Proposed Metal Defense Protocol

Keith A. Brewster
Norman, Oklahoma, USA
kbrews@cox.net
www.ActiveJoints.com
Revised, June 28, 2002

1. Introduction

While considering metal-articulated hip resurfacing surgery, and continuing after the fact, I sought to understand the possible impact of having metal components in the body. This document contains the result of my research on the issue and relates the steps I've decided to take as a sort of insurance measure to protect against any potential long-term effects of having a foreign body in my system. To date there seems to have been no mention in the literature of any proactive actions for the patient beyond limiting wear-producing activity.

Modern metal articulating surfaces are manufactured from an alloy of cobalt, chrome, and other minor constituents. A typical alloy is prescribed by the American Society for Testing and Materials (ASTM) as ASTM-F75, cast cobalt chrome, composed of approximately 65% cobalt, 28% chrome, 6% molybdenum, and less than 1 percent each of several other elements. Cobalt-chrome alloys are extremely hard, resistant to corrosion, and can be machined to a smooth, wettable surface. Additionally, these alloys have the property that they are self-polishing. That is, small defects will tend to become smoothed out over time, rather than growing with additional contact. The body's natural fluid, the synovial fluid, lubricates the articulating surfaces. Despite the lubrication, tiny metal debris can be shed from the surfaces, and the metals may spread through the body as micron-sized (millionths of a meter) particles or metal ions (e.g., Case et al., 1994).

Experiments with hip simulators and various metal-metal hip prostheses have shown that the maximum wear rate occurs in the first one-half to one million cycles (meant to represent walking steps), when the volumetric wear rate is about 0.5-4.0 mm^3 million cycles (e.g., Chan et al., 1999, Nelson et al., 2000). On the average, the hip patient takes about two million steps per year (one million cycles per joint), though there is quite a bit of variance (Schmalzried et al., 1998, Schmalzried et al., 2000). Certainly during the recovery period, the hip patient will have a less-than-average activity level. Thus, the maximum rate of wear would be expected in the first year or two. There is some evidence that the rate of wear may be related to the degree of sphericity of the joint and the extent of clearance between the ball and cup (e.g., Chan et al., 1999, Nelson et al., 2000). The relative lack of machining accuracy available with 1960s technology is thought to be responsible for some of the problems experienced by early metal-on-metal articulating joints in that era (McKee-Farr joints), though some of those joints have gone on to last over 30 years in some patients.

Cobalt (Co) is an essential element in the body as it is a constituent of Vitamin B-12. Vitamin B-12 is involved in the production of red blood cells. There is no recommended daily allowance (RDA) for cobalt, but the RDA for Vitamin B-12 is 6 mcg per day. Cobalt can be found in liver, kidneys, milk oysters, fish, clams, or sea vegetables. Cobalt is also found in some beer, teas and coffees.

The effects of cobalt on the human body through drinking water and supplementation and other exposures are reviewed by a UK Expert Group on Vitamins and Minerals (2000). Cobalt is processed by the kidneys and excess cobalt is quickly eliminated from the body, with a monitored individual showing 90-95% eliminated after 48 hours, and 99% after 30 days (UK EGVM, 2000). There is some evidence from animal studies and from the mid-60s when cobalt chloride was commonly added to beer that cobalt could accumulate in the myocardium. This accumulation was increased by the consumption of alcohol and may have been related to a deficiency in proteins (including L-cysteine) and/or other trace minerals in the diet (Sandusky et al, 1981). The metal may also affect the thyroid as rare cases of patients receiving very high-dose long-term therapeutic cobalt salt treatments (0.17 to 3.9 mg/kg/day) experienced hypothyroid symptoms.

Chromium (Cr) is an essential metal in the body. It is involved in the process of converting sugar and fat to energy by insulin. Chromium deficiencies can result in high blood glucose levels. There is no official RDA for chromium, but the National Academy of Sciences defined an Adequate Intake (based on average intake by healthy subjects) as 35 mcg for young males (NAS 2001). Chromium is a trace metal found in certain vegetables and meats, including brewers yeast, mushrooms, broccoli, calf's liver, mollusks, crustaceans, American cheese and wheat germ. It is included in many all-in-one vitamin and mineral formulas (e.g., Centrum™ contains 65 mcg, other formulas contain up to 200 mcg). Chromium exists in two common oxidation states, Cr(III) and Cr(VI), and as metallic chromium, which also can be denoted Cr(0). One form, Cr(VI), also known as hexavalent chromium, is a known carcinogen; Cr(VI) is the presumed cancer risk raised by some orthopedic surgeons when considering metal-metal components.

