Metals as a Common Trigger of Inflammation Resulting in Non-Specific Symptoms: Diagnosis and Treatment

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ABSTRACT: **Background:** The multiple symptoms of chronic fatigue syndrome (CFS) and fibromyalgia resemble those described in patients suffering from autoimmune/inflammatory syndrome induced by adjuvants (ASIA). It has been suggested that chronic metal-induced inflammation might play a role both in CFS and fibromyalgia as well as in ASIA. Humans are exposed to metals mainly through the release of metal ions from corroding dental restorations and orthopedic implants, food, vaccines and jewelry. Metals readily bind to sulphur and other groups in the mitochondria, enzymes and cell proteins. Metal-bound proteins are recognized by the immune system of susceptible subjects and might trigger an abnormal immune response, including allergy and autoimmunity.

Objectives: To study three subjects with CFS and two with fibromyalgia, all of whom suspected metal exposure as a trigger for their ill health.

Methods: We measured delayed-type hypersensitivity to metals (metal allergy) using a validated lymphocyte transformation test, LTT-MELISA®. All patients except one were sensitized to metals present in their dental restorations. The remaining patient reacted to metals in his skull implant. The removal of sensitizing metals resulted in long-term health improvement. Nine healthy controls matched for gender and age showed only marginal reactivity to the metals tested.

Conclusions: Patients with CFS and fibromyalgia are frequently sensitized to metals found in the environment or used in dentistry and surgery. This allergy to metals might initiate or aggravate non-specific symptoms in metal-sensitized patients.

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KEY WORDS: metal allergy, LTT-MELISA, chronic fatigue syndrome (CFS), fibromyalgia, autoimmune/inflammatory syndrome induced by adjuvants (ASIA), nickel allergy

Scientific studies suggest that heavy and transition metals might play an important role in various allergic and autoimmune diseases such as those affecting the skin, oral cavity, heart, joints, brain and thyroid [1-3]. Chronic exposure to metals occurs mainly through the release of metal ions from corroding dental restorations and orthopedic implants, but also from jewelry, vaccines, coated medical pills, foods and coins. Another important source of metal exposure is cigarette smoke, which contains nickel, cadmium, manganese, mercury, lead and arsenic [4]. Cosmetic products contain metal pigments, including titanium dioxide, iron oxide, cadmium and lead.

The potential risks of heavy and transition metals reside in their physicochemical properties, binding to sulphur and other groups in the mitochondria, enzymes and cell proteins. Fat-containing organs such as the brain or collagen-containing structures are especially rich in sulphur groups and are therefore vulnerable to metal binding. Metals induce free radical formation, inactivate enzyme and mitochondrial activity, and act as triggers of inflammation, hypersensitivity and autoimmunity [5,6].

Some metals such as nickel, gold and mercury are frequent sensitizers and induce delayed-type hypersensitivity (metal allergy) in susceptible individuals. The frequency of titanium allergy is increasing, probably due to the extensive use of titanium dioxide in foods, pills and cosmetics, and as nanoparticles [7]. This type of hypersensitivity is mainly T cell mediated, while the occurrence of metal-specific antibodies is a rare phenomenon.

Diagnosis of metal allergy is routinely performed by application of metal salts on the skin of the back, so-called patch testing. Another method is an in vitro laboratory test, LTT-MELISA® (MELISA), which, following validation [8], is increasingly being used. This test is especially useful for testing metals such as beryllium, which cannot be tested on the skin, or for insoluble metal salts that do not readily penetrate the skin and thus cannot be used in patch testing (as is the case with titanium allergy) [2,9].

MATERIALS AND METHODS

Five subjects, four females and one male, presented with various symptoms and were diagnosed with chronic fatigue syndrome (CFS) and fibromyalgia [Table 1]. The patients suspected metal exposure as a possible reason for their ill health and were referred for MELISA testing [10,11]. Also tested were nine gender- and age-matched healthy subjects selected from a control database. The healthy subjects were exposed to dental metals and all but one had received multiple vaccinations.

Briefly, lymphocytes from blood samples were isolated and incubated with selected metals, based on the patient's exposure. To identify past and current metal exposure, every patient was asked to complete a questionnaire.

