IAOMT ACCREDITATION--
Checklist for Completing Unit 5: Biocompatibility and Oral Galvanism

INTRODUCTION TO UNIT 5

☐ Take the Unit 5 Pre-test. Click here to go to page 3.

☐ Read the “Dental Allergies – Truth or Myth” article by Rehme. Click here to go to pages 4-5.

☐ Read the "A Practical Guide to Biocompatibility Testing" article by Koral. Click here to go to pages 6-10.

REQUIRED (MANDATORY) CONTENT OF UNIT 5

☐ Read the “Autoimmune Diseases and Metal Implants and Devices” article by Just and Kall. Click here to go to pages 11-30.

☐ View the IAOMT online learning module “Biocompatibility and Oral Galvanism” at https://iaomt.org/biocompatibility-oral-galvanism-video-activity. Click here to go to page 31.

☐ Read the “Diagnosis and Treatment of Metal-induced Side-effects” study by Stejskal, Hudecek, Stejskal, and Sterzl. Click here to go to pages 32-41.

☐ Read the “Metal alloys in the oral cavity as a cause of oral discomfort in sensitive patients” article by Procházková et al. Click here to go to pages 42-47.

☐ Read the “Effect of radiofrequency radiation from Wi-Fi devices on mercury release from amalgam restorations” article by Paknahad et al. Click here to go to pages 48-53.

Continued on next page...
TEST FOR UNIT 5

☐ Take the Post-Test for Unit 5 at https://www.cvent.com/d/cvq54n.
   Click here to go to page 54.

☐ If you are interested in learning more about any of the topics in this unit,
   explore the readings in the OPTIONAL Unit 5 PDF file. Note that these
   are not required materials.

☐ Continue on to Unit 6!
   Click here to go to https://iaomt.org/accreditation-materials/.

Record of Unit 5 Updates---
7/2020: Pre-test questions updated to better reflect course content; "A Practical Guide to Biocompatibility Testing" article by Koral (moved to Introduction); “Electric Teeth: Chemical Reactions in the Mouth and the Phenomenon Of Oral Galvanism” article by Kall and Just (removed due to material being covered in updated online learning video activity); “Metal Allergies, Genetic Susceptibility to Mercury, and Toxic Dental Materials Other than Mercury” article by Kennedy and Just replaced with “Autoimmune Diseases and Metal Implants and Devices” article by Just and Kall; “Online Learning Video for “Dental Biocompatibility and Oral Galvanism” (revised for new formatting); “Corrosion and Mercury Release from Dental Amalgam” article by Pleva moved to Optional; “Metal alloys in the oral cavity as a cause of oral discomfort in sensitive patients” article by Procházková et al. (added new research); “Effect of radiofrequency radiation from Wi-Fi devices on mercury release from amalgam restorations” article by Paknahad et al. (added new research); Unit 5 Test (revised all test questions to incorporate new materials)
PRE-TEST FOR UNIT 5 TO BE TAKEN BEFORE STUDYING BIOCOMPATIBILITY AND ORAL GALVANISM

*This is a pre-test, and the results are for your records only. You are not expected to know the answers since you have not studied this material yet. The pre-test is simply designed to assist you in recognizing some of the important information that will be presented in this unit. There is no time limit for this test. Choose the option that BEST answers each question.

1. __________ appears to play a major role in causing metal allergies.
   A. food sensitivities
   B. lack of appropriate nutrition
   C. erratic sleep patterns
   D. ionization of metals

2. Research has shown that dental metal allergies are a potential factor in a type of oral cancer.
   A. True
   B. False

3. Systemic Lupus Erythematosus has been linked to dental metal allergies.
   A. True
   B. False

4. Dental materials implanted in teeth present a systemic exposure, which implies the possibility of __________.
   A. significant brain damage
   B. an immune response
   C. death
   D. none of the above

5. Oral galvanism can be caused by allergies to dental materials.
   A. True
   B. False

Answers: 1. D; 2. A; 3. A; 4. B; 5. A
Dental Allergies – Truth or Myth?

May 7, 2012
By Michael Rehme, DDS, CCN, FIAOMT

For access to all of Dr. Rehme’s articles, visit www.toothbody.com

When an individual discovers they have a food allergy, the obvious thing to do is eliminate that food choice from their diet. Continual exposure to these sensitive foods could create symptoms like itching, nausea, diarrhea and abdominal pain. More severe cases can cause general weakness, immune suppression, lightheadedness, asthma and even anaphylaxis (extreme reaction that could lead to shock).

Common sense dictates that in order to remove the symptoms you must remove the source of the problem. Even in dentistry these same principles can apply. Is there such a thing as dental allergies? Can we actually be sensitive to dental materials or dental procedures that also cause systemic sensitivities?

I honestly believe the answer to this question is yes. Dental research indicates that it takes approximately two minutes for any substance, once exposed to the inner layer of the tooth (dental tubules), to reach the bloodstream. Therefore, when a tooth is prepped for a filling or even a crown, these tubules are uncovered and the dental materials used in the restoration process can and do penetrate directly into the bloodstream.

Recently, I completed a case with a patient who was still experiencing the same symptoms that were bothering him even after his mercury fillings were replaced with tooth-colored fillings. Another dentist had removed his mercury restorations and, upon my initial clinical evaluation, it seemed to be an excellent dental revision and everything seemed to be within normal limits. He was hoping that the mercury removal would reduce or even eliminate some of the anxiety issues he was experiencing as well as the “foggy head” and neck pains. Disappointed with the initial results, he was looking for a second opinion to see if there was anything else that could be done.

As we discussed his case, the only suggestion I could offer this patient was to perform a blood compatibility test to check the dental materials used to replace his mercury fillings. This is useful information for a biological dentist because we recognize the fact that one’s body can be sensitive to certain materials used in the oral cavity. If we can identify the original material used, the compatibility test will assist in our decision making process for our patients.

The results of his test indicated that the materials used in his mouth were highly reactive. Yes, even tooth-colored, composite resins can be a problem. Not all composites are created equally. With our patient’s consent, the tooth-colored fillings were replaced with a new material that was found to be in his least reactive list.
Although I can never promise results to our patients, the blood compatibility test does offer a solution with many of our more difficult cases. It doesn’t surprise me anymore to witness these remarkable changes that can occur once the sensitive materials are removed. Substituting the original composite resin for a new, more compatible material was the key to Jeff’s improved health and wellness.

Here is a testimonial from Jeff: “I came to Dr. Rehme having problems with anxiety, pain in my jaw and a really foggy head. I had a blood compatibility test ordered and found the mercury fillings I had replaced with porcelain fillings two years ago with a different dentist were incompatible with my body. I allowed Dr. Rehme to remove and replace the white fillings with composite materials that my body liked and I feel so much better. I am not having the foggy sensation, no more anxiety and my face and neck pain is so much better that it’s almost totally gone. I am so glad my friend recommended I come see Dr. Rehme, he has allowed me to get my life back.”

The biological concerns must go hand in hand with the methods we use for the mechanical procedures we perform on our patients as we continue to strive for excellence and provide the best dental care available today.
A Practical Guide to Biocompatibility Testing for Dental Materials
2014
By Steve Koral, DMD, MIAOMT

As biologically-minded dentists, we strive to achieve all the goals of modern dentistry while treading as lightly as possible on our patients’ biological terrains. So while we work to maximize strength, durability, comfort, and esthetics, we seek to minimize toxicity, immune reactivity, and galvanic stress.

The restorative materials we use today have all been developed with “most people” in mind. Most people can put up with a bit of toxicity, immune reactivity, and galvanic stress. However, there are outliers, and perhaps their numbers are growing, who can’t stand up to those stresses as well as others. The prevalence of multiple chemical sensitivities (MCS) has been reported to be somewhere between 12 and 33% in the general population, with 2 to 6% having been actually diagnosed as such.

There is a well-documented physiological basis for MCS. Genetic variations leave some people with low-functioning enzymes in critical detoxification pathways, such as methylation, phase-2 conjugation, reduction of oxidized glutathione, membrane transport, and others. The result is that they can’t excrete the chemicals they are exposed to effectively, and they essentially are poisoned. Some researchers have suggested that there are psychological components to the disease as well. Certainly the experience of MCS leads to fear of exposure in the hearts of these patients, including fear of dental materials.

Moreover, there is a significant number of people who are overtly allergic, or otherwise immunologically reactive, to chemicals in their environment. This phenomenon ranges from true allergies to something akin to non-allergic food sensitivities. It results in a range of idiosyncratic, highly individual immune reactions in susceptible people.

These people tend to know who they are, and they are immensely grateful when their dentist acknowledges the problem when prescribing dental materials. After all, people can manage food sensitivities by rotating the diet, but they can’t rotate their permanently installed artificial dental fillings. By practicing individualized biocompatibility testing, and making other common sense choices, we can (almost) always find a combination of professionally recognized restorative materials that will do the job. We can fix teeth and simultaneously help our patients avoid toxicity, immune reactivity, and galvanic stress, and just as important, provide them with peace of mind.

At the same time, “most people” benefit from this precautious level of care, even if they are not, or are not aware of being, chemically sensitive.
**Bad actors**

There are a few common dental materials that are totally out of the pale that should never be used. *Mercury* amalgam – ‘nuff said, but don’t forget the importance of careful barrier techniques when removing them, to protect patient, doctor, and staff from mercury exposure during the procedure.

Nickel allergy is so prevalent in the population that its use in dentistry is outrageous. Unfortunately, due to a difference in immune response between skin and mucosa, the same nickel alloy that would make one’s skin break out if used in an earring will not cause a rash in the mouth. So, it’s hard to point to an obvious problem with the stuff, but it does raise the total level of immune reactivity in the body and should not be used.

This calls into question the safety of stainless steel crowns, especially the NiCro variety. Also, nickel and other non-precious metal alloys tend to contribute disproportionately to galvanic electricity in the mouth.

**Immune reactivity**

Dental materials implanted in teeth present a systemic exposure which implies the possibility of an immune response. Two clinical labs provide “serum compatibility testing” for dental materials which involves testing blood serum for pre-existing antibodies to the more than 140 metals and chemicals that can be found in dental materials. Each chemical is graded according to whether it creates clumps in the serum or not. If it clumps, there’s an antibody against it. If there’s no clump, there’s no antibody reacting.

A computer program then reassembles those components into thousands of name-brand products. If there is a reactive chemical in the product, it is flagged and labeled not acceptable. Both labs provide a booklet of results by product name and by category.

The two labs are:

- Biocomp Laboratories, www.biocomplabs.com, 800-331-2303
- Clifford Consulting Laboratory, www.ccrlab.com, 719-550-0008

There are a couple of differences between the two labs. Biocomp grades products in three levels, “highly reactive,” “moderately reactive,” and “least reactive.” Clifford grades products in a binary fashion as either “satisfactory” or “unsatisfactory.”

An important difference lies in the two labs’ interpretation of aluminum sensitivity. Aluminum is very common in dental materials, and Biocomp treats all aluminum the same— as a problem. Therefore, they kick out most porcelains and ceramics when aluminum sensitivity is detected. Clifford, on the other hand, regards insoluble aluminum compounds such as aluminum oxide and aluminum silicate as not biologically available, so products that contain aluminum in those forms are not graded “unsatisfactory” even if aluminum antibodies are detected. Thus, many more ceramic brands end up on the acceptable list in Clifford reports.
Both labs have very informative websites, and both are very willing to discuss their techniques and preferences. The owners of both labs are longtime IAOMT members, too.

**Serum compatibility routines**

After deciding which lab you want to use, obtain test kits or have them sent directly to the individual patient. Provide the patient with a prescription for blood draw, unless you do that yourself. The patient takes the kit to a nearby blood lab, such as Quest Diagnostics, Labcor, or a local hospital. The patient fills out the enclosed paperwork and includes a check. The blood lab draws one tube of blood, prepares frozen serum, and overnights the sample to the compatibility lab. It’s best to draw the sample early in the week, so Biocomp or Clifford can receive it before the weekend. Both labs are quick at getting the results back to you.

Clifford Consulting Lab will also maintain a list of your favorite materials, and the results for those will appear on the front page of the report.

Who should get tested? Some of our members test all new patients while others test only those who have documented MCS problems. That’s a clinical judgment call.