The effects of chromium on humans through drinking water and other exposure are reviewed by Morry (1999). Much of the concern regarding Cr (VI) arises from occupational exposure by welders and other steel workers exposed to airborne chromium dust or vaporized chromium through working with stainless steel, an alloy of iron that contains chromium and other metals. Under such conditions, chromium can be inhaled and chronic exposure can lead to cancer of the respiratory system. Oral ingestion of hexavalent chromium has shown a slightly increased rate of cancer in the forestomachs of rats (Borneff et al., 1968). No studies have shown a link of oral ingestion Cr(III) to cancer. Rats that ingested Cr(III) showed no adverse effects from consuming up to 1468 mg/kg per day of Cr(III) over a 600 day period (Ivankovich and Preussmann, 1975). Furthermore, it is believed that hexavalent chromium is rapidly reduced to other valence forms in acidic environments such as in the stomach and blood stream (Kerger et al., 1997, D'Agostini et al., 2000, DeFlora, 2000). Chromium is primarily eliminated by the

kidney (Donaldson and Rennert, 1981, Kerger et al., 1997). Metal-metal articulation is contra-indicated for those with chronic kidney failure.

2. Statistical Studies

There have been a few statistical studies concerning cancer risk among patients with artificial hip implants. Besides metal-metal articulating surfaces, there are other aspects of artificial hip components that have raised concern. Metals can be released by corrosion of hip stems, fretting between components in modular hip systems can shed metal debris, and metals can leech from the bone-implant surfaces of uncemented components. The International Agency for Research on Cancer (1999) and Tharani et al. **(**2001) present a comprehensive review of the studies that have been done, and combines the results of several to show no significant difference in cancer rates between those with hip replacements and the general population. In one particular study, Visuri et al. (1996), the registry of hip patients in Finland were studied and they found no difference in mortality between those with metal-metal articulated hips and those who had metal on plastic joints. The rate of cancer was slightly higher in the metal-metal group, but was no different than in the general population, and no sarcomas were found near the prosthesis. There was an elevated occurrence of leukemia, but due to the small number of cases overall, the result was not statistically significant. Sulzer Medica of Switzerland has over 100,000 metal-metal articulated hip implanted in Europe; no alarming health trends have been noted due to the metal-metal articulation thus far, though there is not a coordinated effort of follow-up.

There is concern that the statistical studies are too narrow in their cultural and genetic scope (many rely on Scandinavian disease records) and that in time new trends might arise due to possible latency between chromosomal damage and clinically apparent cancers.

3. Elements of Proposed Metal Defense Protocol

Given the concerns of the possible carcinogenic effects of Cr(VI) and the possible ill-effects of accumulation of metals in tissues, it seems prudent to maintain levels of nutrients in the body that could ensure the rapid the conversion of any Cr(VI) to Cr(III) and to ease the elimination of the metallic ions via the kidneys and liver. I propose the following five-element protocol to get a leg up on any detrimental effects of metals that may result from the hip prosthesis.

3.1 Discontinue Chromium Multi-vitamins

If you are taking a multi-vitamin, discontinue use if you find it contains chromium. Many multi-vitamins contain 65 mg of Cr, some may contain up to 200 mg. This eliminates an unnecessary source of the metal, but obviously, you'll lose any benefit you had been getting from the other ingredients.

3.2 Water

Its generally a good idea to drink several cups of water per day, and this should also help keep the kidneys well hydrated and perhaps better able to flush cobalt from the system. Personally, I am not taking any specific action in this regard, but generally, I like to have some ice water, dilute fruit juice or a soft drink at my desk while I work in the office or at the computer at home. I recognize that soft drinks may not help the hydration issue, but I'm allowed some vices.

Water from your tap or mineral water can contain cobalt or chromium; if you happen to live in an area with high concentrations of these metals, you might consider finding another source for your drinking water. The EPA requires your water treatment plant to measure and report levels of chromium in your drinking water to its costumers. The EPA maximum concentration limit for drinking water is 100 ppb (parts per billion, or micrograms per liter); the State of California and the World Health Organization sets this limit at 50 ppb. The practical measurement limit is 10 ppb. These limits are established in order to prevent excess Cr(VI) ingestion without specifically requiring the monitoring of the separate valence forms of Cr present. If you have a well, you might investigate if you can have it tested for chromium and avoid drinking it if it is has high levels of Cr.

