacts will be discussed biochemically according to origin and target effect. A multi-dimensional diagnosis of the root-filled tooth from a practical local measurement of toxins and laboratory analyses will be shown for a precise and undogmatic diagnosis.

The problem of the biogenic degradation of the pulp is examined and discussed in depth in dentistry, prompting the following questions: Can bacteria survive in endodontically treated teeth and can root-filled teeth therefore cause autoimmunological and subtoxic effects? The website of a company is to be used to clarify the differently assessed terms. Under the key word "Endodontics" it says the following: "The aim of root canal treatment is to clean the root canals of the diseased tooth in order to then seal them with a filler material. The purpose of this is to prevent the development of painful inflammations. However, this procedure is generally very difficult and almost impossible with conventional equipment, with the result that the teeth then often have to be retreated with a resection or still end up having to be removed. Otherwise they can systemically paralyse the body through their remote focal effect and the release of highly toxic substances such as mercaptan and thioether and block key metabolic processes". The last sentence of this industry website for the key area of endodontic tooth preservation contains a few terms that are to be examined in more detail below:

- Remote focal effect
- Release of highly toxic substances
- Mercaptan and thioether
- Systemically paralysing and blocking key metabolic processes

As this area of assessment is largely neglected, this article seeks to open a critical examination of root treatments and their subtoxic-immunological systemic crosstalk.

What is meant by "remote focal effect"?

The unforeseen complexity and the breadth of possible triggers of systemic diseases require new scientific structures and procedures. The systemic response of the body is manifested in a complex set of subtoxic effects with destructive consequences for the rest of the body. Crosstalk takes place at both the cellular level and at the level of the systemic complexity of the network, which in our opinion requires new methods for processing biological data. Further aetiological factors of course also play a role in this system interaction, such as genetic polymorphisms, epigenetic factors, functional modulations, environmental effects and immunological engrams of the neuroendocrine-immune system [7] that are triggered once and then always triggered again in the same form – even without the primary trigger. Chronic-toxic effects in an advanced stage are likely to cause a disconnection of normally harmonised homeostatic procedures between the super systems, making it hard to return to a normal situation [2, 14]. The term remote focal effect therefore describes nothing other than the modern crosstalk and interaction on a wide range of levels of the body, triggered by a local pathogenic and remote effect; in the opinion of the author, the clinical and practical significance of this phenomenon is still neglected in mainstream dentistry [8].

Why do endodontically treated teeth trigger the “release of highly toxic substances”?

Can root-filled teeth trigger systemic diseases through chronic deposits of bacteria, thus causing the development of highly toxic substances?

The carriers responsible for this are anaerobic bacteria in the dental tubules of nonvital and root-treated teeth and their metabolic products. It is strange that the effect of dental bacterial toxins is still neglected, even though tetanus is caused not by the bacteria themselves, but by the toxins released by these bacteria. Are there any investigations on this subject in modern scientific literature? Nagaoka et al established in their study that in the case of vital teeth with fillings left open for more than 150 days, only 1.1% of the dental tubules were infected with bacteria, whereas with the root-filled, nonvital teeth 39.0% of the tubules were infected with bacteria [11] (Fig. 1).

The odontoblasts obviously create a physiological barrier against a bacterial invasion of the vital tooth in the dental tubules. In the nonvital tooth, however, this role of the odontoblasts as a physiological barrier against a bacterial invasion disappears, as the odontoblasts degenerate, thus allowing the bacteria to easily penetrate the tubules. The problem of disinfecting the root canal with the risk of periapical inflammation is of course well-known. Why is there a “release of highly toxic substances”? Gram-negative anaerobes form three types of toxins. Exotoxins are released extracellularly as the bacteria spread, and migrate from one focus of inflammation to remote parts of the body and cause cells to die. Endotoxins are localised in the outer membrane of the bacteria and are released as cells die. They induce local inflammation responses (IL-1, TNF-α, IFN-gamma) by activating a number of immune cells (including macrophages, B and T cells). The third type of toxins is non-protein toxins as by-products of bacterial metabolism in the form of hydrogen sulphide H_2S and its damaging, highly toxic compounds such as methyl mercaptan CH_3SH. This mechanism of methyl mercaptan and hydrogen sulphide production through anaerobic oral microorganisms goes through several stages. Methyl mercaptan is produced from the splitting of the amino acid L-methionine or L-cysteine. This reaction is triggered by the enzyme L-methionine y-lyase or L-cysteine desulfhydrase. L-methionine y-lyase catalyses the dispersion reactions for both L-methionine and its analogues such as homocysteine and S-methylcysteine. Both enzymes are found in a range of anaerobic bacteria that are used for normal colonisation of the oral cavity. These bacteria use the split product of L-methionine, 2-ketobutyrate, as an energy source [12] (Fig. 2).