The following metals were tested: aluminum (Al), beryllium (Be), chromium (Cr), ethyl mercury (EtHg), gold (Au), lead (Pb), mercury (Hg), nickel (Ni), palladium (Pd), phenyl mercury (PhHg), platinum (Pt), silver (Ag), thimerosal (Thim), tin (Sn), titanium dioxide (TiO_2), titanium trichloride ($TiCl_3$) and vanadium (V). Each metal salt was tested in two or more concentrations. After 5 days, lymphocyte proliferation was measured by pulsing with radiolabelled thymidine. In parallel, the presence of lymphoblasts was examined under microscope. Stimulation Index (SI) was used to describe a patient's reactivity to metals. SI is defined as counts per minute (cpm) in metal-treated cultures divided by the mean cpm of cultures cultivated in the absence of metal salts. SI ≥ 3 indicates a positive response to a given allergen, SI 2–2.9 is regarded as weakly positive and SI < 2 as negative. Positive responses were verified by morphologic evaluation.

The highest SI value has been used to describe the metal-specific proliferation. Values above 10 have been rounded off to the nearest whole number. MELISA testing was performed prior to removal of immunologically incompatible dental restorations or implants, and follow-up testing was done at least 6 months later.

Two patients were patch tested. Positive patch responses were evaluated as follows: +++ = strongly positive, ++ = positive, + = weakly positive. The composition of dental restorations and surgical implants was requested from the manufacturers. In three instances, dental restorations were sent for analysis to determine the metal content. Different methods were used: Energy-dispersive X-ray spectroscopy (EDX) (ACTA, Amsterdam, The Netherlands); Inductive Coupled Plasma-Mass Spectroscopy technique (ICP-MS) (Analytica AB, Luleå, Sweden); and Atomic spectrophotometry (AAS) (Laborzentrum Bremen, Bremen, Germany). In one patient, gallstones were also analyzed by the MGD Laboratory (Geneva, Switzerland). The aim of the study was explained to the patients and they gave their informed consent.

RESULTS

The patients' anamnesis and initial MELISA results are shown in Table 1.

PATIENT 1

A 52 year old woman had a history of poor health since she was a teenager, including numerous rashes, hives and recurrent mouth ulcers. She received her first amalgam fillings at the age of 10 years. After undergoing tubal ligation with metal clips at age 30, she experienced intense abdominal pain and was diagnosed with irritable bowel syndrome (IBS). During the subsequent years several dental metal crowns were placed and she was diagnosed with gallstones. At age 45, more metal crowns were placed and she began to suffer from intense prolonged periods of fatigue and was finally diagnosed with CFS. Five years later fibromyalgia was diagnosed. Upon referral, the patient mentioned that she did not tolerate cheap

Table 1. Summary of clinical and laboratory data in patients with CFS and/or FM

Patient	Gender/ age	Diagnosis and clinical symptoms	Metal exposure	Patch test	Positive MELISA (SI)	Treatment	Health outcome
1	F / 52	CFS, FM, IBS, oral ulcers	8 AF 2 Ni-Cr crowns Ni clips	Ni +++ Hg neg	**Ni (19)** **Hg (3.3)** **Pd (29)** **Sn (3.3)** **Au (3.7)**	Removal of metal alloys	After 3 months CFS/FM resolved 3 year follow-up: healthy
2	M / 15	CFS, anorexia, headaches	Skull plate made of Ti-Al-V (with Ni impurities)	Not done	**Ni (8.1)** TiO_2 (2.7) **$TiCl_3$ (4.1)**	Removal of metal plate	Anorexia/headaches resolved immediately CFS after 3 weeks 2 year follow-up: healthy
3	F / 65	CFS, cardiomyopathy, lichen planus, Sjögren's syndrome	1 AF 1 Au 2 MC Multiple vaccines Occupational exposure to Hg	Not done	**Ni (24)** **Pd (46)** PhHg (2.5) **Pt (4.0)** Pb (2.3)	Removal of dental metals	1 year later: Lichen planus and oral problems resolved, CFS improved 2 years: cardiac problems improved, CFS continues to improve
4	F / 28	Severe FM	AF Multiple vaccines containing Thim	Hg + EtHg ++ Thim +++ Ni neg	**Hg (3.1)** **EtHg (4.9)** **Thim (17)** **Ni (3.5)** Al (2.4) **PhHg (4.6)**	Removal of AF	FM improved
5	F / 57	FM, hypothyroidism	3AF 3 Au with Be MC	Not done	**Be (69)**	MCs /AF/Au removed Single Au remains	FM improved 10 years: FM resolved