3.3 Vitamin C and anti-oxidants

Vitamin C, known in the literature as ascorbic acid, is a powerful anti-oxidant. The anti-mutagenic and anti-carcinogenic effects of Vitamin C are well known. Furthermore, Vitamin C is the most effective antidote for cases of Cr(VI) poisoning (Hathaway, 1986).

The National Academy of Science RDA for Vitamin C is 90 mg for adult males and 75 mg for adult females (excluding pregnancy and lactation, which require higher levels). There is evidence that serum levels of Vitamin C are saturated at an intake of 200 mg per day (NAS, 2000). The tolerable upper limit for Vitamin C has been established at 2000 mg per day (NAS, 2000).

I seek then, to get at least 200 mg of Vitamin C per day through diet or supplementation. Many fruits and vegetables contain Vitamin C; a small sample is listed in the following table. In addition, Vitamin C supplements are available everywhere and are very inexpensive. However, the most commonly found products contain 500 mg or 1000 mg tablets.

Vitamin C Content of Several Fruits

Fruit	mg Vitamin C/serving
Grapefruit (half)	44
Cantaloupe (eighth)	29
Guava	165
Honeydew Melon (eighth)	20
Kiwifruit	74
Mango	57
Orange	70
8 oz. Orange Juice	96
Papaya	47
Tangerine	26
Tomato	23
Watermelon (large slice)	27

Although no specific benefits of Vitamin A and E have been uncovered specific to cobalt and chrome, it seems reasonable to have a team of anti-oxidants on the job, also these vitamins are not as quickly flushed from the system as the water soluble Vitamin C. The following table is a specific anti-oxidant formula (Spring Valley, price: ~$6.00 for 60 softgel tablets) I found at Wal-Mart, but I have seen similar combinations in other products at chain drug stores. One can get the serum-saturating dose of Vitamin C as well from one of these tablets.

Nutrient	Amt per tab	Adult
Vitamin A	10,000 I.U.	200%
Vitamin C	250 mg	277%
Vitamin E	200 I.U.	667%
Zinc	7.5 mg	50%
Selenium	15 mcg	21%
Copper	1 mg	50%
Manganese	1.5 mg	75%

3.4 NAC (N-Acetyl-L-Cysteine)

NAC is an amino acid that is used in the production of glutathione (GSH). GSH has an important role in binding reactive metals. NAC has been shown to increase the anti-oxidant properties of Vitamin C (Agostini et al., 2000), and the combination of ascorbic acid and GSH has been shown to decrease the production of Cr(V) in the reduction of Cr(VI) by ascorbic acid in mice (Liu et al., 1995). The production of reactive Cr(V) has been suggested as a step in the carcinogenic mechanism of Cr(VI). In short, there are circumstances in which Vitamin C can actually act as a pro-oxidant but when combined with NAC, the pro-oxidant effect is effectively neutralized. NAC has also been shown to effective in increasing the body's immune response to the influenza virus (De Flora et al.,

1997). NAC, when injected in the abdomens of rats, has been shown to increase the rate of cobalt excretion in the urine and to decrease the accumulation of cobalt in the liver and spleen, and it overall it was the most effective among five tested chelators (Llobet et al., 1988). No studies have been done to establish the long-term safety of NAC supplementation.

NAC is naturally produced in the body and is contained in animal proteins, but supplementation can help to insure the body has adequate supplies. I take 1200 mg per day. Label directions suggest taking 1 to 2 of the 600 mg tablets per day. I buy NAC at my local General Nutrition Center, two bottles of 60 600 mg capsules cost about $28.00 including sales tax and the discount for buying two bottles at one time.

Chromium can also be bound by other chelating agents such as EDTA. A chelating agent works in a way that is analogous to soap, it binds certain insoluble molecules and makes them soluble so that may be processed and potentially eliminated. It has been suggested that EDTA treatments (which must be done intravenously, by administration of calcium-EDTA) might increase chromium elimination from the body. EDTA is best known as a treatment for lead poisoning. In one study of humans (Anderson et al., 1996) EDTA treatments did not increase the elimination of chromium. In a study of metal workers (Sata et al., 1998) EDTA treatments did increase the elimination of chromium but also increased the elimination of lead, zinc and magnesium. In another study (Araki et al., 1998) the EDTA treatments increased the chromium elimination by just 10% but increased the rate of elimination of lead, manganese, zinc and cadmium by much higher rates. Zinc and manganese are necessary trace minerals, for which the additional elimination would be considered a detrimental side effect for the orthopedic patient without additional sources of these trace minerals. EDTA **does not** seem to be well suited for preferentially eliminating chromium.

