I. Tower's Experience with Arthroprosthetic Cobaltism

I am a practicing orthopedic surgeon with 30 years experience in primary and revision hip, shoulder, and knee arthroplasty. I have a 30-year association with Dartmouth Biomedical Engineering Center, one of the world’s foremost nonpartisan, academic, arthroprosthetic explant research facilities, including multiple collaborative peer-reviewed publications. My 40-year medical research experience (onset 1975, CDC) combined with my Internal Medicine Internship (1983-4, Dartmouth Hitchcock), 4 years of research, general-medical, and surgical practice (Orthopedic and General) predating my orthopedic residency in the Alaskan Indian Health Service (1984-8), my 4 years of Orthopedic Residency training (OHSU) with peer reviewed publications (1988-92), and my 27-year private practice career in Anchorage (1992-2019) with a focused interest with the systemic (cobalt poisoning) and periarticular failure mechanisms of joint replacement designs and materials along with multiple peer-reviewed publications focused on cobalt-chrome metallosis complications and additional publications and presentations touching on the topic of societal-harm related to the American-Medical-Industrial-Complex wherein market forces can drive research and medical education, medical practice, and government regulation rather than science, would seem to qualify me as an “expert” on the topic of the metallosis complications of prosthetic joints yet I was denied membership on the FDA Expert Panels addressing these complications in 2010 and 2019.

My personal (as patient), professional (as surgeon), and scientific (as researcher), qualifications directly bearing on arthroprosthetic cobalt-chrome metallosis and my education and experiential foundation that allowed for publication primacy (2010), in the discovery that systematic cobalt poisoning (cobaltism) is a complication of primary (first-time) hip replacement, modern (since the archaic Mckee-Farrah metal-on-metal hip of the 1970s) hip replacements utilizing cobalt-chrome as an arthroprosthetic material with multiple peer-reviewed publications over the past decade based on focused study of my patients and the peer-reviewed publications of other investigators.
2. Cobalt-Chrome is inherently unsafe for arthroprosthetics compared to proven alternatives

Modern hip, shoulder, and knee joint replacements employ metal, ceramic, or plastic materials to replace one or both articular surfaces. Iron (FeCrNi), Cobalt (CoCr), and Titanium (TiAlV) are the base metals of arthroprosthetic alloys. Of the three base metals (Cobalt, Iron, Titanium), only cobalt is notably toxic in the laboratory and in humans to the cells of periprosthetic tissues (hip capsule, ligaments, synovium, tendons, muscle, and bone). Cobalt has been known to result in systemic metal poisoning (encephalopathy, cranial and peripheral neuropathy, cardiomyopathy, and thyroid failure) since the 1950s and is carcinogenic.

Cobalt is in vitamin B-12; humans absorb B-12 produced by bacteria in the gastrointestinal tract because we lack the ability to make it. Cobalt deficiency occurs in cows not in humans. Industry funded retrospective anti-science argues that the historical use of oral cobalt-chloride as a hematemic proves that its use in arthroprosthetic devices is safe. In the 1950s cobalt-chloride was thought to be salubrious for anemic patients and was widely used to treat anemic children and adults with anemia related to kidney failure. By the end of that decade it was known that such treatment was of little benefit to anemic, kidney failure patients because of its toxicity to the brain, nerves, heart, and thyroid gland, by the 1970s the practice of treating anemia with cobalt-chloride was abandoned due to this toxicity Exposure of workers to cobalt ores and powders resulted in same syndrome sometimes resulting in death or heart transplantation. Low-grade, long-term, industrial, or arthroprosthetic cobalt exposure is linked to cognitive decline, thyroid dysfunction, cardiomyopathy, and cancer.

CoCr is a stronger alloy than FeCrNi and that was a rationale for its popularity as an arthroprosthetic material but the strength of a femoral stem is more determined by its dimensions than its composition. The rare fatigue failures of Charnley’s historically peerless FeCrNi stem were solved by upsizing its shape rather than switching to the potentially toxic CoCr alternative.