**Multiple lenses**

The sicker or more sensitive the patient, the more reassurance they need about the safety of our materials. Frankly, the differences among most current composites are minimal, and it probably doesn’t matter which you use for healthy patients. For the true MCS patient, or the suspected, or the nervous, there are more lenses that can be brought to bear on the compatibility question.

If you have a list of acceptable materials from a Biocomp or Clifford test that fits into your range of clinical choices, you might give the patient a physical sample of the proposed filling or crown, etc., to take home and try for themselves in a fully reversible fashion. Remind them that this material has passed the blood test, and tell them to hold it in the cheek for a few minutes or a few hours, and see if a familiar reaction starts. Taping a sample to the skin can be a revealing test, but it must be accompanied by a blank control.

Some people subscribe to the more “holistic” methods, like muscle testing or electrodermal testing. The patient can take your physical sample to another practitioner, too, for this type of corroboration. (It helps if you know the other practitioner, because once in a while, dealing with someone who does not understand dentistry can lead to more, rather than less misunderstanding.)

To whatever extent there is a psychological component to chemical sensitivity, going through all these motions for compatibility testing will go a long way toward reassuring that sensitive patient and recruiting his or her belief system.

In the end, you, as a licensed dentist, must decide your own comfort level and adjust your techniques accordingly.
Problems with metals

Metals are much more allergenic than we typically give them credit for. Does anyone remember being told in dental school to ask patients, especially women, if their skin breaks out with jewelry? Very few patients ever report having been asked that by a dentist.

It is more possible than ever to perform good dentistry without the use of any metals at all, but sometimes we still need them. Some metals, most notoriously nickel, will create Type I immediate hypersensitivity, or a skin rash, upon exposure, and these are easily discovered by history and by serum testing. Other metals, most notoriously titanium, will never make a skin rash, but can lead to Type IV delayed hypersensitivity, a much more insidious cause of malaise and other vague varied symptoms.

For patients where you plan a metal-based prosthodontic procedure, especially if there is any history of metal sensitivity, the most revealing test is the MELISA test (www.melisa.org). This is the only test that will show titanium sensitivity. (Of those tested, only 4% have tested positive to titanium on MELISA.)

MELISA is short for “memory lymphocyte activation,” and it takes four to six tubes of blood to get enough cells. The cells are isolated and cultured with the suspected antigen and tritiated thymidine. Cell proliferation, uptake of radioactivity, and morphological changes are taken as evidence of reaction. The MELISA test was created by immunologist Vera Stejskal, PhD, of Sweden, who has been a frequent speaker at IAOMT meetings.

Several labs around the world perform this test, listed on their website. Two labs in the United States perform MELISA:

- European Laboratory of Nutrients/ Vitamin Diagnostics, www.europeanlaboratory.nl, 732-731-1234.
- Pharmasan Laboratory, www.pharmasan.com, 715-294-1705

Avoiding oral galvanism

Aside from their power to provoke immune reactivity, metals are also electrically active. Oral galvanism has been talked about for well over 100 years, but dentists generally ignore it and its implications. You will read more about oral galvanism in the next unit of the IAOMT Accreditation Program, but below is an introduction to the issue.

Remember the electromotive scale from inorganic chemistry? Remember the potato clock, where a copper nail and a zinc nail stuck in a potato make enough electricity to run a digital clock?

Here are some representative voltage numbers (standard hydrogen electrode) for typical dental metals:

<table>
<thead>
<tr>
<th>Metal</th>
<th>Voltage</th>
</tr>
</thead>
<tbody>
<tr>
<td>titanium</td>
<td>-1.63</td>
</tr>
<tr>
<td>chromium</td>
<td>-0.74</td>
</tr>
<tr>
<td>nickel</td>
<td>-0.26</td>
</tr>
<tr>
<td>silver</td>
<td>0.79</td>
</tr>
<tr>
<td>mercury</td>
<td>0.85</td>
</tr>
<tr>
<td>palladium</td>
<td>0.95</td>
</tr>
<tr>
<td>gold</td>
<td>1.69</td>
</tr>
</tbody>
</table>
This means that gold and titanium grouped together in an electrolyte like saliva can create a battery of over three volts! (This is very oversimplified; for more details, ask a corrosion chemist!) But considering that the nervous system works on membrane potentials of 0.140 volts, electricity from dental metals that is conducted randomly or unpredictably through anatomical structures and spaces can overwhelm normal neuronal control. Often the manifestation is inappropriately elevated muscle tone, – as in jaw tension, TMJ, temporal headache, skin pallor due to low level vasoconstriction, etc.

Why do the best stories still come from the old student days? I was covering the ER oral surgery clinic one Sunday afternoon when a homeless, disoriented woman came in. Her complaint was that the aliens in flying saucers were sending poison rays into her face, and they were spreading down her arm. I figured there must be some reason she was in my clinic, so I looked in her mouth. She had the typical assortment of metal restorations, some non-precious crowns, some gold crowns, amalgam fillings, all topped by a cast metal partial denture. You could almost see sparks when she bit down. “Poison rays from space!” I had her remove the partial, and bite. “No poison rays!” Put the partial back in. “Poison rays from space!”

Avoid poison rays from space. Don’t be cavalier about mixing metals in people’s mouths. The old standard in the gold days would have been to make all restorations in a person’s mouth, including removable frameworks, from the same high noble alloy and not to mix metals at all.

Now we can choose flexible nylon-base partial dentures, all-ceramic crowns and bridges, even all-ceramic implants – all the contemporary non-metallic methods we are currently blessed with, and all the ways we can do our jobs while walking more softly through our patients’ lives.
Introduction to autoimmune diseases and metal implants and devices

There are over 80 recognized autoimmune diseases, with some of the most common being diabetes, lupus, multiple sclerosis, rheumatoid arthritis, and celiac disease.\(^1\) In the United States, estimates of people afflicted by these debilitating health conditions range from 14.7 million to 50 million.\(^2\) The majority of those suffering from autoimmune diseases are women, and the consensus among health groups and researchers alike is that autoimmune diseases are on the rise, with more and more people being stricken with these illnesses each year.

In spite of this growing problem and the increasing burden it carries for patients, their families, the medical community, and society at large, there are still massive gaps in scientific knowledge about autoimmune diseases. However, it is generally agreed that these illnesses are related to genetics and environmental factors. (“Environmental factors” is a phrase that encompasses all aspects of the environment with which humans interact, including bacteria, viruses, chemicals, etc.).

In particular, along with recognizing genetic components of autoimmune diseases, researchers have clearly identified that these health conditions can be caused by metals, pharmaceutical drugs, pollen, infectious agents, molds, and food allergies (such as gluten).\(^3\) The fact that the average person’s overall exposure to chemicals, including metals, has drastically increased over the past century cannot be overlooked when discussing the synonymous rise of autoimmune illnesses. Dr. Vera Stejskal has explained: “Disregulation of the immune system by chemicals may be one of the reasons why the frequency of allergies and autoimmune diseases increases.”\(^4\)

What is autoimmunity and how does it relate to metal implants and devices?

In simple terms, autoimmunity can be defined as a misdirected immune response that occurs when the immune system attacks the body, resulting in autoimmune disease when there is a progression to pathogenic autoimmunity.\(^5\) Allergy and autoimmunity share characteristics in that both are triggered by an abnormal immune response and both can produce local and systemic inflammation.\(^6\)

Metals have been widely recognized as one of the triggers capable of producing such inflammation. In a 2014 publication, Dr. Vera Stejskal wrote: “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.”\(^7\)

In this regard, it is suspected that metal ions released from dental and medical implants and devices can cause inflammation in susceptible subjects.\(^8\) The release of metal ions from these implants and devices occurs locally (i.e. at the site of the implant/device), but the metal ions are processed both locally and in other parts of the body, and this can prompt an immune reaction.\(^9\)
Reactions are more likely to occur for individuals who are genetically predisposed to having lower excretion rates of metals,\textsuperscript{10} as well as other individualized factors. For example, Dr. Ivan Sterzl and his colleagues have reported: “Hypersensitivity to metals results in [a] wide range of clinical and sub-clinical symptoms such as chronic fatigue, depression, sleep disturbances and others. Patients with these symptoms often report intolerance to metal earrings and other metallic devices such as jeans buttons, watches, and intrauterine devices.”\textsuperscript{11}

**Autoimmune diseases associated with metal implants and devices**

Reactions to metal implants and devices can be manifested on the skin or in the oral mucosa, but they can also include more complex immune reactions at the site of the implant (local), at other parts of the body, and/or throughout the body (systemic). Even trace amounts of metals can potentially cause a reaction.\textsuperscript{12}

While numerous health conditions have been related to the presence of metals in the body, this report focuses on autoimmunity. Because autoimmune diseases include more than 80 health conditions, the table below represents an abridged list of autoimmune illnesses that have been associated with metals used in dentistry and medicine, including metals in implants, devices, and adjuvants (substances added to vaccines such as aluminum and mercury). Citations for the table are likewise truncated, as there are a large number of scientific research articles about this topic.

<table>
<thead>
<tr>
<th>Abridged List of Autoimmune Diseases Associated with Metals Used in Dentistry and Medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyotrophic Lateral Sclerosis (Lou Gehrig’s Disease)\textsuperscript{13 14 15}</td>
</tr>
<tr>
<td>Autoimmune/Inflammatory Syndrome Induced by Adjuvants (ASIA)\textsuperscript{23 24 25 26}</td>
</tr>
<tr>
<td>Chronic Fatigue Syndrome (Myalgic Encephalomyelitis/Chronic Fatigue Syndrome)\textsuperscript{32 33 34 35 36 37 38 39 40}</td>
</tr>
<tr>
<td>Diabetes (Type 1 Mellitus)\textsuperscript{42}</td>
</tr>
<tr>
<td>Gulf War Syndrome\textsuperscript{47 48} (listed separately here, although technically classified as ASIA)</td>
</tr>
<tr>
<td>Macrophagic Myofasciitis\textsuperscript{51 52} (listed separately here, although technically classified as ASIA)</td>
</tr>
<tr>
<td>Oral Lichen Planus\textsuperscript{56 57 58 59}</td>
</tr>
</tbody>
</table>
Sources of exposure from metal implants and devices that affect autoimmunity

Metals are ubiquitous in our daily lives, and it is basically impossible to eliminate exposure to them given their presence in our air, water, food, and an increasing number of consumer products. Some metals are recognized as essential to human life and serve important roles within the human body, including chromium, cobalt, copper, iron, manganese, molybdenum, and zinc. However, the beneficial effects of trace elements are based on safe and adequate intake levels, with too little resulting in deficiencies and too much resulting in toxicities.

Other metals used in dentistry and medicine have no established function in the human body, and in addition to aluminum, which is both a neurotoxin and an immune stimulator, these include gold, mercury, nickel, palladium, platinum, silver, and titanium. Mercury is recognized as being toxic to humans even in low doses, and researchers have identified chromium, cobalt, copper, gallium, gold, iron, lead, manganese, mercury, nickel, platinum, silver, tin, vanadium, and zinc (among others) as metals of concern due to residential and occupational exposure.

Researchers have also established that chronic exposure to low doses of metals can elicit autoimmunity in genetically susceptible humans. Dr. Ivan Sterzl and his colleagues have elaborated: “The key factors governing the harmfulness of metals are the cumulative concentration, duration of exposure, and genetic susceptibility. Many harmless metals may become allergens or exert toxicity if administered on a chronic basis.”

Dental and medical implants and devices placed directly into the human body merit significant consideration when evaluating the impact of metal exposure levels, especially in susceptible populations. This scrutiny is particularly crucial because the use of metals in dentistry and medicine continues to rise, as the table below helps to demonstrate, even though it is only an abridged list.