3.5 Blood Donation

Once every two months I go to the local office of the Red Cross and donate a unit (approximately 1 pint) of blood. The average human has 9-11 pints of blood in their system, so if there are any metals in my bloodstream, the result of each donation is a reduction by about one-tenth of the total amount of metal in the bloodstream. (Since it will be diluted about 1-to-9 in the body of the recipient, so I am not concerned about any ill effects on the recipient). The reduction may seem small, but the cumulative effect can be dramatic, especially considering that the period of run-in wear may be limited.

If you are concerned about the potential effects on the recipient you may be able to opt to have your blood held back from distribution. The Red Cross has a system of confidential notification that the donor believes their blood may be a risk to the recipient. If you choose to withdraw your blood donation you may want to make a tax-deductible contribution to the Red Cross to cover their costs for drawing your blood. Alternatively, it might be possible to obtain a prescription to have your blood drawn periodically as is done for those with hemochromatosis. Given the lack of demonstrable risk, it may be difficult to obtain such a prescription, however.

4. Summary

Some nutritional supplements and actions have been identified that might mitigate any possible effects of metal ion activity for those with implanted metals. There are few known side effects to the proposed protocol with possible beneficial side effects

	Target Dose/ Frequency	**Intent**	**Positive Side Effects**	**Negative Side Effects**	**Estimated Monthly Cost**
Vitamin C	250-500 mg 1 x/day	Anti-oxidant	Cold and flu defense	Considered safe below 2000 g/day	$1.00
Anti-oxidant Formula	1 softgel/day	Anti-oxidant			$3.00
NAC n-acetyl-l-cysteine	600 mg 2x/day	Anti-oxidant Cobalt chelator	May reduce flu symptoms		$14.00
Blood Donation	1 Unit/ 8 weeks	Dilution	Medical benefits to blood recipients		1-2 hours of time every two months

.
identified for many of the actions. The cost of the protocol is quite reasonable, and the supplements are available in the United States through many sources.

It is not my intent to raise the fear level over metal, rather provide some positive action that may make the patient feel more in control of any possible risks.

Note it is beyond the scope of this report to consider reproductive health issues. Consult your OS or Ob-Gyn for possible risk factors. Some information on the subject can be found online at Reprotox.org.

Although the author believes this to be a safe and defensible protocol, much of the research evidence is based on animal and in-vitro experiments. This protocol has not been clinically proven, nor has it been reviewed in any way by the U.S. Food and Drug Administration. It is beyond the author's knowledge to judge the methods and other details of the cited publications, for a few only the abstract was readily accessible. Any treatment should be done in consultation with a medical professional. Taking any nutritional supplements could affect test results or interact with medications; keep your physician informed of your actions.

4. References

Anderson R.A., N.A. Bryden, and R. Waters, 1999: EDTA chelation therapy does not selectively increase chromium losses. *Biol. Trace Elem. Res.*, **70**, 254-272.

Agostini, F.D., R.M. Blansky, A. Camoirano, and S. De Flora, 2000: Interactions between N-Acetylcysteine and ascorbic acid in modulating mutagenesis and carcinogenesis. *Int. J. Cancer*, **88**, 702-707.

Araki S., H. Aono, and K. Murata, 1986: Mobilisation of heavy metals into the urine by CaEDTA: relation to erythrocyte and plasma concentrations and exposure indicators. *Br. J. Ind. Med*., **43**, 636-641.

Borneff, I, Engelhardt, K, Griem, W, et al. (1968). [Carcinogenic substances in water and soil. XXII. Mouse drinking study with 3,4-benzpyrene and potassium chromate]. *Arch.Hyg*. **152**, 45-53. (German) {As reported in Morry, 1999}

Case C.P., V.G. Lingkumer, C. James, M.R. Palmer, A.J. Kemp, P.F. Heap, L. Solomon 1994: Widespread dissemination of metal debris from implants. *J Bone Joint Surg (Br.)*; **76 (B)**, 701-712.

Chan, F.W., J.D. Bobbin, J.B. Medley, J.J. Krygier, S. Yue, M. Tanzer, Engineering issues and wear performance of metal on metal hip implants, *Clin. Orthop. Res*., **333**, 996-107.