FM = fibromyalgia, CFS = chronic fatigue syndrome, IBS = irritable bowel syndrome, AF = amalgam fillings (consisting of inorganic mercury, silver, tin, copper, zinc and nickel traces), Au = gold crowns, MC = metal ceramic crown, SI = Stimulation Index

Numbers in bold = positive responses, normal print = weakly positive

Figure 1. Lymphocyte responses before and after removal of metals in **[A]** patient 1, **[B]** patient 2, **[C]** patient 3, **[D]** patient 4 and **[E]** patient 5

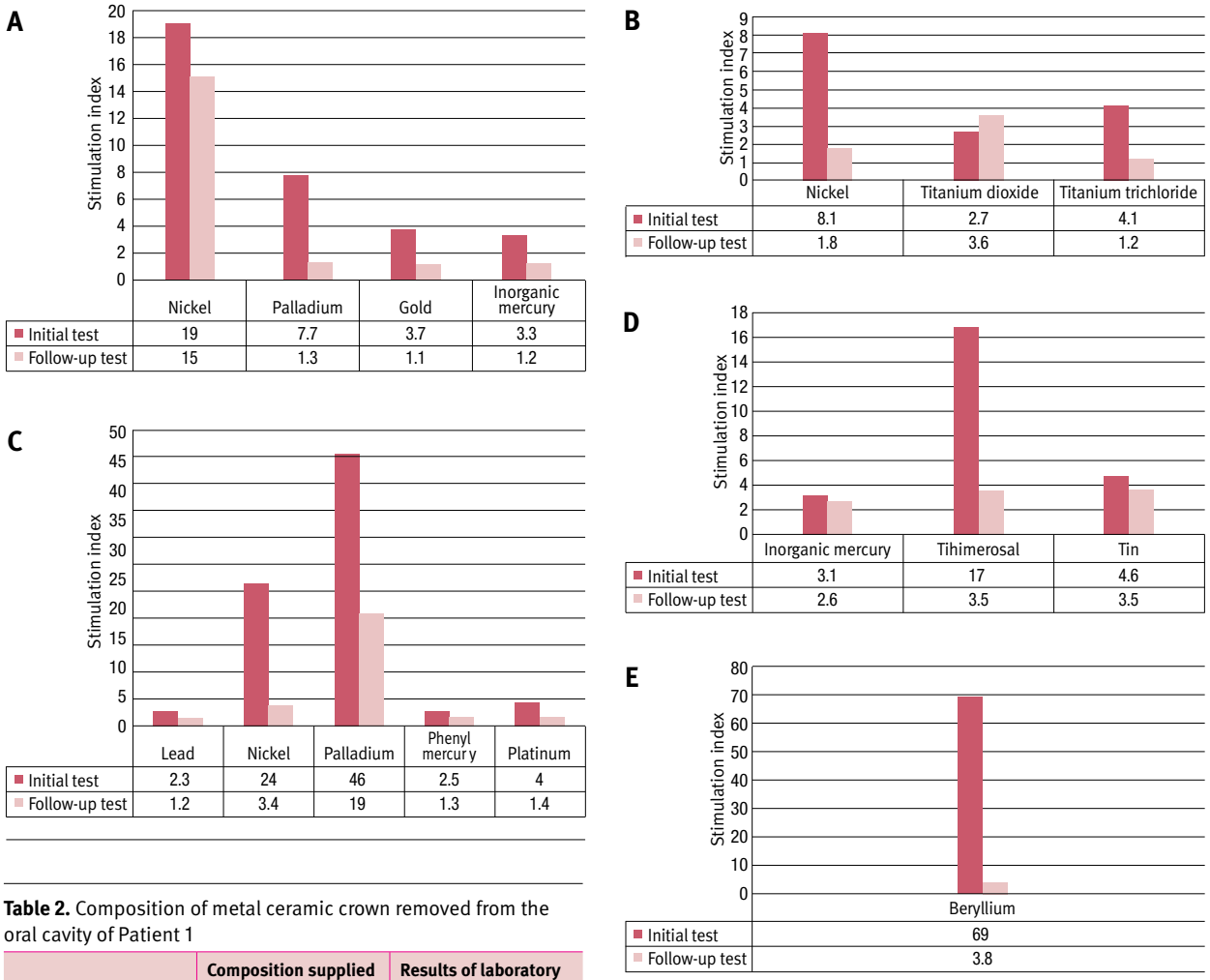

Table 2. Composition of metal ceramic crown removed from the oral cavity of Patient 1