Abridged List of Metals Used in Dentistry and Medicine

<table>
<thead>
<tr>
<th>Product</th>
<th>Metals</th>
</tr>
</thead>
</table>
| Dental Bridges, Crowns, Partial Dentures, and Implants | • These items can contain aluminum, chromium, cobalt, copper, gallium, gold, indium, iridium, iron, manganese, nickel, palladium, platinum, silver, titanium, vanadium and more.  
• Items made of cobalt-chromium-molybdenum steel contain those elements in addition to aluminum, nickel, titanium, and others.  
• Research has found that some of these dental materials can contain lead. |

www.iaomt.org and www.theSMARTchoice.com
<table>
<thead>
<tr>
<th><strong>Dental Fillings</strong></th>
<th>• Amalgam (silver) fillings contain about 50% mercury mixed with copper, silver, and tin, and they can also contain zinc and other metals, including lead and cadmium. Some composite fillings, as well as dental cements and root-fillings, can contain titanium dioxide. Dental gold alloys can also contain copper, gallium, indium, iridium, palladium, nickel, silver, tin, titanium, and zinc, as well as beryllium.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gynecologic Devices</strong></td>
<td>• Some intrauterine devices (IUDs) contain copper, and possible contaminants include manganese, nickel, and zinc. Permanent contraceptive devices and clips (i.e. tubal ligation) can contain nickel and titanium.</td>
</tr>
<tr>
<td><strong>Intravascular Devices</strong> (i.e. coronary stents, perforated foramen occluders, pacemakers, and implantable defibrillators)</td>
<td>• Cardiac/intravascular devices can be made of stainless steel (which can contain chromium, manganese, molybdenum, and nickel). They can also be made of chromium, cobalt, molybdenum, and/or nitinol (which is 45% nickel and 55% titanium). Stents can be coated in gold. Pacemakers can contain aluminum, nickel, and titanium, and can be coated in gold.</td>
</tr>
<tr>
<td><strong>Medication</strong></td>
<td>• Pills can contain titanium dioxide and other metal oxides. Antacids can contain aluminum.</td>
</tr>
<tr>
<td><strong>Orthodontic Appliances (i.e. bands, braces, brackets, retainers, and wires)</strong></td>
<td>• These can contain nickel and titanium. They can also contain aluminum, chromium, cobalt, copper, iron, molybdenum, niobium, and vanadium, as well as silicon and other elements.</td>
</tr>
<tr>
<td><strong>Orthopedic Implants</strong> (i.e. hip replacements, screws, nails, and clips)</td>
<td>• These often contain chromium, cobalt, nickel, and/or titanium. Items made with stainless steel contain a large amount of nickel with chromium, manganese, and molybdenum, in addition to other elements. Items made with cobalt-chromium molybdenum steel contain those elements in addition to aluminum, iron, manganese, nickel, titanium, and tungsten. Items made with titanium can also contain aluminum, vanadium, trace amounts of nickel, and other elements. Items made with nitinol contain nickel and titanium. Items made with Vitallium™ contain cobalt, chromium, manganese, molybdenum, iron, and other elements.</td>
</tr>
</tbody>
</table>
Surgical Clips and Staples
- Items made with stainless steel can contain chromium, manganese, molybdenum, nickel, and other elements.\textsuperscript{112}
- Items made with titanium alloy contain aluminum, nickel, titanium, and vanadium.\textsuperscript{113}

Vaccines/Flu Shots/Immunoglobulin Preparations
- These can contain aluminum\textsuperscript{114} \textsuperscript{115} and/or mercury (as thimerosal).\textsuperscript{116} \textsuperscript{117} \textsuperscript{118}

**Additional considerations for metal exposures:**
- Cigarette smoke
- Coins
- Containers including beverage cans and canned food
- Cookware and utensils
- Cosmetic products
- Detergents
- Diet (i.e. fish containing mercury; foods high in nickel such as chocolate, nuts, oatmeal, soya beans, etc.)
- Eye drops, contact lens solution, and eyeglass frames
- Jewelry, belts, watches, accessories, etc.
- Occupational exposures
- Pipes for drinking water, etc.
- Pollution
- Sunscreen
- Toothpaste
- Well water
- Other consumer products

**Metal implants and devices and adverse reactions related to autoimmune diseases**

To reiterate, metals such as aluminum and mercury are known to be toxic to humans, and it might seem like a moot point to discuss adverse reactions to toxic chemicals. It should also be emphasized that exposure to any metal can elicit a harmful reaction. However, since these metals are still being used in dentistry and medicine, once these obvious dangers are acknowledged, it is helpful to chronicle the array of adverse reactions that can occur with metal exposures, which include toxicity, allergies, and more.

First, it must be understood that genetics play a role in a person’s unique response to metal exposure. Jenny Stejskal, MD, and Vera Stejskal, PhD, have explained: “Depending on genetically determined detoxification systems, an individual may tolerate more or less exposure to toxic metals before showing adverse effects. The immunological effects of metals are either non-specific such as immunomodulation or antigen-specific such as allergy and autoimmunity.”\textsuperscript{119} What this means is that patients sensitive to metal can experience reactions in the oral mucosa or skin and/or fatigue and autoimmune diseases.\textsuperscript{120} \textsuperscript{121}
Another important factor to consider is the release of metal ions, which can increase the possibility of an immunologic or toxic reaction. The release of metal ions from metal implants and devices can occur due to mechanical wear, cellular processes, and corrosion from contact with biological fluids such as blood, sweat, and saliva. Electrolytic conditions in the body can also provoke corrosion of metals by generating electrical currents in a phenomenon known as galvanism. This can occur when a combination of metals interacts with other elements in the body. For example, the combination of mercury and gold in the mouth (with saliva serving as the electrolyte) has been recognized as the most common cause of dental galvanic corrosion. Yet, other metals used in dentistry can similarly produce this effect. As another example, fluoride-containing mouthwash has been recognized as a factor in the corrosion of orthodontic appliances (with the galvanic coupling of metallic orthodontic wires and brackets). Fluoride has also been linked to the corrosion of titanium dental implants and dental amalgam fillings (all of which contain approximately 50% mercury).

In some genetically susceptible individuals, metals can also trigger allergies. Dr. Vera Stejskal conducted a series of studies that evaluated patients with suspected reactions to their metal devices and implants. Patients were tested for metal hypersensitivities, and results were collected that demonstrated the prevalence of these metal hypersensitivities. While each study included testing for different metals, the studies collectively identified nickel as the most common sensitizer, followed by other metals, including inorganic mercury (i.e. dental amalgam mercury), thimerosal, lead, cadmium, palladium, and gold. Dr. Stejskal also noted that the frequency of titanium allergy is increasing.

Documented rates of metal allergy in other research support Dr. Stejskal’s findings and establish that millions of Americans are in danger of having a reaction to dental amalgam fillings and/or medical implants placed into their bodies. According to data presented in a study published in 2018 that used North American Contact Dermatitis Group (NACDG) patch testing results from 5597 patients, nickel was the most commonly detected allergen at 17.5%, and cobalt was the second most common metal allergen at 6.2%. Another study published in the same edition of the journal Dermatitis was conducted on 686 adults who were patch tested with the NACDG series and demonstrated that “38.9% of patients had 1 or more positive patch-test reactions to a metal allergen, most commonly nickel (17.4%), mercury (12.3%), and palladium (9.2%)…Among patients with positive reactions to nickel, 34.5%, 15.1%, and 5.0% had positive reactions to 1, 2, or 3 additional metals, respectively.”

Both of the studies mentioned above involved individuals with suspected allergies; yet, the statistics are relevant, as studies involving the general population and the prevalence of metal allergies are rare. Nonetheless, recent studies and reports tend to agree that metal allergies are on the rise. Part of this could be caused by increased exposure to metals, including ear/body piercings, because exposure to metals has been cited as a potential trigger for the development of allergies to them. It has also been hypothesized that contact with metals during an infection could increase chances of developing a metal allergy later in life. At any extent, in a 2016 review, researchers from Harvard School of Medicine qualified: “Dermal hypersensitivity to metal is common and can affect up to 15% of the population.”
However, one issue with calculating the number of patients with adverse reactions to a metallic material is that the onset of symptoms can be delayed and therefore might not be associated with the implant or device. For example, researchers writing about dental amalgam fillings warned: “Sensitization appears most frequently after the amalgam has been present in the mouth for more than 5 years.”148 Another issue is that there may not be any local reaction to help the patient and doctor identify the metal as the culprit in ill health,149 and even if hypersensitivity reactions are noticed, they can be misdiagnosed as infection.150

Clinical screening for metal allergy has been recommended,151 and the importance of patients reporting reactions to metals to their doctors has also been emphasized in the scientific literature.152 153 154 155 156 157 In addition to reporting any rashes from jewelry, watches, or other metal exposures, it is essential for each patient to recognize the gamut of symptoms that can be related to the presence of a metal implant or device in their body. It is also vital for patients to remember that sensitization to metal can develop years after an implant or device has been placed and that adverse effects can occur with or without the sign of a rash or eruption on the skin or in the mouth.

Allergy testing can be used to assist in identifying some of the individuals susceptible to adverse reactions to metals. Patch testing is generally regarded as the “gold standard” in allergy testing; however, patch testing has also been criticized because it involves directly applying the allergen to the skin, it can exacerbate symptoms in patients, it can result in sensitization, and the results can be affected by other conditions.158

One relatively new alternative to skin patch testing is known as the Lymphocyte Transformation Test (LTT), which was first used in the 1960s to evaluate certain types of antigens. Two relatively new alternatives to skin patch testing are a modified version of the Lymphocyte Transformation Test (LTT) known as MELISA159 and the Lymphocyte Response Assay (LRA) by ELISA/ACT.160 The MELISA test was introduced by Dr. Vera Stejskal in 1994 to test for type IV delayed hypersensitivity to metals, including sensitivity to mercury.161 Much of Dr. Stejskal’s work has involved using the testing to help diagnose patients with reactions to metals, thus facilitating the decision to have the metal implants and devices safely removed and replaced with safer alternatives, and then, recording the health outcomes, the majority of which have involved significant improvement.

Another option for testing has been created specifically for dental materials. If this biological testing is used, a patient’s blood sample is sent to a laboratory where the serum is evaluated for the presence of IgG and IgM antibodies to the chemical ingredients used in dental products.162 The patient is then provided with a detailed list of which name-brand dental materials are safe for their use and which ones could result in a reaction. Two labs that currently offer this service are Biocomp Laboratories163 and Clifford Consulting and Research.164

Unfortunately, in some reported cases, the only way to fully establish that a metal implant or device was causing health problems was to have it removed and then document the results. Researchers from Harvard School of Medicine wrote in 2016: “Paradoxically, a patient can sometimes only be diagnosed with metal allergy when the symptoms resolve upon replacement with an immunologically inert implant.”165
Removal of metal implants and devices and potential recovery from autoimmunity

Removal of metal implants and devices is an obvious course of action when adverse effects occur. Indeed, the scientific literature is abundant with studies and cases of individuals improving or recovering from autoimmune diseases *usually within a year or two after removal* of the offending metal, as the following table of selected examples from research shows:

### Sampling of Research Documenting Improvement in Autoimmunity upon Metal Implant/Device Removal

<table>
<thead>
<tr>
<th>Health Condition/s Improved or Recovered</th>
<th>Implant/Device Removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyotrophic Lateral Sclerosis (Lou Gehrig’s Disease) Variant: Progressive Muscular Atrophy</td>
<td>Metal denture and titanium screws in knee, among other therapies(^\text{166})</td>
</tr>
<tr>
<td>Autoimmune Thyroiditis/ Fatigue</td>
<td>Dental amalgam mercury fillings(^\text{167 168 169 170})</td>
</tr>
<tr>
<td>Autoimmune/Inflammatory Syndrome Induced by Adjuvants (ASIA)</td>
<td>Nickel-titanium chin implant(^\text{171})</td>
</tr>
<tr>
<td>Chronic Fatigue Syndrome (Myalgic Encephalomyelitis/Chronic Fatigue Syndrome)</td>
<td>Dental amalgam mercury fillings and other metallic dental restorations(^\text{172 173 174 175 176})</td>
</tr>
<tr>
<td>Chronic Fatigue Syndrome (Myalgic Encephalomyelitis/Chronic Fatigue Syndrome)</td>
<td>Nickel clips from tubal ligation, dental amalgam mercury fillings and other metallic dental restorations(^\text{177})</td>
</tr>
<tr>
<td>Chronic Fatigue Syndrome (Myalgic Encephalomyelitis/Chronic Fatigue Syndrome)</td>
<td>Skull plate made of aluminum, titanium, and vanadium with nickel impurities(^\text{178})</td>
</tr>
<tr>
<td>Chronic Fatigue Syndrome (Myalgic Encephalomyelitis/Chronic Fatigue Syndrome)</td>
<td>Titanium screws in cervical vertebra and titanium dental implants(^\text{179})</td>
</tr>
<tr>
<td>Condition</td>
<td>Cause</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Crohn’s Disease</td>
<td>Dental amalgam mercury fillings and other metallic dental restorations</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>Cobalt-chromium prosthesis and dental amalgam mercury fillings</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>Copper IUD</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>Dental amalgam mercury fillings and other metallic dental restorations</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>Dental amalgam mercury fillings and other metallic dental restorations</td>
</tr>
<tr>
<td>Multiple symptoms</td>
<td>Dental amalgam mercury fillings and other metallic dental restorations</td>
</tr>
<tr>
<td>Oral lichen planus</td>
<td>Dental amalgam mercury fillings and other metallic dental restorations</td>
</tr>
<tr>
<td>Sjögren's Syndrome</td>
<td>Dental amalgam mercury fillings and other metallic dental restorations</td>
</tr>
<tr>
<td>Systemic Lupus Erythematosus</td>
<td>Dental amalgam mercury fillings</td>
</tr>
</tbody>
</table>

The removal of metal implants and devices should only be conducted by a qualified healthcare professional. This is because an unsafe removal process can cause serious injury (and even death) to the patient, in addition to the possibility of increased metal exposure. For example, if dental amalgam fillings are removed unsafely, patients can be exposed to increased levels of mercury. In her research, Dr. Vera Stejskal specifically warned about applying safety measures during amalgam filling removal. Furthermore, in a clinical study published in 2013, Dr. Paolo Pigatto and his colleagues reported “one major adverse outcome related to dental amalgam removal without safe procedures,” but no side effects were reported with a safe and effective dental amalgam removal.