De Flora, S., C. Grassi, and L. Carati, 1997: Attenuation of influenza-like symptomatology and improvement of cell-mediated immunity with long-term N-acetylcysteine treatment. *Eur. Resp. J.*, **10**, 1535-1541.

DeFlora, S., 2000: Personal communication.

Gillespie, W.J., D.A. Henry, D.L. O'Connell, S. Kendrick, E. Juszczak, K. McInneny and L. Derby, 1996: Development of hematopoietic cancers after implantation of total joint replacement. *Clin. Orthop*., **329 Suppl.**, S290-S296.

Hathaway, 1986: Treatment of acute chromium poisoning. In D.M Sernone, (ed.), Chromium symposium 1986: an update, pp. 87-99. Industrial Health Foundation, Pittsburgh. (Cited by D'Agostini et al., 2000.)

International Agency for Research on Cancer (IARC), 1999 Evaluation of cancer risks to humans: Surgical implants and other foreign bodies. *IARC Monographs*, Volume 74.

Ivankovic, S and R Preussmann, 1975: Absence of toxic and carcinogenic effects after administration of high doses of chromic oxide pigment in subacute and long-term feeding experiments in rats. *Food Cosmet. Toxicol.,* **13**, 347-351. {As reported in Morry, 1999}

Kerger, B.D., B.L. Finley, G.E. Corbett, D.G. Dodge, D.J. Paustenbach, 1997: Ingestion of chromium (VI) in drinking water by human volunteers: Absorption, distribution, and excretion of single and repeated doses. *J. Toxicol. Environ. Health*, **50**, 67-95.

Llobet J.M., J.L. Domingo, and J. Corbella, 1988: Comparative effects of repeated parenteral administration of several chelators on the distribution and excretion of cobalt. *Res. Commun. Chem. Pathol. Pharmacol*., **60**, 225-233.

Mathiesen, E.B., A. Ahlbom, G. Bermann, and J.U. Lindgren, 1995: Total hip replacement and cancer. A cohort study. *J. Bone Joint Surg*. Br., **77**, 345-350.

Morry, D., 1999: *Public Health Goal for Chromium in Drinking Water, Report of Office of Environmental Health Hazard Assessment*, State of California Environmental Protection Agency. 26 pp.

National Academy of Science (U.S.), Institute of Medicine 2000: *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*, National Academy Press, Washington, D.C., available online at http://www.nap.edu/books/0309069351/html/index.html

National Academy of Science (U.S.), Institute of Medicine 2001: Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc National Academy Press, Washington, D.C., available online at http://www.nap.edu/books/0309072794/html/index.html

Sata F., S. Araki, K. Murata, and H. Aono, 1998: Behavior of heavy metals in human urine and blood following calcium disodium ethylenediamine tetraacetate injection: observations in metal workers. *J. Toxicol. Environ. Health*, **54**, 157-178.

Schmalzried T.P., E.S. Szuszczewucz, M.R. Northfield, K.H. Akizuki, R.E. Frankel, G. Belcher, and H.C. Amstutz, 1998: Quantitative assessment of walking activity after total hip or knee replacement. *J. Bone Joint Surg*., **80**, 54-59.

Schmalzried T.P., E.F. Shepherd, F.J. Dorey, W.O. Jackson., M. dela Rosa, F. Fa'vae, H.A. McKellop, C.D. McClung, J. Martell, J.R. Moreland, and H.C. Amstutz, 2000: Wear is a function of use, not time. *Clin. Orthop.,* **381**, 36-46.

Shamberger, R.J., 1984: Genetic toxicology of ascorbic acid. *Mutat. Res.,* **133**, 135-159.

Tharani, Ravi, F.J. Dorey, and T. P. Schmalzried, 2001: The Risk of Cancer Following Total Hip or Knee Arthroplasty, *J. Bone J. Surgery*, **83**,774-780.

United Kingdom Expert Group on Vitamins and Minerals, 2000: *Review of Cobalt*. 21 pp. Available online at: http://www.foodstandards.gov.uk/committees/evm/papers.htm

Visuri T., E. Pukkala, P. Paavolainen, P. Pulkkinen and E.B. Riska, 1996: Cancer risk after metal on metal and polyethylene on metal total hip arthroplasty. *Clin. Orthop*., **329 Suppl.**, S280-289.