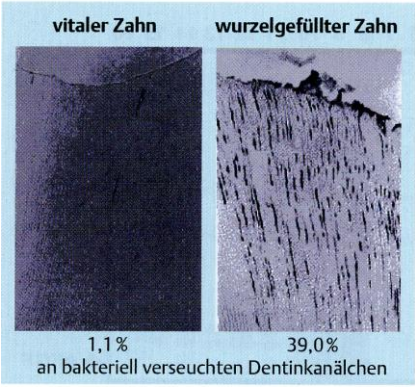


Fig. 1: Quantity of bacteria in dentinal tubules in a comparison of a vital and nonvital tooth.

Key to illustrations/captions:
Vitaler Zahn = Vital tooth
Wurzelgefüllter Zahn = Root-filled tooth
1.1%, 39.0%
an bakteriell verseuchten Dentinkanälchen = of bacterially infected dentinal tubules

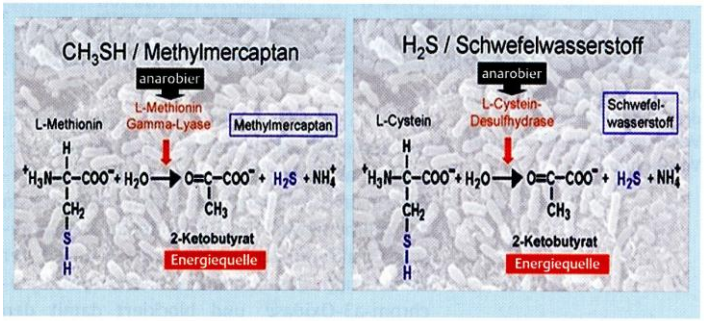


Fig. 2: The amino acids L-methionine and L-cysteine are converted from the bacteria to methyl mercaptan and hydrogen sulphide in order to extract ketobutyrate as an energy source innate within the bacteria.

CH_3SH/methyl mercaptan
Anaerober = Anaerobes
L-Methionin = L-methionine
L-Methionin Gamma Lyase = L-methionine gamma-lyase
Methylmercaptan = Methyl mercaptan
2-Ketobutyrat = 2-ketobutyrate
Energiequelle = Energy source

H_2S/hydrogen sulphide
Anaerober = Anaerobes
L-Cystein = L-cysteine
L-Cystein-Desulfhydrase = L-cysteine desulfhydrase
Schwefelwasserstoff = Hydrogen sulphide
2-Ketobutyrat = 2-ketobutyrate
Energiequelle = Energy source

Why can these metabolic products "block key metabolic processes"?

The toxicological systemic aspect of H_2S

The volatile gas hydrogen sulphide is also responsible for the dreaded halitosis and is referred to as a "volatile sulphur compound", although the effect on the nerve system is considerably more destructive: A research group from the University of Calgary in Canada discovered that hydrogen sulphide blocks the neurotransmitter GABA in the brains of young rats, reducing the neurotransmitter receptors and their sensitivity, and the levels of taurine, glutamate and aspartate. From this the authors conclude that structural abnormalities and functional behavioural disorders are to be expected as a result of this [6, 15]. The nerve ganglia, where these toxins are primarily deposited, play a particular role here [5]. H_2S inhibits the Na+/Ka+ ATPase, thus disturbing the ionic exchange in the cell membrane [13]. H_2S bonds to metal ion cofactors of the enzymes such as the Fe^{3+} of the haem group of the mitochondrial enzyme cytochrome a3 oxidase, thus blocking the last stage of the electron transport system, or to the Zn^{2+} of the carboanhydrase in the place of the hydroxyl group, thus inhibiting the conversion of CO_2 and H_2O to bicarbonate [1]. H_2S reduces the complement factor C3bi, thereby blocking phagocytosis and bactericidal properties of the immune system [3].