Based on scientific research, the International Academy of Oral Medicine and Toxicology (IAOMT) has developed recommendations known as the Safe Mercury Amalgam Removal Technique (SMART) to assist in mitigating the potential negative outcomes of mercury exposure during amalgam removal. The IAOMT also offers education about alternatives to dental amalgam fillings so that patients can opt for a more “biocompatible” replacement (i.e. one that is best suited for the patient based on safety and personal healthcare needs).
It is important to note that other factors can influence whether or not a patient improves after the removal of a metal implant or device. While many patients improve or even recover, there are some who do not. One obvious reason for this is if the patient is still being exposed to the metal or a different sensitizer through another implant, device, or other source. In a most unfortunate circumstance, patients can even have a reaction to the new implant or device. Thus, it is critical to select a biocompatible replacement. Fortunately, in most cases, metal-free devices such as ceramic options are now available.

Dr. Vera Stejskal has also noted that in order to get well, some patients further require the eradication of *Heliobacter pylori*, the cessation of smoking, and/or the adoption of a low nickel diet. Some medical professionals and researchers have also suggested the need for detoxification and supplements to assist the body in recovering from metal exposure.

Additional impediments in achieving improved health can include the presence of another illness and/or allergy, exposure to certain pesticides, solvents, molds, and foods, hormonal imbalances, stress, a sedentary lifestyle, and countless other factors. For all these reasons and more, it is imperative for patients battling autoimmune diseases to work with their doctors and other healthcare professionals so that toxins and allergens are kept out of their bodies and healthier, safer options are put in to replace them.

*For more information about the research of Dr. Vera Stejskal, visit [http://www.melisa.org/articles/](http://www.melisa.org/articles/).*

---


International Academy of Oral Medicine and Toxicology (IAOMT) Page 13
www.iaomt.org and www.theSMARTchoice.com


YOU NOW NEED TO VISIT IAOMT’S “ONLINE LEARNING CENTER” TO WATCH THE BIOCOMPATIBILITY AND ORAL GALVANISM VIDEO AT https://iaomt.org/biocompatibility-oral-galvanism-video-activity

UPON COMPLETION OF THE “BIOCOMPATIBILITY AND ORAL GALVANISM” VIDEO, YOU WILL NEED TO CONTINUE WITH THE ADDITIONAL REQUIREMENTS FOR UNIT 5.
Diagnosis and treatment of metal-induced side-effects

Vera Stejskal¹, PhD; Romuald Hudecek², DDS; Jenny Stejskal³, MD & Ivan Sterzl¹, MD, PhD

¹ Dept. of Immunology and Microbiology, 1st Medical Faculty, Charles University Prague, Czech Republic.
² Biomedical Dental Centre, Uppsala, Sweden.
³ Mörby General Practice, Stockholm, Sweden.

Correspondence to: Vera Stejskal, PhD
August Wahlströmsväg 10
182 31 Danderyd, SWEDEN
TEL/FAX:+46 8 753 23 22
EMAIL: vera@melisa.org

Submitted: December 2, 2006  Accepted: December 18, 2006

Key words: autoimmunity; allergy; chronic fatigue syndrome; genetics; lymphocyte; LTT; MELISA⁺; patch test; metals; mercury; gold; titanium

Abstract

Environmental factors are recognized as a cause of the increasing frequency of allergic and autoimmune diseases. In addition to external pollutants, metal ions released from dental restorations or from other body implants might trigger inflammation in susceptible subjects. In humans, genes governing metal-induced inflammation and autoimmunity are not yet known.

In clinical praxis, metal-sensitive patients will present various symptoms ranging from oral mucosal changes and skin disease to excessive fatigue and autoimmune diseases. Since genetic markers of genetic susceptibility in man are not known, one has to rely on the phenotypic markers. Such biomarkers might be certain detoxification enzymes but also the presence of metal-specific memory cells in the blood.

With the increasing use of metal implants in medicine and dentistry, it is important to have a proper tool for the diagnosis of metal allergy in susceptible subjects.

In addition to patch test, an in vitro blood test, an optimized commercially available lymphocyte transformation test (MELISA⁺) is discussed. Both tests were used for the diagnosis of metal allergy in a selected group of 15 patients who suffered from clinical metal sensitivity in addition to other health problems. The concordance of the two tests was good but MELISA⁺ detected more metal allergies than patch test.

The removal of incompatible dental material (RID) resulted in long-term health improvement in the majority of patients. We postulate that in vivo, metal ions activate T-cells, initiating systemic inflammation, which, through cytokines, affects the brain and hypothalamus-pituitary-adrenal axis.

The treatment and rehabilitation of metal sensitive patients is based on a firm understanding and recognition of individual susceptibility. RID has to be done with extreme caution and according to standard working protocol. If performed properly, this treatment can result in decreased systemic inflammation and improved health in sensitized patients.
Background

Mankind is exposed to toxic particles, such as metals, on a daily basis through contaminated food and air. Environmental toxins can be one of the etiological factors behind the increase of so-called modern illnesses: allergies, autoimmunity and cancer [14, 28, 33, 66, 67]. The role of the organic mercury (Hg) compound thimerosal as a factor contributing to the increased frequency of autistic disorders has also been widely discussed [16, 17, 42]. In addition, metal-based medical devices such as dental restorative materials (e.g. amalgam and gold alloys) release metal ions and contribute to internal pollution.

Dental restorative materials are developed for replacement of tooth substance which is lost and are placed in the teeth for long periods of time. Previously, the majority of such materials were based on various metal alloys, but in modern dentistry, the use of non-metallic dental materials, for example ceramics, is steadily increasing.

Such materials should preferably be free from toxic and/or allergenic substances which might affect the patients' and dental staffs' health. Special care has to be taken in patients with known allergy and/or autoimmunity.

Metals affect the immune system in several ways. In the oral cavity, a high concentration of metal ions may be toxic and act as a local immunosuppressant. This may explain why the oral mucosa contains only a low number of dendritic cells, and why mucosal changes adjacent to dental metal fillings are infrequent [35]. Nielsen and Klaschka [45] have shown that a 5–12 times higher concentration of the allergen has to be applied on the oral mucosa than on the skin to elicit microscopic reaction.

Certain metals stimulate the immune system nonspecifically as shown by increased levels of serum immunoglobulins in workers professionally exposed to Hg [5]. Further, an abnormal antioxidant system with reduced levels of glutathione and catalase activity was found in Hg exposed workers [54]. In the general population, anti-oxidant capacity of serum is inversely related to the number of amalgam fillings, as described by Pizzichini and coworkers [49]. Interestingly, glutathione depletion inhibits TH1-associated cytokine production and/or favors TH2-associated responses [46]. This might explain the TH1 to TH2 switch in animals treated with low concentrations of inorganic Hg [19, 50]. In contrast, in some hereditarily predisposed individuals, metals may act as specific allergens [6, 11, 21, 29, 37, 51].

The majority of metals used in dental alloys belongs to the group of transition metals in Mendeleev's periodic table. A general characteristic of these elements is the strong binding capacity to various groups of enzymes and cells in the body. Transition metals form strong complexes with both organic and inorganic ligands [85]. Metals bind to sulfhydryl (SH) and other groups, thus altering the molecular structure of autologous proteins. T-lymphocytes mistakenly recognize metal-modified cells as foreign and start the autoimmune process [20]. The term “allergy” was coined by von Pirquet to describe a deviant immunological reaction – hypersensitivity [48].

It has to be emphasized that metals are only one of several agents which may trigger chronic inflammation and thus significantly contribute to chronic fatigue syndrome (CFS) and autoimmune diseases. The role of other agents, such as microbial [79] or viral, in inflammatory processes is reviewed elsewhere [15].

Biomarkers of harmful effects of metals and other environmental pollutants include detoxification enzymes, such as apolipoprotein E, where the substitution of cystein with arginin – an amino acid lacking SH-groups – predisposes for increased risk for Alzheimer’s disease [18] and increases vulnerability to chronic mercury toxicity [91]. Other detoxification enzymes of importance are glutathione s transferase T1 (GSTT1) and glutathione s transferase M1 (GSTM1). As shown by Westphal’s group [90], homozygous deletion of GSTT1 and combined deletion of GSTT1-/GSTM1- was markedly more frequent in patients sensitized by thimerosal, than in healthy controls.

Regarding metal susceptibility, measurement of beryllium (Be) specific memory cells in the blood of exposed workers is currently the golden standard for detection of Be-susceptibility [30, 31, 44]. Since clinical reactions to metals, such as local skin reactions or systemic reactions (fever, profound fatigue, multiple chemical sensitivity) are not experienced by all exposed individuals, standard case-control studies with a small number of participants, who are not matched for the susceptible genotype, are of limited value [89]. Instead, a suitable cohort should consist of patients suffering from the same symptoms but selected on the basis of susceptible phenotype; for example, patients suffering from CFS and clinical metal sensitivity [52, 76, 78].

Thus, the best way to study the possible role of metals in the pathogenesis of diseases seems to be first, the selection of susceptible patients from a heterogeneous multi-factorial cohort; second, therapy based on the elimination of the exposure to putative allergen(s); and third, long-term follow-up of patient’s health. Finally, it is also important to bear in mind that exposure to metals can originate from all types of metal-containing medical devices, and not only from dental appliances. Other...
sources are foods [55], jewelry, cosmetics, vaccines, metallic razors [12] and contaminated air (cigarette smoke, pollution).

**T-lymphocytes are key players in inflammation and autoimmunity**

T-lymphocytes play a key role in all types of allergic and autoimmune reactions [19, 20, 56]. After contact with an allergen, allergen-specific T-lymphocytes, together with B-cells and macrophages, are activated and inflammation may occur locally or in other parts of the body. The allergen specificity is retained on the surface of memory cells. Memory lymphocytes (Fig. 1a) circulate in the blood and lymph, which explains why allergy is a systemic phenomenon. Exposure to the same or chemically similar (cross-reacting) substance will induce a faster, secondary reaction. Cytokine release by activated lymphocytes and macrophages will result in deregulation of the hypothalamus-pituitary-adrenal axis, as well as in multi-systemic symptoms such as profound fatigue, psychosomatic problems and sleep disturbances [9, 39, 65, 68, 84].

**In vivo testing**

Currently, the patch test is the only test available for routine in vivo diagnosis of delayed type hypersensitivity. Although the test is useful in clinical praxis, it has several disadvantages [36, 43, 66, 87]. Direct application of the allergen under occlusion on the skin might boost already existing sensitivity, which might aggravate patients’ symptoms [36]. Some allergens, such as gold (Au) salts, may carry the risk of sensitization [43, 58] and positive patch test reactions may persist for months. Patch test results can also be affected by the condition of the skin; fair-haired patients usually have more sensitive skin. In pre-menopausal women, the patch test results may vary depending on the menstrual cycle [80]. Under standard conditions, only 7% out of the total amount of nickel (Ni) applied will penetrate the skin [13]. If the permeability of the skin is increased by local pretreatment by a surfactant such as sodium lauryl sulfate (SLS), the penetration of metals through the skin increases, which improves the accuracy of patch testing [62]. SLS might be beneficial in patch testing but its presence as an ingredient in toothpaste, soap and shampoo should be questioned.