Element	Composition supplied by manufacturer (%)	Results of laboratory analysis by EDX (%)
Nickel	› 75	79
Chromium	‹ 15	11.9
Molybdenum	‹ 11	0
Aluminum	‹ 3	0
Beryllium	‹ 2	Not determined
Copper	0	4.5
Zinc	0	4.2

nickel-containing earrings. The patch test was strongly positive to nickel but negative to other metals including mercury. MELISA testing confirmed the results of the patch test; her lymphocytes reacted strongly to nickel in vitro. In addition, other metal sensitivities to palladium, gold, tin and inorganic mercury were demonstrated [Table 1].

The treatment consisted of replacement of amalgam fillings and metal crowns and bridges with metal-free composites and ceramics. During gall bladder surgery her tubal ligation clips containing nickel were removed. Analysis by EDX of one of the dental metal ceramic crowns showed that it was made of more than 75% nickel, in addition to other metals [Table 2]. However, the manufacturer's information stated that it also contained minute amounts of beryllium.

Rapid health improvement followed and she became symptom free. Six months after removal of metals she was retested and the results showed no reactivity to palladium, gold, tin and inorganic mercury [Figure 1A]. However, lymphocyte reactivity to nickel was still high, perhaps due to difficulty to completely avoid nickel exposure through diet. The patient returned to work and is still symptom free 3 years later. Her gallstones were analyzed by ICP-MS, which showed deposits of nickel (0.1 ppm). Other metals found were mercury (0.1 ppm), tin (0.8 ppm) and molybdenum (0.3 ppm).

PATIENT 2

A 15 year old boy diagnosed with CFS, anorexia and severe headaches had been bedridden for 6 months when his mother inquired about the possibility of MELISA testing. His questionnaire revealed the presence of titanium alloy plates in his skull. Previously, a titanium rod in his arm had to be removed due to an intense fibrous reaction around the implant. He had no dental restorations. MELISA testing showed that his lymphocytes reacted to titanium and nickel [Table 1]. The skull plates (made up of 90% titanium, 6% aluminium, 4% vanadium) were removed and 2 weeks later the patient was able to return to school on a part-time basis. Three weeks after the operation he was able to attend an intern training program in a local restaurant. Four years later he is symptom free and enjoys good health.

Follow-up MELISA testing 2 years later showed a decrease in lymphocyte reactivity to nickel as well as to one type of titanium salt [Figure 1B]. Some reactivity to titanium dioxide was still present, possibly due to the difficulty to completely avoid titanium from exposure to daily items such as cosmetics, foods etc.

PATIENT 3

A 65 year old woman presented with profound fatigue, atrial fibrillation, gum inflammation and blackouts, and was diagnosed with CFS, lichen planus, cardiomyopathy and Sjögren's syndrome. Her questionnaire revealed that she had received multiple mercury-containing vaccines in the past, and had dental amalgam, gold crowns and a metal ceramic crown in the oral cavity. She reported hypersensitivity to nickel and certain types of jewellery. MELISA showed a strong reaction to nickel and palladium, and a positive reaction to platinum [Table 1]. Her amalgam filling and crowns were removed and replaced by metal-free alternatives. EDX analysis of four metal ceramic crowns showed that the crown contained 52% palladium.

Due to her nickel allergy, the patient decided to follow a strict low nickel diet, avoiding foods high in nickel, and to avoid using cookware/kettles containing nickel. Her oral health improved dramatically with the disappearance of redness and soreness, and no evidence of lichen planus. Together with constant health improvement, her energy levels were slowly returning to normal. Finally, the patient's heart rhythm became more regular and the previous daily episodes of fainting ceased.

A follow-up MELISA test showed a decrease in lymphocyte reactivity to nickel, palladium and platinum as compared to the results prior to removal of the dental metal [Figure 1C]. The reduction in reactivity to nickel may be due to the patient's adherence to a nickel-free diet and the removal of dental restorations which might have contained traces of nickel.

PATIENT 4

This 28 year old woman was diagnosed with primary fibromyalgia. As a child she had received at least eight thimerosal- and aluminium-containing vaccines.