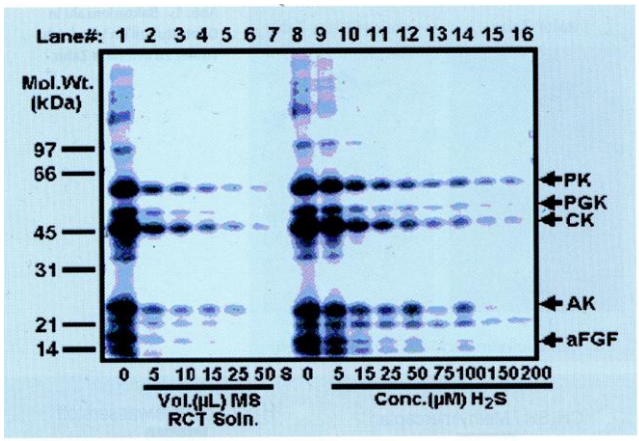
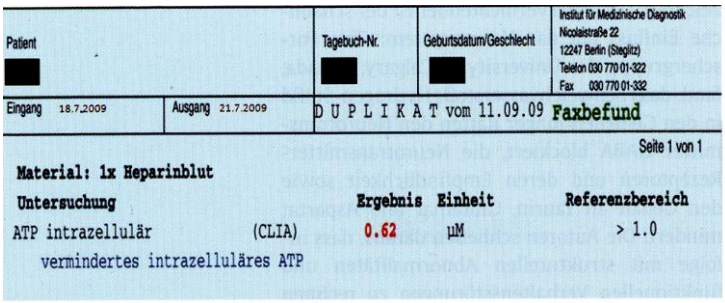


Fig. 3: Toxic effect of hydrogen sulphide compounds from a root-filled tooth compared to H_2S.



Patient	Tagebuch-Nr.	Geburtsdatum/Geschlecht	Institut für Medizinische Diagnostik Nicolaistraße 22 12247 Berlin (Steglitz) Telefon 030 770 01-322 Fax 030 770 01-332
Eingang 18.7.2009	Ausgang 21.7.2009	D U P L I K A T vom 11.09.09	**Faxbefund**

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Material: 1x Heparinblut

Untersuchung	Ergebnis	Einheit	Referenzbereich
ATP intrazellulär (CLIA)	0.62	µM	> 1.0
vermindertes intrazelluläres ATP			

Fig. 4: Intracellular ATP as a marker of mitochondrial dysfunction as a result of a blocked respiratory chain possibly caused by mercaptan/thioether and recovery of ATP.

Seite 1 von 1 = Page 1 of 1
Material: 1 x Heparinblut = Material: 1x heparin blood
Untersuchung = Examination Ergebnis = Result Einheit = Unit Referenzbereich = Reference range
ATP intrazellulär (CLIA) = ATP intracellular (CLIA)
vermindertes intrazelluläres ATP = reduced intracellular ATP

Why can hydrogen sulphide compounds with an endodontic origin "block key metabolic processes"?

The toxicological aspect of thioether compounds

A substance is toxic if it blocks vital processes in the body. Let us first look at the effect of tooth root toxins on vital enzymes: enzymes are the motors of life. Without the catalytic effect of enzymes the reactions in the cells would not take place, or only incredibly slowly. The raison d'être of the enzymes is to store substances and process them accordingly. The docking of these substances takes place within the enzyme in an active centre. These active centres of the enzymes generally consist of hydrogen sulphide groups (HS groups). One of the most important enzyme functions in the human body takes place within the mitochondria: Adenosintriphosphate (ATP) is supplied within the cell through a chain of enzymes. ATP is the actual energy store available to the body. Without ATP no metabolic process is conceivable or possible. Muscle and brain activity are the processes that use the most ATP. The problem is that the body only has 35 grams of ATP at its disposal that has to be built up and reduced approximately 2000 times a day. This is done exclusively by the enzymes in the cell motors, the "mitochondria". An insufficient supply of ATP results in a reduction of overall cell function within each cell. A reduction in cell function means less resistance, less brain activity, less muscle power, less strength and increased susceptibility to stress. However, this intracellular mitochondrial blockade of the "volatile sulphur compounds" features little in the discussion of root-filled teeth and systemic diseases [9]. Prof. Boyd Haley (USA) with the help of affinity labelling verified the systemic effect of volatile hydrogen sulphide compounds on enzymes of the respiratory chain in mitochondria in vitro [4]. The sample material consisting of a diluted solution of root-filled teeth (RCT = root canal treatment) is incubated with ATP-binding enzymes for 60 minutes and then saturated with radioactively marked ATP, [32P]N3ATP. The more ATP bonding sites on enzymes are occupied by toxins, the lower the radioactive radiation. A practical application of this procedure is shown in the autoradiograph with an inhibition of enzymes using diluted solutions from a root-filled tooth: (Fig. 3).
Interpretation of representations in radioactive marking technology: The darker the spot, the less enzyme activity is blocked. The zero line in the right-hand margin shows the original, unrestricted enzyme activity. Figure 2 shows that pure H_2S does not have more of a toxic effect on the enzymes of the mitochondrial respiratory chain than the solutions examined from a root-filled tooth (root canal treatment solution). For example, the blocking effect of the enzyme pyruvate kinase (PK) is double that of pure H_2S with a solution from a root-filled tooth of the same concentration (e.g. 15 µl) and H_2S (µM): unfortunately rather a shocking result. The quantitative verification of the ATP level in peripheral leucocytes can be used to assess the systemic effects