In spite of the fact that the patch test is regarded as golden standard, the test, as such, is for many allergens not standardized. Allergens can be diluted in water or applied in undiluted form in petrolatum.

Finally, the evaluation of patch testing is subjective and depends on the skills of the evaluating specialist. The results of patch testing with skin-irritating substances such as Hg salts or formaldehyde may be unreliable since toxic reactions due to irritation are difficult to discriminate from allergic reactions [12].

**In vitro testing**

The lymphocyte transformation test (LTT) uses the property of memory cells to be re-stimulated by a specific allergen. Lymphocytes are isolated from peripheral blood on a density gradient and cultivated with metal salts for 5 days in 37°C. If memory cells are present in the blood, they start to divide and differentiate to so-called lymphoblasts (Fig. 1a). Proliferation is measured by the uptake of radiolabeled thymidine into newly synthesized DNA. The proliferation in metal-treated cultures is compared with cells incubated in the absence of metal salts and expressed as an Stimulation Index (SI). SI=counts per minute in metal-treated cultures divided by counts per minute in control cultures. SI ≥ 3 is considered as a positive response while SI 2–3 is considered a weakly positive response [73, 74].

In the case of low molecular substances, allergen-specific memory cells are found in the blood of subjects experiencing exposure-related clinical symptoms but not in the majority of healthy non-allergic subjects [30, 60, 64, 69–74, 76, 77].

Memory cells can be detected in the blood of sensitized individuals already prior to the appearance of visible clinical reactions. Thus, workers with Be-specific in vitro lymphocyte responses have been diagnosed as Be-allergic even if the symptoms of the chronic lung disease berylliosis were not yet apparent [30, 31, 44]. Following the relocation to a Be-free environment, these workers did not develop berylliosis and remained healthy.

For decades, it has been known that inorganic Hg salt (HgCl₂) activated human lymphocytes in vitro regardless of the donor’s Hg allergy status [8, 61]. Hence, to be able to use LTT for diagnosis of Hg allergy, it was necessary to modify the test in such a way that only lymphocytes from patients with Hg-induced symptoms were activated [74]. This was achieved by reducing the concentrations of Hg salts added to cultures to suboptimal concentrations (0,5 µg per 1 ml culture)[73, 74]. The same turned out to be true for Ni [59, 60, 64] as well as Au and palladium (Pd) salts, where a concentration of 5 µg per culture is routinely used [73]. This modified LTT was named MELISA*, an acronym for Memory Lymphocyte Immuno Stimulation Assay [73]. Another important modification was the increase of the total number of lymphocytes to 1 × 10⁶ cells instead of 2 × 10⁵ cells used in standard LTT. The key importance of lymphocyte concentration for optimal results has been described by Valentine-Thon [86]. Further, since the number of monocytes (Fig. 1b) increased during the preparation procedure, it was necessary to bring the amount of monocytes back to the normal value by partial monocyte depletion. Although necessary for antigen presentation to T-cells, activated monocytes produce prostaglandins [27] which negatively affect lymphocyte activation [57].

At Astra Pharmaceuticals, the MELISA* test was originally used for the diagnosis of occupational allergy to drugs in the pharmaceutical industry [69, 70]. Later
**Table 1.** The results of patch test and MELISA* in 15 patients with clinical metal sensitivity and temporary worsening of symptoms in connection with dental treatment (2–3 days later).

<table>
<thead>
<tr>
<th>Pat. nr</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Clinical symptoms</th>
<th>Dental metal exposure</th>
<th>Patch test</th>
<th>MELISA* Stimulation Index (SI)</th>
<th>Therapy</th>
<th>Clinical effect of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>BE</td>
<td>M</td>
<td>48</td>
<td>CFS, sinusitis, dry eyes, joint pain</td>
<td>17 AF (previously)</td>
<td>Au ++</td>
<td>Hg -</td>
<td>Removal of all metals</td>
<td>1 yr later: much better, joint pain gone, eye dryness decreased. Sinusitis persists.</td>
</tr>
<tr>
<td>EH</td>
<td>F</td>
<td>48</td>
<td>Crohn’s disease, abnormal fatigue, oral problems</td>
<td>AF in all teeth</td>
<td>Au +</td>
<td>Pd -</td>
<td>1. AF replaced with Au crowns</td>
<td>1. Worsening of health.</td>
</tr>
<tr>
<td>GCH</td>
<td>M</td>
<td>53</td>
<td>Urticaria on the back after dental treatment eczema, acne, psychiatric problems, anxiety, depression</td>
<td>25 AF</td>
<td>Au +</td>
<td>Hg -</td>
<td>Replacement of all metals</td>
<td>2 yrs after replacement: decreased skin problems and psychiatric symptoms.</td>
</tr>
<tr>
<td>AS</td>
<td>F</td>
<td>45</td>
<td>Neurological symptoms and eczema after insertion of MBP</td>
<td>10 AF</td>
<td>Ni +</td>
<td>Cu +</td>
<td>Removal of most metals</td>
<td>2 yrs after replacement: some symptoms disappeared and some became worse.</td>
</tr>
<tr>
<td>IH</td>
<td>F</td>
<td>62</td>
<td>Polymyalgia rheumatica following replacement of AF with Au crowns and bridges</td>
<td>AF (previously)</td>
<td>Ni +</td>
<td>Pd -</td>
<td>Removal of all metals including corroded screws in RF</td>
<td>2 yrs after replacement: long-term health improvement. Decrease in lymphocyte responses to Cu (SI 2) and Ni (SI 4.2)</td>
</tr>
<tr>
<td>LL</td>
<td>F</td>
<td>44</td>
<td>CFS, fibromyalgia, oral symptoms, eczema, headache</td>
<td>13 AF</td>
<td>Ni ++</td>
<td>Pd +</td>
<td>Removal of all metals</td>
<td>1 yr later: partly better, still fatigued, back pain, muscle pain better. 2 yrs later: further health improvement</td>
</tr>
<tr>
<td>IB</td>
<td>F</td>
<td>41</td>
<td>Oral symptoms and eczema after insertion of Pd-containing bridge</td>
<td>AF (previously)</td>
<td>Ni ++</td>
<td>Hg -</td>
<td>Removal of AF anti-oxidant therapy</td>
<td>2 yrs after replacement: marked improvement in oral health</td>
</tr>
<tr>
<td>EV</td>
<td>F</td>
<td>52</td>
<td>Thyroiditis with autoantibodies, fatigue, endocrine problems</td>
<td>9 AF</td>
<td>Ni ++</td>
<td>Hg -</td>
<td>Removal of AF anti-oxidant therapy</td>
<td>2 yrs later: improved health and decrease of lymphocyte reactivity to Hg (SI 5), Ni (SI 11) and MeHg (SI 1.7). 9 yrs later: good health persists.</td>
</tr>
<tr>
<td>DF</td>
<td>F</td>
<td>39</td>
<td>CFS, joint pain, provocation with Hg positive</td>
<td>25 AF</td>
<td>Hg -</td>
<td>Ni -</td>
<td>Removal of all metals</td>
<td>Health improvement</td>
</tr>
<tr>
<td>CD</td>
<td>F</td>
<td>66</td>
<td>Oral symptoms after placement of Au bridge, fibromyalgia</td>
<td>AF MBP bridge containing Au, Pd and Ag</td>
<td>Au -</td>
<td>Ni -</td>
<td>Removal of all metals</td>
<td>No health improvement</td>
</tr>
<tr>
<td>BZ</td>
<td>F</td>
<td>64</td>
<td>Mucosal problems around metal prosthesis, gingivitis</td>
<td>AF (previously)</td>
<td>Ni ++</td>
<td>Hg -</td>
<td>Improvement of oral health</td>
<td></td>
</tr>
</tbody>
</table>

*Stimulation Index (SI) ranges from 0 to 100, where higher values indicate greater stimulation. Positive reactions include Au, Hg, Pb, and Ni.
on, the test was developed for detection of cell-mediated immune responses to formaldehyde [69], industrial epoxides [69], Kathon CG [71], mercurials [73, 74, 76], as well as for other metals [73, 75, 76]. In addition to type 4 allergy, the test has also been used for the diagnosis of immediate hypersensitivity (type 1 allergy) due to psyllium exposure in geriatric wards [72]. It can also be used for the monitoring of desensitization to insect venoms (unpublished). Recently, the value of LTT in the diagnosis of drug allergy has been reviewed by Pichler and Tilch [47], and for the measurement of ni allergy by Sanchez and colleagues [60].

Comparison of patch test with MELISA® test

Clinically, patients with intolerance to dental materials often display multiple metal allergies which can be demonstrated by patch test or by MELISA®. From a larger group of patients monitored by us for several years, 15 are described in detail in Table 1. In addition to inorganic Hg, reactivity to Au, Pd and Ni was often present. Patch test results and in vitro lymphocyte responses were usually in accord. However, in some patients, patch test was negative despite of positive MELISA® test. The limited value of patch test for diagnosis of Hg allergy has been reported elsewhere [66]. In the majority of patients, replacement of metallic appliances with ceramic and composite materials resulted in long-term health improvement. This is in agreement with previous publications [51, 76, 77, 87, 92]. Together with improved health, lymphocyte responses to dental metals also decreased after RID, reflecting the down-regulation of inflammation in vivo.

Undesirable effects of dental materials

Regarding side-effects caused by dental materials, the focus has until now been primarily on local oral problems (Fig. 2). This is despite of the fact that already in 1982, Swedish researchers described that “allergens released in the mouth may result in allergic reactions in other parts of the body, or worsen or maintain such reactions without any local reaction in the oral mucosa” [35]. Only a few reports describe reactions in other parts of the body. For example, Hay [22] describes a case of recurring facial dermatitis after dental treatment. The patient had facial symptoms as well as lichenoid reactions near the dental amalgam; the same reactions were induced by dental gold. The patch test showed a strong reaction to cobalt (Co), Ni, copper (Cu), and Pd – and a
weak reaction to inorganic Hg and Au thiosulphate. The tests were negative to all other materials tested, including latex and acrylic materials (methyl-hydroquinone).

Laine and co-workers in Finland [32] studied allergy to different restorative materials in 118 patients with oral lichenoid changes adjacent to metal fillings. The contact allergy was determined by patch testing. Eighty patients (68%) showed positive results. Seventy-six patients (64%) were reactive to Hg, 11 (9%) to Au, 4 (3%) to Co, and 2.5% reacted to tin (Sn), silver (Ag), or Pd. Allergic reactions to acrylics, a composite component, was not detected. Removal of metal fillings was performed in 62 out of 80 patch test-positive patients and healing of the oral mucosa was observed in almost 50% of the cases. The authors point out that allergy to acrylics may be caused by negligent use of non-hardened acrylate monomers during dental work, but it is not a problem following hardening in oral cavity.

Metallic Au used in dental alloys has previously been regarded as inert and Au-induced contact allergy as a rare phenomenon. This changed when Björkner and co-workers reported that 8.6% of patients referred to the Dermatology Clinics in Malmö, Sweden, reacted positively to Au thiosulfate in patch test [6]. This was later confirmed by Marcusson [37] who tested 397 patients with multi-symptoms suspected to be caused by dental restorative metals. The frequency of patch test-positive patients was 23% for Au, 8% for Pd, and 4% for inorganic Hg and ethyl Hg. In contrast, a study of 2,853 patients in Portugal demonstrated that only 0.8% of the patients – all women – suffered from Au allergy [63]. The authors speculate that the reason for the low frequency of Au allergy is that golden alloys are rarely used in dentistry in Portugal. Swedish researchers [1, 2] further reported that Au-positive patch test correlated with the number of patients’ Au restorations, and that the concentration of Au in saliva and serum correlated with the number of Au restorations as well. These findings corroborate the original findings of Drasch and co-workers [10] regarding correlation of Au and Pd in the saliva with the number of Au restorations. Hence, the aggressive environment in the oral cavity, including oral bacteria and acidic pH, as well as the presence of galvanic streams among disparate metals [41, 53, 88] may contribute to increased corrosion and to a higher frequency of Au sensitization.

Titanium allergy: does it exist?