The patient worked as a chemist and had been occupationally exposed to metals, including mercury vapor from several broken mercury thermometers. Additional exposure was through numerous dental amalgams. At the age of 18, she had silicone breasts implanted. Since she experienced post-vaccination side effects, she was patch tested twice with various mercury compounds including thimerosal. Patch testing showed a strong reaction to thimerosal and ethyl mercury and a positive reaction to inorganic mercury [Table 1]. She was, however, negative to nickel. MELISA was strongly positive to thimerosal and positive to inorganic mercury, phenyl mercury (present in the eye drops she used) and weakly positive to aluminium. Another positive result was to tin, present together with mercury in dental amalgam. After removal of the amalgams, her fibromyalgia subsided and when retested 9 months later her metal-specific lymphocyte responses showed normal values [Figure 1D]. She continues to avoid mercury in all forms – vaccines, cosmetics and medical products.

PATIENT 5

This 57 year old nurse was diagnosed with both fibromyalgia and hypothyroidism. Suspecting that amalgam was the cause of her ill health, she underwent dental treatment to replace the amalgam with non-metallic materials. However, when her symptoms did not improve she was referred for MELISA testing to determine whether there was any sensitizing metal in her gold restorations.

Her lymphocyte reactivity to frequent metal allergens such as mercury, palladium, gold and nickel was negative [Table 1]. Surprisingly, MELISA showed a strong positive response to beryllium (SI 69). In the search for possible beryllium exposure, one of the gold crowns was removed and analyzed for the presence of beryllium. Beryllium was detected at a concentration of 0.7 mg/kg (ICP-MS). The remaining gold restorations, except for one in her front teeth, were removed.

Three years later a second MELISA test [Figure 1E] showed a significant reduction in beryllium-specific reactivity. After 10 years she no longer suffers from fibromyalgia.

CONTROLS

Lymphocyte proliferation in nine healthy controls is shown in Table 3. In the majority of controls, MELISA was negative, indicating non-responsiveness to metals at the lymphocyte level.

DISCUSSION

In this study, the use of an in vitro test based on the identification of memory T cells helped to determine the triggers of inflammation in the patients. First, possible allergy-inducing metals were identified through a patient questionnaire, which was then followed by laboratory testing with MELISA. The results showed that all patients reacted to one or several metals

Table 3. Lymphocyte reactivity in healthy controls

	Age	Gender	Ag	Au	Be	Hg	EtHg	Ni	Pd	PhHg	Pt	Sn	Thim	TiO_2	$TiCl_3$
C1	50	F	0.7*	0.7		1.9	1.1	**3.2**	1.9	0.4		1.0	0.7		1.2
C2	54	F	0.6	1.9		**3.2****		2.7	1.9	**3.7**	0.7	1.5	1.4		1.5
C3	19	M	1.1	1.0		1.8	1.1	1.5	0.7	1	0.3	0.8	1.0		0.9
C4	17	M	0.4	0.6		1.1	0.6	1.1	0.8	0.9		0.5	0.9		
C5	62	F		2.1		1.3				0.5			1.3		
C6	64	F	0.6	2.0		1.8	1.5	2.0	2.0	**3.9**	0.7	1.1	1.3		1.2
C7	27	F				1.5				1.2		2.9	1.8		
C8	28	F				2.3				**3.7**		1.2	1.5		
C9	59	F		2.0	1.1	1.3		1.4	1.0	0.9				1.3	

*Stimulation Index

**Positive responses are shown in bold

they were exposed to. As it is increasingly recognized that an important source of metal exposure is the release of corrosion products from metal alloys [12], the patients contacted their dentist or surgeon to discuss possible removal or replacement of sensitizing implants or fillings.

Lymphocytes from the five CFS and fibromyalgia patients described in this study often reacted to several metals, but one fibromyalgia patient showed a strong reactivity to beryllium only. Beryllium is a potent allergen and can cause berylliosis as well as contact dermatitis. The presence of beryllium in the patient's gold crown was unexpected. Occupational exposure to beryllium is strictly regulated, and the same should apply to the use of beryllium in dental materials.

Another concern is the use of metal ceramics with a very high concentration of nickel, as illustrated in Patient 1. Nickel allergy is frequent, especially among women, and nickel-allergic patients react to even trace amounts of nickel [13]. Thus, nickel-containing dental restorations as well as orthodontic braces might contribute to ill health in nickel-sensitized patients.