of an endodontically induced intoxication [10]. The mitochondrial dysfunction was objectified with a description of a cellular PK blockade in a 44 year-old female patient with chronic fatigue/multiple chemical sensitivity syndrome (CFS/MCS) using the laboratory verification of intracellular ATP (www.imd-berlin.de). A respiratory chain blocked by mercaptan/thioether and limited recovery of ATP must also be taken into consideration for the diffuse clinical picture of a patient with CFS/MCS (Fig. 4).

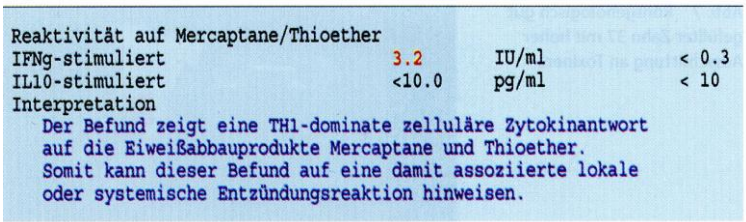
Why can these metabolic products "have a systemic effect"?

The immunological aspect of thioether compounds

Mercaptan/thioether can have a damaging effect on the body through two different mechanisms. Firstly, we have the aforementioned toxic mechanisms associated with reduced ATP formation. Secondly, it is known that some patients with pre-existing exposure to these substances show signs of immunological sensitisation. Consequently, inflammatory cells – particularly lymphocytes – can be activated where there is a pre-existing exposure and these cells can trigger both a local and a systemic immune response. In this respect, a positive result means that the protein degradation products are an inflammation trigger specific to this patient. To this extent, this laboratory method can be used to clarify immune activations and immune dysfunctions caused by tooth toxins (www.imd-berlin.de). Figure 5 shows such a finding.

Local diagnosis of endodontic intoxications

Modern endodontics is of course aware of the problem of bacterial colonisation in the tubules and new procedures are constantly being developed to minimise these risks. To date there is no scientific verification method for correctly identifying teeth suspected of being infected with toxins. The X-ray is not helpful, as a chemical product cannot be identified on the picture [9, 10]. How can the dentist check from the chair whether the root-filled tooth is really free of volatile sulphur compounds? A semi-quantitative chairside test (OroTox®, www.orotox.de) is available for this purpose. The dentist can thus decide within minutes whether this tooth is releasing toxins and answer the following question for himself: Is this tooth releasing toxins that are blocking vital enzymes or over-stimulating the immune system? The answer derived from the measurement of the toxins assists with the decision of whether a root-filled tooth should be extracted in a systemically diseased patient, must be restored and filled, or can be capped, even if the X-ray shows no changes. The measurement of volatile hydrogen sulphide compounds using this test enables the dentist to preserve teeth without this increasing the risk of bacterial toxins spreading through the body. The advantage for the patient and dentist, apart from an extremely good cost-benefit ratio, is the simple, non-invasive and pain-free process: A paper tip is inserted in the sulcus of the suspect tooth, where it is left for 1 minute. The paper tip is then placed in the test tube provided and the colour of the indicator fluid is checked after 5 minutes. The more thiols, polyamines or hydrogen sulphides the sample contains, the more yellow the indicator fluid turns. The quantity of absorbable toxins in the sulcus is thus determined semi-quantitatively (Fig. 6).



Reaktivität auf Mercaptane/Thioether			
IFNg-stimuliert	3.2	IU/ml	< 0.3
IL10-stimuliert	<10.0	pg/ml	< 10

Interpretation
Der Befund zeigt eine TH1-dominate zelluläre Zytokinantwort auf die Eiweißabbauprodukte Mercaptane und Thioether. Somit kann dieser Befund auf eine damit assoziierte lokale oder systemische Entzündungsreaktion hinweisen.