Titanium (Ti) is increasingly used in dental and body implants. It is rapidly oxidized to titanium dioxide, TiO₂, a white coloring agent added to drugs, candy, food, cosmetics, sunscreen, toothpaste and chewing gum [75]. The reactivity of Ti with oxygen is due to its physiochemical properties as a transition element and this reactivity is greatly enhanced by the presence of fluoride ions [83]. Protein reactivity together with the ability to trigger free radicals [23, 81] should be of concern when evaluating the possible adverse effects of Ti in humans.

In dermatology, the allergenic potential of Ti is virtually unknown since patch test invariably turns negative [24, 40]. This could be due to the fact that testing is performed with a suspension of TiO₂ which has only limited diffusion through the skin.

In 650 Swedish patients with clinically verified or suspected metal hypersensitivity, 3% were positive to TiO₂ in MELISA* testing [75]. Valentine-Thon and colleagues [87] found similar results among 700 patients in northern Germany, where 4.2% reacted to TiO₂. Finally, Müller et al. [40] reported on 56 patients who developed health problems after receiving Ti-based implants. In the MELISA* test, more than half responded with increased proliferation to Ti, although they were all patch test negative. In patients who did not respond to Ti in vitro, a majority responded to other metals. Clinical symptoms disappeared or improved dramatically after implant replacement.
Diagnosis and treatment of metal-induced side-effects

In vitro responses in patients and controls

The frequency of metal-induced lymphocyte responses was examined in 3,162 patients in three European laboratories (two Swedish and one German) using MELISA® [76]. Patients suffered from oral symptoms such as oral lichen planus, burning and itching and systemic symptoms resembling CFS. In both countries, the most frequent metal allergen found was Ni, followed by inorganic Hg, Au, phenyl Hg, Pd, cadmium and Ti. Positive responses to other metals such as Ag, platinum (Pt) and Cu were only rarely observed. Similar results were later published by others who also validated the MELISA® method [86, 87].

Sterzl et al. [77] reported that lymphocytes from fatigued patients suffering from autoimmune thyroiditis responded more frequently to Ni and inorganic Hg than healthy controls. The increased Ni allergy in CFS patients was also demonstrated by patch testing [37, 38]. Regland et al. [55] have shown that female patients with Ni allergy suffering from fibromyalgia will improve on a low Ni-diet.

Tibbling et al. [82] used magnetic resonance imaging (MRI) to examine 32 patients with central nervous system (CNS) and systemic multi-symptoms suggestive of metal-induced pathology. Metal responsiveness at the lymphocyte level was examined by MELISA® and lymphocyte phenotype was analyzed with flow cytometry. One hundred twenty age-matched patients without CNS symptoms served as controls for the MRI study, 77 healthy subjects with dental amalgam fillings served as controls for MELISA® and 75 served as controls for phenotype determination. Pathological MRI findings were present in 81% of the patients, most of them with signs of degeneration in the basal ganglia, but none was found in the controls. The MELISA® test showed a higher frequency of metal-specific responses in patients than in controls. The difference in metal reactivity was highly significant for inorganic Hg (p<0.001), phenyl Hg (p<0.002), and Au (p<0.005), weakly significant for lead (p=0.05) and not significant for the remaining metals. In both patients and controls, Ni was the most frequent allergen. The lymphocyte phenotype determination was pathological in 58% of patients. Sixty-two of the patients

Figure 2. Metal-ceramic crowns on teeth 24 and 45. In the roots of these teeth Ti posts have been placed (centre). Observe the changes in the adjacent mucosa (black coloration of the gingiva) due to corrosion products of metals.

Figure 3. Rubber-dam and Clean-up® applied during amalgam removal.
had atopic diseases and 35% suffered from hypothyroidism. The authors concluded that dental restorative metals may play an important role in the development of the brain lesions in patients with basal ganglia disorders.

The impact of RID

Anneroth and co-workers [3] studied 10 patients who suspected amalgam replacement as a cause of aggravation of their symptoms. Six of 10 patients had contact allergies due to metals; three of them were induced by inorganic Hg. The changes in laboratory tests prior and after amalgam removal indicated that amalgam drilling might have activated the immune system.

The effect of dental metal replacement with metal-free restorations was studied in 111 CFS patients with metal allergy [76]. Following RID, 83 patients (73%) reported long-term health improvement. Twenty-four patients (22%) reported unchanged health and two (2%) reported worsening of symptoms. There was a marked decrease in lymphocyte reactivity to inorganic Hg as well as to other metals used as components or dental alloys. These data have been confirmed in larger studies [34, 92].

Prochazkova and coworkers [52] were first to show that amalgam removal in Hg-sensitive patients suffering from various autoimmune diseases, such as multiple sclerosis or rheumatoid arthritis, resulted in down-regulation of Hg-specific responses in vitro and long-term health improvement. This also correlated with the decrease of anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) antibodies [78]. In contrast, Hg-sensitive patients who refrained from amalgam replacement did not show any health changes half a year later. In this group, the level of autoantibodies and lymphocyte responsiveness to inorganic Hg in vitro remained the same as at the start of the study. The authors conclude that removal of dental amalgam in patients with Hg-sensitivity might contribute to successful treatment of autoimmune diseases.

The following case illustrates the importance of proper diagnosis and dental treatment for the rehabilitation of a patient. A female nurse suffered from electro-sensitiveness, fatigue, depression, and social phobia. She had on several occasions been exposed to broken Hg-containing therometers, and suspected dental amalgam as the cause of her ill health. Amalgam was replaced with a white Au bridge but health problems persisted. Analysis of the cerebrospinal fluid showed a negligible amount of Hg (0.6 μg/l, reference range <1 μg/l), but a high concentration of Pt (5 μg/l), a component of the bridge. The patient’s lymphocytes reacted positively in vitro to Pt (SI=5.4), Pd (SI=5.3) and weakly to Sn (SI=2.8). Lymphocyte responses were negative to thimerosal, Ti, Ag, Cu, Au, methyl Hg, phenyl Hg and inorganic Hg. Since Pd, Sn and Pt were components of her white Au bridge, it was replaced with a ceramic bridge. The patient’s fatigue, electrosensitivity, depression and social phobia diminished and 10 years on she still enjoys good health.

The dentist’s role in the treatment of patients with clinical metal allergy is of utmost importance. All mechanical work in the oral cavity may result in increased exposure to potentially allergenic substances and consequently to temporary worsening of patient’s symptoms (Table 1). By strict use of precautionary measures and safety devices it is possible to reduce the exposure to a level where serious side-effects are rare and only occur in particularly sensitive patients.

Precautionary measures during RID is the use of rubber-dam, Clean-up® (CleanDent, Sweden) (Fig. 3), traps that remove Hg vapor from the air, and fresh-air outlets. The choice of instruments, such as the type of drill, drilling speed and the use of manual instruments for removal of fillings, has been described in detail previously [25, 26].

In addition to ceramics and composites, zirconia holds the promise of one of the future’s immuno-compatible implant materials [7]. Finally, a patient’s detoxification capacity and other genetic factors may play a crucial role in the patient’s recovery. During rehabilitation, the patient’s physician should consider prescribing supporting therapy, such as antioxidant treatment.

Conclusion

Dental materials and implants can induce sensitization in genetically susceptible individuals. The frequency of metal allergy is significantly higher in patients with autoimmune disorders and CFS than in healthy controls. Metal allergy can be tested by patch test (in vivo) and by LTT (in vitro). The identification of metal-sensitive patients is the first step to successful treatment, which may involve RID. Many case reports and clinical studies show that the replacement of amalgam or other metal alloys in allergic individuals can lead to dramatic clinical improvement. To avoid side-effects, it is important to follow a strict working protocol, which minimizes the risk of metal exposure for the patient.

Acknowledgement

The authors wish to thank Margit Forsbeck MD and Jan Marcusson MD for the skillful performance of patch tests, and to Linda Nelson for the help with the preparation of the manuscript.

This work was supported by grant NR 9414-3 of the Internal Grant Agency of Ministry of Health, Czech Republic, which is gratefully acknowledged.

REFERENCES


36 Marcusson JA. Psychological and somatic subjective symptoms as a result of dermatological patch testing with metallic mercury and phenyl mercuric acetate. Toxicol Lett. 1996 Feb; 84(2): 113–22.


Toxic metals as a key factor in disease

Vera Stejskal, Romuald Hudecek, Jenny Stejskal & Ivan Sterzl


58 Rytter M, Schubert H. Gold allergy as a result of primary epiphanic sensitization from a gold ring. Dermatologica. 1971; 142(4): 209–18.


Metal alloys in the oral cavity as a cause of oral discomfort in sensitive patients

Jarmila Procházková1, MD, PhD; Štěpán Podzimek1, PhD; Milan Tomka1, MD; Hana Kučerová1, MD; Martin Mihaljevič2, PhD; Karel Hána3, Ing; Martin Mikšovský1, MD; Ivan Šterzl4, MD, PhD & Jana Vinšová5, PhD

1 The Institute of Dental Research 1st Medical Faculty, Charles University, and General Faculty Hospital; 2 The Institute of Geochemistry, Mineralogy, and Mineral Sources, Faculty of Nature Sciences, Charles University; 3 The Centre of Bio-Medical Engineering, Czech Technical University; 4 The Institute of Immunology and Microbiology, 1st Medical Faculty, Charles University, and General Faculty Hospital; 5 Information and Advisory Centre of Charles University; Prague, Czech Republic

Correspondence to: Dr. Jarmila Procházková, The Institute of Dental Research 1st Medical Faculty, Charles University, and General Faculty Hospital Vinohradská 48, Prague 2, CZECH REPUBLIC TEL: +420 224 256 718; FAX: +420 224 247 034 EMAIL: prochazkova@vus.cz

Submitted: December 14, 2005 Accepted: December 28, 2005

Key words: galvanism; dental metals; saliva; oral discomfort

Abstract

OBJECTIVE OF THE STUDY: The occurrence of galvanism with its heterogeneous symptomatology is often the source of considerable problems. Abrasion and corrosion not only damage dental alloys but also burden the organism by release of metallic particles. The objective of this study is to evaluate the hypothesis that measurement of galvanic currents could be a useful diagnostic method.

PATIENT GROUPS AND METHODOLOGY: Three hundred fifty-seven persons with dental metal restorations were divided into groups according to abnormal values of galvanic currents and by oral discomfort. In all persons a detailed examination of the oral cavity was performed, and galvanic currents were measured. In one hundred fifty-nine patients abnormal galvanic currents were found. Measurement of metallic elements in saliva was performed in these patients and in a group of 21 healthy volunteers without any metals in the oral cavity. Thirty-three patients agreed to treatment which involved removal of the causative alloys and their replacement by non-metallic restorations.

RESULTS: No correlation was found between the values of measured currents and the number of teeth treated by metal restorations. However, patients with metal restorations had significantly higher contents not only of mercury, but also of tin, silver, copper, and gold in the saliva than patients without metallic restorations. After removal of the electro-active restorations, both the contents of metals in saliva and galvanic currents decreased in comparison with the levels before the treatment.

CONCLUSIONS: Galvanic effects as well as metal particles may induce a series of local or systemic pathological phenomena in sensitive individuals. The occurrence of pathologically acting galvanic effects is influenced not only by the composition and combination of different dental alloys, but to a significant degree also by the quality of used materials and processing.
**Introduction**

After dental treatment, dental materials remain in close contact with the tissues in the oral cavity. Due to the functional burden and the specific environment of the oral cavity, all alloys undergo more or less mechanical and electrochemical changes, which may cause oral discomfort [32]. The intensity of the galvanic effect is determined by the difference of electrode potentials between the causal metals [4, 7]. This effect is further influenced by creation and function of passivation layers on the metal-electrolyte interface [28].

The presence of different metal alloys in the oral cavity may influence the induction and the adverse effects of electrochemical corrosion in which the metallic materials act as electrodes and the liquids in the oral cavity, such as saliva as crevicular fluid, as electrolytes [1, 9, 35]. Patient's own mucous membrane often acts as an electrode for the electrochemical dissolution rather than metals [18].

Electrodes with different potentials have the tendency to change the potential difference. This occurs by an electric current passing from one electrode to the other in the conducting environment of the oral cavity [27].

These processes may affect the development of inflammation of the oral mucosa and the tongue (Fig.1 and 2), paresthesia, glossodynia, stomatodynia, hyperaemia of the pulp, neuralgy, etc. An electric current may also manifest its effects in mucosal changes.