Dental gold is an alloy of gold mixed with other metals with allergenic potential; palladium especially should be mentioned in this respect. Sensitization to tin, copper and silver exists but is rare. It is important to mention that titanium allergy is increasing, probably due to excessive exposure in humans to titanium in the form of a white metal pigment, titanium dioxide (E171) [7]. Contrary to common belief, titanium is not inert. Titanium belongs to the group of transition metals in the periodic table, which means it can initiate free radical formation, inflammation and specific T cell-mediated hypersensitivity, as described previously [9].

One of the patients developed CFS following the placement of a titanium skull plate. MELISA showed a low positive reaction to titanium and a strong reaction to nickel. The metal plate was not available for analysis of metal content, but according to the literature [14] small quantities of nickel are always present in titanium alloys. This case report is in agreement with other findings showing that inflammation due to metals in orthopedic implants not only contributes to implant loosening and implant failure but may also cause non-specific symptoms, such as ASIA syndrome [15,16].

Metal-induced inflammation may be involved in the pathology of various autoimmune and allergic diseases, where abnormal fatigue, joint and muscle pain, cognitive impairment and other non-specific symptoms are often present. These symptoms can be explained by the deregulation of the hypothalamic-pituitary-adrenal (HPA) axis by inflammatory cytokines affecting the brain [17,18]. It should be pointed out that deregulation of the HPA axis and the resulting non-specific symptoms can be caused not only by metals but by other inflammatory triggers as well, such as pharmaceutical drugs, pollen, infectious agents, molds and food allergens (such as gluten). Increased prevalence of atopy and allergy to certain foods and other allergens in CFS patients has been described previously [19].

In addition to increased frequency of lymphocyte responses to metals, many CFS patients had visible signs of metal intolerance, as manifested by local mucosal reactions around dental restorations as well as skin reactions upon contact with jewelry or metal-containing items. These observations, together with metal-positive patch tests, support the clinical relevance of our in vitro findings.

In agreement with previously published data [20], lymphocytes from healthy controls did not show any significantly increased lymphocyte reactivity to the metals tested, despite exposure through dental restorations, vaccines and the environment. The clinical relevance of in vitro testing is shown by the down-regulation of metal-specific responses following the removal of sensitizing agents in allergic patients [2,20]. The disappearance of CFS-like symptoms after removal of dental metal alloys in 120 patients has been reported [21].

Thimerosal (thiomersal, ethyl mercury thiosalicylate), a mercury-based preservative, has been used in the past in pediatric and adult vaccines. This substance causes mitochondrial

dysfunction, oxidative stress and neurotoxicity [22] and has been implicated in the etiology of autistic disorders. In addition to toxicity, thimerosal is a potent allergen, a fact well recognized by dermatologists but hardly known in other medical disciplines [23]. At present, thimerosal has been removed from childhood vaccines but is still present in adult vaccines such as certain brands of influenza vaccine. Thimerosal-specific lymphocytes were detected in one of our patients who developed primary fibromyalgia. This patient had had multiple vaccinations in the past, dental amalgams as well as silicone breast implants. The role of silicone as a potent adjuvant causing inflammation and autoimmunity is well recognized [24], and leakage of silicone from implants might have contributed to the development of fibromyalgia in this patient. Aluminium, also present in vaccines, is a potent adjuvant as well [25].

CONCLUSIONS

In this study, reduction of inflammation-causing metals resulted in an alleviation of symptoms and long-term health improvement. The decrease of metal-specific lymphocyte responses in vitro after removal of sensitizing metals supports the clinical relevance of these findings.

In addition to their well-known toxic effects, heavy and transition metals might function as immunologically active haptens as well as possess potent adjuvant inflammatory potential. In susceptible patients, chronic low dose exposure to metals may trigger inflammation and exacerbate already existing diseases. Cytokine release will deregulate the HPA axis and trigger non-specific symptoms, including profound fatigue and joint pain. In patients suffering from CFS, fibromyalgia or ASIA, laboratory markers of metal allergy, such as metal-specific memory lymphocytes, should always be measured. The proposed treatment protocol follows the standard procedure used in allergology and dermatology: namely, avoidance of exposure to sensitizing agent(s).

Lastly, it is of utmost importance to increase awareness among health professionals regarding the risk for systemic side effects caused by metal exposure in immunologically sensitized patients.

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"Every man is guilty of all the good he didn't do"

Voltaire (1694-1778), French Enlightenment writer, historian and philosopher famous for his wit, his attacks on the established Catholic Church, and his advocacy of freedom of religion, freedom of expression, and separation of church and state