Fig. 5: A positive result in the test shows not only that exposure must exist or must have existed, but in particular that antigen-specific TH1 cells are present that can cause an inflammation triggered by mercaptan/thioether.

Reactivity to mercaptan/thioether
IFNg-stimulated
IL-10-stimulated

Interpretation

The findings show a TH1-dominant cellular cytokine response to the protein degradation products mercaptan and thioether. These findings may therefore point to an associated local or systemic inflammatory response.

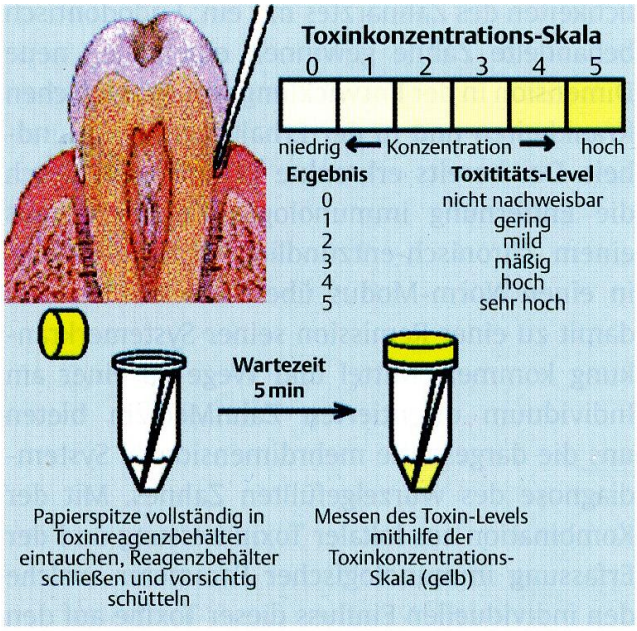


Figure 6: Semi-quantitative determination of the quantity of absorbable toxins in the sulcus.

Toxinkonzentrations-Skala = Toxin concentration scale
niedrig = Low
Konzentration = Concentration
Hoch = High
Ergebnis = Result
Toxizitäts-Level = Toxicity level
nicht nachweisbar = none identified
gering = negligible
mild = low
mäßig = moderate
hoch = high
sehr hoch = very high
Wartezeit 5 min = Waiting time 5 mins

Papierspitze vollständig... = Immerse paper tip fully in toxin test tube, close test tube and shake carefully
Messen des Toxin-levels... = Measuring the toxin level using the toxin concentration scale (yellow)

How great the difference between a root filling that looks satisfactory on the X-ray and the quantity of toxins that may be picked up with a semi-quantitative test can be is demonstrated in the clinical example shown in Figure 7. With a value of 5 on the yellow scale, tooth 37 shows an extremely high dispersion of volatile sulphur compounds.
The chairside test (OroTox®, www.orotox.de) measures a biological metabolic product. As the bacterial activity of the oral environment is constantly changing, the same tooth can show different values in measurements taken at different times. This is not unusual, however, as the metabolic activity of the bacteria also changes according to the environment. The semi-

quantitative measurement is therefore merely an indicator that is only an approximate determiner of the systemic impact of an endodontically treated tooth.

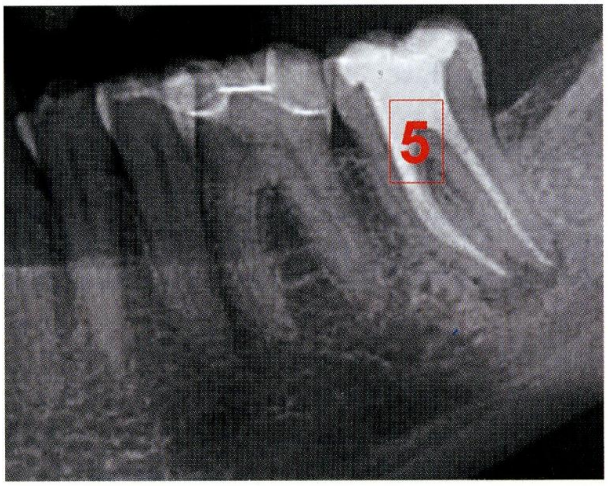


Figure 7: Tooth 37 that looks satisfactorily filled on the X-ray with a high dispersal of toxins.