Release of metal ions from the dental alloys depends not only on their composition but also very significantly on the quality of their processing [3, 10, 17, 29, 31, 32].

The protecting passivation layers are continuously damaged by abrasion [34]. Neither abrasion nor corrosion can be completely eliminated but can be minimized by the choice of suitable materials and strict observance of the optimal technology [33].

An objective characterization of the galvanic effects may be attained by detection of metal elements in saliva and/or by measurement of galvanic potentials and currents [16, 18, 19, 27, 33].

Both of these approaches have their proponents and opponents [6, 14, 33]. Therefore, an intensive interdisciplinary investigation with precisely-defined conditions of measurements and parameters of the apparatus as well as unified interpretation is highly desirable.

**Patients and Methods**

**Patients**

In this study we examined a set of 357 patients, 81 men and 276 women, of average age 51 years. Three hundred thirty-six patients were referred to this investigation because of suspicion of “galvanic problems”. These symptoms were either local, such as pain of tongue, painful, peeling lips and oral mucosa, taste sensations, metallic taste, coloring of prosthetic structures, metallic pigmentation, inflammatory signs of mucosa, or systemic, such as chronic fatigue, drowsiness, skin eruptions, digestive disorders, headaches, painful joints, breathing difficulties, and heart arrhythmia. The common description, as used by referring dentists, general practitioners, dermatologists, or psychiatrists, was “oral discomfort of unspecified origin”. All patients had amalgam fillings and a variety of other dental alloys in the mouth.

Pathological values of the measured galvanic current were the guide for the choice of patients for treatment. Galvanic currents between 5–50 µA were found in 159 patients, 34 men and 125 women (average age 53.5 years) forming Group 1. Thirty-three patients agreed to therapy consisting of removal of the electro-active dental restorations and their replacement.

---

**Figure 1:** Inflammatory lesion on the oral mucosa due to the galvanic features of the electro-active amalgam filling on the left lower first molar.

**Figure 2:** Inflammatory lesion on the tongue due to the galvanic features of the electro-active amalgam fillings on the lower molars.
Group 2 consisted of 21 volunteers with intact teeth, without subjective oral problems. These 12 men and 9 women (of average age 32.5 years) formed the standard control group. The content of metallic elements in saliva as well as galvanic currents were determined in both groups at the beginning of the study and in follow-up examination.

**Detailed clinical examination of the oral cavity**

We performed detailed examination of the hard and soft tissues in the oral cavity, which included acquisition and evaluation of panoramic x-ray images and detailed determination of the number of teeth treated by metal alloy restorations.

**Measurement of galvanic currents**

The currents flowing between dental alloys and gingiva, tongue, lips or cheek mucosa or between alloys were measured using the specialized voltmeter / amperemeter “Odontologik 2000” (Embitron). It determines the peak values of direct current (dc) and voltage in the oral cavity. The currents flowing were consecutively measured.
between all affected locations as follows: metal-gum, metal-metal, metal-tongue or other soft tissue in the oral cavity.

A galvanic current of 5 µA was considered as the limit of pathological values [2, 8, 13, 16, 20, 22].

**Material sampling**

To determine metallic elements in saliva, samples of 1 ccm of non-stimulated saliva were taken into polyethylene test tubes and immediately frozen to −18°C. The frozen samples were transported to the laboratory of the Institute of Geochemistry and Faculty of Natural Science, Charles University and examined by ultra-trace element analysis using the mass spectrometer ICP-MS LA (mass spectrometer with inductively coupled plasma in connection with laser probe). The content of individual elements is presented in μg per liter of saliva (parts per billion). The metals tested were silver (Ag), aluminum (Al), gold (Au), cadmium (Cd), cobalt (Co), chromium (Cr), copper (Cu), mercury (Hg), nickel (Ni), lead (Pb), palladium (Pd), platinum (Pt), tin (Sn), and zinc (Zn).

**Therapy**

The treatment consisted mostly of removal of amalgam fillings and their replacement by glass-ionomer cements, composite plastics, or composite or ceramic inlays. In one case, the problematic amalgam fillings were replaced, in accordance with the wish of the patient, by new amalgam restorations.

Subjective evaluation of the therapy by the patients was obtained by means of a questionnaire filled in by the patients after 1 month. The patients were asked to grade the results of the therapy treatment as follows: 1) Small effect (don’t know, not much, maybe), 2) Good effect (yes, it helped, certainly, it is better), or 3) Very good effect (it helped a lot, it is much better, big improvement).

Objective evaluation of the therapy involved measurement of galvanic features as well as of metallic elements in the saliva before and after removal of the metal restorations from the oral cavity.

**Statistics**

The qualitative data were statistically analyzed using paired and unpaired Student’s t test and the quantitative data using the Pearson’s χ² test and Fisher’s exact test. Values of probability p < 0.05 are considered as significant.

**Results**

Pathological values of the current from 7–25 µA were detected in 150 patients. Nine additional patients had the critical value 5 µA. These 159 patients subsequently formed the basis for Group 1. The patients had values of galvanic currents in the range 7 to 25 µA. The persons in Group 2 (controls) showed no galvanic phenomena in their mouth.

Mercury constituted the largest part of metallic elements in saliva in Group 1 (594.6 μg/l, Fig. 3). Comparison with the control Group 2 showed that Group 1 had significantly higher amounts not only of Hg (p = 0.05) but also of Sn (p = 0.01), Ag (p = 0.01), and Cu (p = 0.01). The amounts of Cr, Co, and Ni in saliva were markedly lower (0.98 to 16.4 μg/l), and not significantly different from Group 2 (Fig. 4). On the contrary, the amount of Al; (220.3 to 560.9 μg/l)(Fig. 5) was high in both examined groups (220.3 to 560.9 μg/l). The content of Au was higher in saliva of patients in Group 1 (87.5 μg/l; p = 0.02; Fig. 5). The values of other measured metals were low and showed no significant differences between the groups.

After removal of the electro-active restorations, pathological values of galvanic currents normalized in all patients. Due to their chemical composition and according to our experience, these materials always exhibit high values of voltage. Therefore we did not take into account the voltage values in patients treated in this way.

Further, we detected a decreased amount of some metallic elements, present in amalgam, in saliva of patients in Group 1, as compared to values before the treatment. A significant decrease was found for Sn (p = 0.03), Au (p = 0.05) and Cu (p = 0.01) but not for Hg (p = 0.07). The comparison of Group 1 after treatment with the control Group 2 shows no statistically significant differences in the contents of the examined metals (Figs 3, 4, 5).

The results of the questionnaire survey in Group 1 showed that 91% of treated patients reported a good or very good effect of the treatment, such as disappearance or a marked reduction of the feeling of oral discomfort. Only 9% of the treated patients reported only a mild or no improvement. None of the treated patients observed deterioration of health.

The occurrence of pathologically acting galvanic effects was influenced not only by the composition and combination of the employed dental alloys, but also by the quality of processing of used materials (Fig. 6). When correctly processed restoration replaced a bad restoration, the pathologic galvanic currents were not present any more (Fig. 7a and 7b).

**Discussion**

The findings of higher amounts of Hg, Sn, Ag, Cu and Au in Group 1 were expected due to the difference in dental status between the examined groups. The high amount of Al detected in both groups could be caused by common environmental exposure e.g. by alimentation etc. These findings are in agreement with published studies [6, 14].

The removal of amalgam fillings in patients of Group 1 resulted in a significant decrease of the amount of Sn, Ag, and Cu, but the decrease of Hg in saliva was not significant. This could be due to larger dispersion of values in the samples. On the other hand, the decrease
of metal concentrations in saliva after amalgam removal to the levels found in Group 2 points to the influence of galvanic phenomena on the corrosion of metallic restorations.

Dental alloys in the oral cavity may induce adverse side effects in sensitive individuals [8, 15, 21, 29, 30]. Our results indicate that galvanic effects can play an important role in this phenomenon.

Oral discomfort, such as burning and itching, may often occur in individuals with various systemic disorders along with usually non-characteristic objective diagnosis. These conditions occur in patients who often have other health problems such as climacterium changes, senium, virosis, stress, neuroses) [8, 11]. The removal of electro-active dental restorations could be one of the treatment tools for these patients.

Metallic elements may be deposited in soft as well as in hard tissues of the oral cavity and this may cause discoloration of other structures made of dental alloys [12, 25, 30]. Saliva may play a protective role against the induction of galvanic currents, particularly if its molecules have a high molecular weight [10]. This could explain why some patients with various alloys in the oral cavity have galvanic phenomena while the other have not. Our results may suggest that the amount of metal particles in saliva is influenced more by environmental factors than by the primary saliva composition.

In ionised form, certain metals such as Hg and Ni easily bind to body proteins, and then as haptons they may activate the immune system [23]. The Hg+ ions enhance the sensitivity to other metals [26].

Intolerance to metals may be demonstrated by skin tests, which are subjective and may carry a risk of sensitization [5], or by a less distressing objective in vitro immunological test, MELISA [24, 25]. On the basis of such examinations, further therapeutic options could be designed.

Prevention of galvanism is based on strict adherence to optimal technology in dental alloy processing [33], during production as well as in the final application, and on minimization of their amounts and combinations.

Acknowledgement

This study was supported by grant no. NR 8324-3 from the Internal Grant Agency of the Czech Ministry of Health.

REFERENCES


Effect of radiofrequency radiation from Wi-Fi devices on mercury release from amalgam restorations

Maryam Paknahad¹, S. M. J. Mortazavi²,³*, Shoaleh Shahidi¹,⁴, Ghazal Mortazavi³ and Masoud Haghani³

Abstract

Background: Dental amalgam is composed of approximately 50% elemental mercury. Despite concerns over the toxicity of mercury, amalgam is still the most widely used restorative material. Wi-Fi is a rapidly using local area wireless computer networking technology. To the best of our knowledge, this is the first study that evaluates the effect of exposure to Wi-Fi signals on mercury release from amalgam restorations.

Methods: Standard class V cavities were prepared on the buccal surfaces of 20 non-carious extracted human premolars. The teeth were randomly divided into 2 groups (n = 10). The control group was stored in non-environment. The specimens in the experimental groups were exposed to a radiofrequency radiation emitted from standard Wi-Fi devices at 2.4 GHz for 20 min. The distance between the Wi-Fi router and samples was 30 cm and the router was exchanging data with a laptop computer that was placed 20 m away from the router. The concentration of mercury in the artificial saliva in the groups was evaluated by using a cold-vapor atomic absorption Mercury Analyzer System. The independent t test was used to evaluate any significant differences in mercury release between the two groups.

Results: The mean (±SD) concentration of mercury in the artificial saliva of the Wi-Fi exposed teeth samples was 0.056 ± .025 mg/L, while it was only 0.026 ± .008 mg/L in the non-exposed control samples. This difference was statistically significant (P = 0.009).

Conclusion: Exposure of patients with amalgam restorations to radiofrequency radiation emitted from conventional Wi-Fi devices can increase mercury release from amalgam restorations.

Keywords: Amalgam, Wi-Fi, Mercury release, Radiofrequency, Electromagnetic fields

Background
Dental amalgam is still the most widely used restorative material in the last 150 years especially in posterior teeth because of its high mechanical strength, durability, ease of manipulation, and low cost [1–5]. Dental amalgam is an alloy comprised of 50% elemental mercury and a mixture of other metals such as silver, tin, copper, and sometimes palladium, indium and zinc [6–8]. Dental amalgam is considered as the primary source of continuous mercury exposure in general population [1, 9–11]. Mercury is a toxic element which can damage various organs such as central nervous system, renal, respiratory and hematologic systems [12, 13]. Because of the mercury toxicity, the use of mercury has been banned in some European countries [14]. The amount of mercury which releases from amalgam restorations depends on several factors such as number and size of the fillings, composition of amalgam, any other factors that causes load over the restorations like tooth brushing, chewing habits, and bruxism [8, 15].

Wi-Fi is a local area wireless computer networking technology and has been used drastically in houses and public places such as schools and hospitals during recent
years [16]. It allows electronic devices such as personal computers, video-game consoles, smart phones, digital cameras and tablet computers to network using Institute of Electrical and Electronics Engineers (IEEE) 802.11 standards. These standards mainly use the 2.5 gigahertz (12 cm) UHF and 5 gigahertz (6 cm) SHF ISM radio bands [17]. The lower cost and easier deployment of these devices than wired computer networks lead to rapidly increase of Wi-Fi devices [18]. However, this also raised great public concern about the potential adverse effects of exposure to electromagnetic fields (EMFs) emitted from these devices [19].

