17 years) suggest a role of this solvent at the level of the central nervous system. So our hypothesis might provide a novel PD neurotoxicant. In future studies, *n*-hexane might be developed to produce animal models of PD. The development of animal models is essential for better understanding pathogenesis and progression of PD and testing therapeutic agents for the treatment of PD patients.

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Hypothesis: Chronic fatigue syndrome is caused by dysregulation of hydrogen sulfide metabolism

Chronic fatigue syndrome (CFS), which is also known as myalgic encephalomyelitis (ME), is a debilitating, multi-system disease whose etiology is unclear, and for which there are as yet no reliable treatments. Here the hypothesis is advanced that the multi-system disturbances in CFS/ME are caused by disturbances in the homeostasis of endogenous hydrogen sulfide (H_2S) and result in mitochondrial dysfunction.

Research on H_2S – the gas that causes the characteristic smell of rotten eggs – dates to the 1700's and has shown a remarkable range of effects in both animals and humans. At high concentrations, H_2S has a variety of biological toxicities including being instantaneously deadly; at low concentrations some evidence suggests that H_2S has beneficial effects and can act as an endogenous biological mediator – the third such gaseous mediator discovered (after nitric oxide and carbon monoxide). The brain, pancreas and the gastrointestinal tract produce H_2S. Endogenous H_2S plays a role in regulating blood pressure, body temperature, vascular smooth muscle, cardiac function, cerebral ischemia, and in modulating the hypothalamus/pituitary/adrenal axis. It even has been called a "master metabolic regulator".

Recent research has demonstrated that at low, non-toxic doses, exogenous H_2S produces a reversible state of hibernation-like de-animation in mice, causing a decrease in core body temperature, an apnea-like sleep state, reduced heart and respiration rates, and a severe metabolic drop [1]. These characteristics are not unlike the symptoms and extreme "de-animation" experienced by CFS/ME patients. Moreover, H_2S affects biological networks that are disrupted by CFS including neurologic, endocrine and immunologic systems. Therefore, a plausible etiology of CFS is an increase in the activity of endogenous H_2S, thereby inhibiting mitochondrial oxygen utilization.

H_2S and Mitochondria

In this view, fatigue and the other CFS/ME symptoms could be due to diminished physiological and cellular energy due to reduction in the capacity of mitochondria to utilize oxygen and synthesize ATP. Specifically, H_2S binds to the mitochondrial enzyme cytochrome c oxidase, which is part of Complex IV of the electron transport chain, and attenuates oxidative phosphorylation and ATP production.

Consistent with this finding, recent research on low level H_2S toxicity points to increased formation of free radicals and depolarization of the mitochondrial membrane, a condition that would decrease ATP synthesis [2]. If poisoning renders mitochondria inefficient, one would expect cells to shift to anaerobic mechanisms, a shift that has been reported for CFS patients. Also consistent with this hypothesis is the fact that mitochondria are organelles descended from ancient eukaryotic sulfur-utilizing microbes. Thus, it is not surprising that they show a very high affinity for sulfide.

Of course, H_2S or sulfide may not directly affect mitochondria by binding to them. Genomic changes could mediate some of the effects of H_2S. Some studies have found evidence for the involvement of the cytochrome c oxidase gene in CFS/ME. Also, investigators have found CFS abnormalities in genes related to fatty acid metabolism, apoptosis, mitochondrial membrane function, and protein production in mitochondria. Given a predisposing genetic background, H_2S may lead to genomic instability or cumulative mutations in the mitochondrial DNA [3].

Alternatively, the effects of H_2S could be initially mediated by changes in the redox potential of cells or changes in their sulfur metabolism, especially in glutathione. Another possible mechanism is a direct effect of H_2S on the immune system. Recent research indicates that exogenous hydrogen sulfide induces functional inhibition and cell death of cytotoxic lymphocyte subsets of CD8 (+) T cells and NK cells.

Finally, H_2S plays a pivotal role in both aerobic and non-aerobic organisms as a signaling molecule. Bacteria in the gut both produce H_2S and utilize it as a substrate alternative to oxygen. This is of particular relevance in the gastrointestinal tract, where unusually high levels of gram-negative bacteria, which increase intestinal permeability, have been found in patients with CFS/ME [4]. In addition to bacteria, yeast, mold and other fungi also emit H_2S.

CFS/ME is a model disease for multisystem disturbance. It is my hypothesis that mitochondria, organelles required by every cell to sustain life, are unable to adequately utilize oxygen. This mitochondrial disturbance could be due to the combined effects of anaerobic conditions known to occur in CFS and associated low-level H_2S toxicity. This increase in H_2S alters fine signaling necessary

for body homeostasis, and causes CFS. Understanding the role of H_2S in the body, and, in particular, in mitochondrial function, may provide a unifying lens through which to view the diverse manifestations of this complex disease.

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A novel approach in preventing the occurrence of diabetic foot infections – The finger socks

Diabetic foot infections with eventual dramatic consequences continue to be a challenge for practitioners. Given the high cost of the treatment of these usually polymicrobial and resistant infection [1], preventing measure are to be taken primarily into consideration.

The skin as the first line in defense system is to be preserved intact. Many microorganisms enter to deep tissues of the foot via cracks and splits resulting from either the neurophatic foot or other traumatic factors. The fore-foot, mainly the toes, is the origin of many foot infections. The interdigital space of the foot, as it is overlied by a thinner skin, is subjected to skin cracks more than any other areas of the foot. Another threatening factor to skin breaks is the adjacent toe itself. A callus formation, a toe deformity or an overgrown nail causes continuous trauma to the nearby toe consequently impairing the skin integrity.

Many measures are taken to decrease the incidence of diabetic foot infections. "The finger socks" (Fig. 1) may play a novel role in adding to this decrease rate. This recently manufactured and still not worldwide known interesting design, the finger socks, by covering each toe independently could be promising to prevent the web spaces from providing a nidus for microbial invasion as well as to prevent the above mentioned adjacent threat and subsequent cracks to the interdigital space consequently lowering the rate of deep tissue infections.

Fig. 1. The finger socks.

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