Summary and outlook

Dentistry is primarily concerned with reparative restoration of the mechanism of the chewing apparatus – “The patient should ultimately be able to chew”. Recently, however, an increasing focus is also being placed on preventative aspects with respect to systemic manifestations of local processes. For example, a growing number of publications and guidelines are discussing the connections between local focuses of inflammation in periodontitis and atherosclerosis, apoplexy, premature births or even diabetes. Holistic, systemically oriented dentistry also includes the curative possibilities of dentistry: Endodontically treated teeth are taking on a whole new dimension in the development of systemic diseases and in the maintenance of good health. An already diseased patient can be placed from a chronically inflammatory alarm mode into a normal mode by removing the immunological trigger, thus resulting in a remission of the systemic disease. The ways and means of dentistry geared to the individual open up the options of a multidimensional systemic diagnosis of a root-filled tooth. With the combination of measuring toxins locally and recording immunological parameters objectifying the specific effect of these toxins on the patient concerned, a good assessment can be made of the significance of the problem of toxins in root-filled teeth for the individual patient. In this respect, the aforementioned procedures can help prevent a trivialisation of the problem that the Deutsche Gesellschaft für Umwelt-Zahnmedizin [German Association for Ambient Dentistry] (www.deguz.de) has set itself the task of resolving.

Conflict of interests:
The author declares that OroTox is marketed by MindLink in Germany; his wife, Christiane Lechner, is the owner of this company. He is also a member of DEGUZ.

Bibliography

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References

1. Beauchamp R, Bus JS, Popp JA, Boreiko CJ, Andjelkovich DA: A Critical Review of the Literature on Hydrogen-Sulfide Toxicity CRC Crit. Rev. Toxicol. 1984; 13(1):25-97

2. Godin, P.J.; Buchman,T.G. (1996):Uncoupling of biological oscillators: a complementary hypothesis concerning the pathogenesis of multiple organ dysfunction syndrome. Crit.Care Med.24:1107-1116

3. Granlund-Edstedt M, Johansson E, Claesson R, Carlsson J: J. Periodont. Res. 28(5):346-353 (1993).

4. Haley, B. Photoaffinity Labeling of Adenosine 3', 5'-Cyclic Monophosphate Binding Sites. Methods in Enzymology, Jacoby and Wilchek, Editors. Academic Press, Waltham USA; 1976; 46:339-346

5. Hannah RS(1991). Chronic exposure to low concentrations of hydrogen sulfide produces abnormal growth in developing cerebellar Purkinje cells. *Neurosci. Lett.* **28**:225-228.

6. Hannah RS, Hayden LJ, Roth SH, Hydrogen sulfide exposure alters the amino acid content in developing rat CNS, Neurosci Lett. 1989 May 8;99(3):323-7.

7. **Kirkpatrick CJ** , Fuchs S, Peters K, Brochhausen C, Hermanns MI, Unger RE. Visions for regenerative medicine: interface between scientific fact and science fiction. **Artificial Organs** 2006; 30: 822-827
8. Lechner, J. Mayer, W. Immune messengers in Neuralgia Inducing Cavitational Osteonecrosis (NICO) in jaw bone and systemic interference, European Journal of Integrative Medicine, 2 (2010) 71–77)

9. Lechner, J; Kavitätenbildende Osteolysen des Kieferknochens, Eigenverlag München 2011 ISBN 978-3-931351-19-9; 276 Seiten

10. Limburg Stirum J.v.; Der Nachweis von oraltoxischen Belastungen und ihre klinische Bedeutung. Ganzheitliche Zahnmedizin. 2000(1):16-19.

11. Nagaoka S., Bacterial Invasion into Dentinal Tubules of Human Vital and Nonvital Teeth; Journal of Endodontics, Vol. 21, No. 2, pp.70-73, 1995

12. Piannotti R, Lachette S, Dills S. Desulfuration of cysteine and methionine by Fusobacterium nucleatum, *J. Dent. Res.* **1986; 65(6)**:913-917

13. Reiffenstein RJ, Hulbert WC, Roth SH. Toxiciology of hydrogen sulfide. Annu Rev Pharmacol Toxico 1992; 32:109-134

14. Straub, R. H.; Herfarth, H.; Falk, W.; Andus, T.; Schölmerich, J. (2002): Uncou pling of the sympathetic nervous system and the hypothalamic-pituitary- adrenal axis in inflammatory bowel disease? J. Neuroimmunol. 126: 116— 125.

15. Tansy MF, Kendall FM, Fantasia J, Landin WE, Oberly SR, Sherman W. Acute and subchronic toxicity studies of rats exposed to vapors of methyl mercaptan and other reduced-sulfur compounds. *J Toxicol Environ Health* **1981; 8**:71-88.