The adverse health impacts associated to exposure to some common sources of electromagnetic fields including laptop computers, mobile phones, MRI and mobile phone jammers have been evaluated by our laboratory in our previous investigations [20–24]. To the best of our knowledge, this is the first study that evaluates the effect of exposure to Wi-Fi signals on mercury release from amalgam restorations.

**Methods**

**Teeth samples**

This study was approved by the Ethics Committee of Shiraz University of Medical Sciences. Twenty non-carious premolar teeth which were extracted as a part of orthodontic treatment were used in this study. The teeth were stored in isotonic saline solution for not longer than 3 months after surface debridement. The teeth were randomly divided into 2 groups of exposure and control, each containing 10 teeth.

**Amalgam fillings**

Standard class V cavities (3mm length, 2mm depth and 5 mm width) were prepared on the buccal surface using carbide burs (SS White Burs, Lakewood, NJ) and a high speed turbine under water spray. The cavities were restored with Cinalux (non-gama-2, spherical amalgam, Faghihi Dental, Tehran, Iran) amalgam. The amalgams were triturated according to manufacturers’ directions, and then they were condensed incrementally towards the cavity walls. All the procedures for restoration of the cavities were performed by the same clinician. The restored teeth were plunged in saline solution at 37° C for 14 days because as it was discussed by Muller Miny et al., the mercury release from amalgam restorations decrease gradually to a constant level 14 days after the filling [25]. Following that and before exposing the teeth, samples were poured into plastic tubes filled with artificial saliva. The thickness of the artificial saliva covered over teeth samples was 1.5 cm to mimic soft tissue.

**Wi-Fi exposure**

The exposure group was exposed to radiofrequency radiation emitted from standard Wi-Fi devices at 2.4 GHz for 20 min. The distance between the Wi-Fi router (D-Link, China) and samples was 30 cm and the router was exchanging data with a laptop computer that was placed 20 m away from the router. The control group was kept outside the experiment room. The geometry used for exposure is shown in Fig. 1.

**Mercury measurement**

Based on our previous experiments, it was clearly revealed that the pre-exposure mercury concentration in the saliva containing teeth samples with exactly identical fillings (the same cavities and amalgam type), was the same for all samples (the differences were not statistically significant). Therefore, the mercury levels were measured in the artificial saliva after exposure by cold vapor atomic absorption spectrometry (CVAAS; Analytical Jena, vario 6, Germany).
Statistical analysis
The data were statistically analyzed using SPSS version 16.0 (SPSS Inc., Chicago, IL) (http://www-01.ibm.com/software/analytics/spss). The independent t test was used to compare the level of mercury release in the exposure and control groups to identify any statistically significant differences. P value <0.05 was considered significant.

Results
Descriptive statistics were presented as the mean, standard deviation, minimum and maximum in Table 1. The mean (±SD) concentration of mercury in the artificial saliva of the Wi-Fi exposed group was 0.056 ± .025 mg/L, while it was only 0.026 ± .008 mg/L in the non-exposed control samples. Therefore, the mean concentration of mercury in the Wi-Fi group was about twice of the control group. The observed difference in the concentration of mercury in the artificial saliva of the exposure and control group was statistically significant (P =0.009).

Discussion
Public concern about the possible adverse health effects of using Wi-Fi technology is increasing because of the widespread use of wireless communication systems [19]. In the present study, it was concluded that radiofrequency radiation emitted from Wi-Fi devices significantly increased mercury release from amalgam restorations.

Mortazavi and Mortazavi have recently reviewed the published reports on the increased release of mercury from dental amalgam fillings after exposure to different sources of electromagnetic fields (e.g. MRI, mobile phones) [26]. These studies are summarized in Table 2. The first report on the role of exposure to MRI or microwave radiation emitted by mobile phones in increasing the release of mercury from dental amalgam filling was published by Mortazavi et al. in 2008 [27]. To overcome the limitations of their previous study, Mortazavi and his colleagues have recently studied the effects of stronger magnetic fields (1.5 T in their recent study vs. 0.25 T in their previous report). This study confirmed the previous findings and provided further support for increased release of mercury from dental amalgam fillings after MR imaging [28].

It should be noted that the results obtained in the studies performed on the role of exposure to electromagnetic fields in magnetic resonance imaging on the microleakage of amalgam are strongly in line with the findings of Mortazavi et al. [29, 30]. To the best of our knowledge, our current study is the first study that investigates the effect of radiofrequency radiation emitted by Wi-Fi routers on mercury release from amalgam restorations.

Mercury is a toxic element which has adverse biological effects even at low doses [31]. Therefore, it seems to be necessary to apply a sensitive and reliable analytical technique to determine mercury content. Various analytical techniques have been used previously for the determination of mercury in environmental and biological samples such as cold vapor atomic absorption spectrometry (CVAAS), cold vapor fluorescence spectrometry (CVAFS), inductively coupled plasma optical emission spectrometry (ICP OES), electrothermal atomic absorption spectrometry (ET AAS), neutron activation analysis, mass spectrometry, anodic stripping voltammetry, and cold vapor inductively coupled plasma mass spectrometry (CV ICP-MS) [32–35]. This study employed CVAAS method for measuring mercury released from dental amalgam. Because CVAAS is the most widely technique used in previous studies for detecting this element at low concentrations due to its high sensitivity and selectivity and because of its low cost [36, 37].

To improve the outcome of the west possible mercury release, we did not polish the cavities after restoration, because according to Ferracane et al. greater amounts of mercury would release from unpolished than polished surfaces [38].

Although the adverse health effects of the exposure to radiofrequency radiation emitted by Wi-Fi routers on some challenging phenomena such as human reproductive capabilities is well documented by some researchers around the world [39, 40], as far as we know, there is no report on the role of Wi-Fi radiation on the release of mercury from amalgam restorations. The mercury release from dental amalgam into saliva has been evaluated in previous studies both in vitro and in vivo conditions [25, 31, 41–43]. One of the limitation of in vivo studies, as Mortazavi et al. discussed in their study, was that the participants were referred by their own physicians and the investigators did not have control over the number and surface of amalgam fillings [41]. However, in our in vitro study, we could control these factors by using identical class V fillings with the same dimensions through application of a template during cavity preparations since the mercury exposure correlates significantly to the number and surface of fillings [8, 15]. We also could control some other confounding factors which differ inter individually such as chewing.

### Table 1 The mean, standard deviation, minimum and maximum of the mercury release in the two groups

<table>
<thead>
<tr>
<th>Mercury release (mg/L)</th>
<th>Group</th>
<th>(P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Wi-Fi</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.026 ± .008</td>
<td>0.056 ± .025</td>
</tr>
<tr>
<td>(Range: min -max)</td>
<td>(0.016 – 0.039)</td>
<td>(0.020-0.100)</td>
</tr>
<tr>
<td>Radiation source</td>
<td>Endpoint</td>
<td>Methods</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------------------------</td>
<td>--------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Mobile Phone</td>
<td>Release of Mercury</td>
<td>Urine samples were collected from 14 female students</td>
</tr>
<tr>
<td>MRI (0.23 T)</td>
<td>Release of Mercury</td>
<td>Stimulated saliva collected in 30 persons</td>
</tr>
<tr>
<td>MRI (1.5 T)</td>
<td>Release of Mercury</td>
<td>Urinary concentrations of mercury in the MRI exposed and control subjects</td>
</tr>
<tr>
<td>X-ray</td>
<td>Release of Mercury</td>
<td>Teeth samples were exposed to X-rays in a soft tissue-equivalent material</td>
</tr>
<tr>
<td>MRI</td>
<td>Release of Mercury</td>
<td>Teeth samples were exposed to MRI in a soft tissue-equivalent material</td>
</tr>
<tr>
<td>MRI (3 T)</td>
<td>Microleakage of amalgam</td>
<td>60 extracted teeth divided into experimental and control groups exposed/shamexposed to a magnetic field of 3 T for 20 min</td>
</tr>
<tr>
<td>MRI (1.5 T)</td>
<td>Microleakage of amalgam</td>
<td>63 human freshly extracted premolars were divided into 3 groups (3 different amalgams). In each group, 50% of the samples were exposed to MRI.</td>
</tr>
<tr>
<td>MRI (1.5 T)</td>
<td>Microleakage of amalgam</td>
<td>40 teeth were randomly divided into four groups. The first and third groups were exposed to MRI.</td>
</tr>
<tr>
<td>Wi-Fi</td>
<td>Mercury release</td>
<td>20 extracted teeth were randomly divided into 2 groups of Wi-Fi exposure and control.</td>
</tr>
</tbody>
</table>
habits and thermal effects [15, 44]. On the other hand some factors that may decrease the mercury release such as the liberation of corrosive products by contact of food and bacteria did not also interference with our findings.

Conclusion
To the best of our knowledge, this is the first study which assesses the effect of exposure to Wi-Fi signals on mercury release from amalgam restorations. We speculated that exposure to radiofrequency emitted from Wi-Fi devices may result in mercury release from amalgam restorations. Further in vitro and in vivo studies are necessary to prove this contention.

Abbreviations
CV ICP-MS; cold vapor inductively coupled plasma mass spectrometry; CVAAAS, cold vapor atomic absorption spectrometry; CVAFS, cold vapor fluorescence spectrometry; EMF, electromagnetic fields; ET AAS, electrothermal atomic absorption spectrometry; ICP OES, inductively coupled plasma optical emission spectrometry; MRI, magnetic resonance imaging; SHF, super high frequency; UHF, ultra high frequency; Wi-Fi, wireless fidelity.

Acknowledgement
This study was supported by the Biomaterial Research center, School of Dentistry and Ionizing and Non-ionizing Radiation Protection Research Center (INIRPRC), Shiraz University of Medical Sciences (SUMS), Shiraz, Iran. The authors would like to thank Dr. Sh. Hamedani (DDS, MSc) for his editorial assistance.

Funding
This study was funded by Shiraz University of Medical Sciences (SUMS). This research project received funding from SUMS to conduct the project. However, conception, design, acquisition of data and data analysis, interpretation and drafting of the manuscript were solely the responsibility of the authors. Moreover, the decision to submit the manuscript was solely the decision of the authors.

Availability of data and materials
The authors agree to make the raw data and materials described in their manuscript freely available to any scientist wishing to use them for non-commercial purposes (http://cris.sums.ac.ir/fa/index.html).

Authors’ contributions
MP carried out the filling of the teeth and drafted the manuscript. SMJM participated in the design of the study and carried out the exposures and revised the manuscript. GM and MH performed the exposures and mercury measurements. Shoaleh Shahidi participated in the design of the study. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
This study was approved by the medical ethics committee of Shiraz University of Medical Sciences (No. 91-01-73).

Author details
1Department of Oral and Maxillofacial Radiology, School of Dentistry, Shiraz University of Medical Sciences, Shiraz, Iran. 2Medical Physics and Medical Engineering Department, School of Medicine, Shiraz University of Medical Sciences, Imam Hossein Square, 7134845794 Shiraz, Iran. 3Ionizing and Non-ionizing Radiation Protection Research Center (INIRPRC), Shiraz University of Medical Sciences, Shiraz, Iran. 4Biomaterial Research Center, School of Dentistry, Shiraz University of Medical Sciences, Shiraz, Iran.

Received: 30 June 2015 Accepted: 1 July 2016
Published online: 13 July 2016

References
24. Mortazavi S, Parsanezhad M, Kazempour M, Ghaframani P, Mortazavi A, Davari M. Male reproductive health under threat: Short term exposure to...


YOU NOW NEED TO TAKE THE UNIT 5 TEST AT https://www.cvent.com/d/cvq54n.

IT IS AN OPEN BOOK TEST AND CONSISTS OF 25 QUESTIONS. YOUR SCORE WILL BE AUTOMATICALLY CALCULATED AND SENT TO YOU VIA EMAIL.

UPON COMPLETION OF THE UNIT 5 TEST, YOU WILL NEED TO CONTINUE WITH THE REST OF THE ACCREDITATION REQUIREMENTS. ACCESS THE MATERIALS FOR UNIT 6 BY USING THE LINK TO THE IAOMT COURSE PDFs AT https://iaomt.org/accreditation-materials/.