Industry argues that Cobalt-Chrome (CoCr) is a superior prosthetic material to stainless steel (FeCrNi) for use in cemented polished stems with cemented femoral stems. The “state-of-the-art” material for any cemented polished femoral stem is indisputably FeCrNi based on its superior survivorship (comparative to cemented CoCr stems and uncemented TiAlV stems) in tens of millions of patients that have benefited from the matt-finished FeCrNi Charnley femoral stem or the polish-finished finished FeCrNi Exeter stem. This is not just my opinion: new hip designs and materials are generally benchmarked against the FeCrNi Charnley Low-Friction-Arthroplasty because of its common use, long history (50-years), and its seldom surpassed safety and survivorship, particularly for geriatrics. In the Mayo series of 2000 patients with FeCrNi Charnley arthroplasties now followed > 40 years the annual risk of failure (revision) for geriatric patient to a material or design problem is < 0.5% per annum. The failure of my own Zimmer Heritage polished CoCr stems as early as 8-years (based on elevation of blood and urine cobalt levels) or at 12-years (based on time to revision) due to gross corrosion at the stem-cement interface is both concerning and exceptional.
Industry “experts” argue that corrosion is inevitable at the interface between a metallic femoral stem regardless of alloy and that corrosion when it does occur is only “clinically significant” in “rare” cases. Both assertions are unsupported by the medical literature and are counter to my extensive hip revision experience. Millions of Charnley’s cemented FeCrNi stems have been implanted. Early in the evolution of Charnley’s stem design fatigue fracture of the early “flat-back” variant stem with coincident corrosion of the 316L or EN58J stainless steel alloys were occasionally described. This infrequent complication was remedied by beefing-up the stem, making it stiffer and stronger, and thereby less prone to fatigue failure. Even in the rare instances in which corrosion was found during revision of a fractured Charnley stem the amount of corrosive debris was minor compared to what I uncovered when I revised Patients A-C’s well fixed CoCr Zimmer Heritage polished stems.

The Charnley Elite stem (DePuy, Warsaw IN) like the Heritage uses CoCr alloy rather than FeCrNi but has a matt finish, a more robust collar, and a dorsal flange, these features limit micro-motion at the stem-cement interface. I cannot find literature report of corrosion occurring with the Charnley Elite implant (matt finished CoCr) and it is reported to have a 1% failure-rate at 12 years in young high-activity patients that are know to be prone to premature implant failure compared to the 4.0% for the Heritage (polished CoCr) at 7-years in a low-demand, elderly, population. The DePuy Charnley Elite CoCr stem (matt finished, robust collar, proximal dorsal flanges) is a “shape-closed” design that limits the micro-motion at the stem-cement interface, the Zimmer Heritage stem (CoCr alloy, polished finish, minimal collar, no dorsal flanges) is a “force-closed” design which allows for stem-cement micro-motion. Micro-motion is sine qua non of Mechanically-Assisted-Crevice-Corrosion (MACC), the phenomena that I observed in spades at the time of multiple revisions of Zimmer Heritage stems revised for periprosthetic and systemic cobalt toxicity. Femoral stems with an effective “shape-closed” design (matt-finish, robust collar, dorsal flanges) rarely exhibit “significant” corrosion at the stem-cement interface. “force-closed” femoral designs such as Zimmer’s CoCr Heritage and CPT, DePuy CoCr Ultima stem, Stryker’s FeCrNi Exeter stem, and several abandoned TiAlV femoral stems predictably corrode in patients and on the bench.
The Exeter femoral stem (Stryker, Kalamazoo MI) is made of FeCrNi and has a polished finish and is shaped to encourage micro-motion between the stem and the cement mantle. This has been reported to result in corrosion and the stem-cement interface but generally of a lesser magnitude that I witnessed in my patients A-C with polished CoCr Zimmer Heritage stems. The Exeter hip outperforms even the Charnley hip in National Joint Registry 15-year survivorship data indicating that although corrosion can occur at the stem-cement interface of a polished FeCrNi stem it is of limited periprosthetic or systemic consequence because the byproducts of FeCrNi corrosion are fundamentally less toxic than those liberated by corrosion of a CoCr implant. CoCr should never be used for a force-closed (polished) femoral stem because cobalt, in excess, is fundamentally toxic to the periprosthetic tissues and to distant human organs (central and peripheral nervous system, heart, and thyroid). It was know at the time of the design and promotion of the Heritage CoCr stem that polished (force-closed) femoral stems, regardless of alloy, were at risk for corrosion at the stem-cement interface.
know then that cobalt is fundamentally toxic to the periprosthetic tissues\textsuperscript{20,22,23} and systemically toxic to the human brain, nerves, heart, and thyroid gland.\textsuperscript{20,41} Although corrosion has been reported with the smooth finished classic Charnley FeCrNi “flat-back” stem\textsuperscript{11} and polished FeCrNi dual taper Exeter stem\textsuperscript{118} it is rarely periprosthetically or systemically toxic because the major constituent the Stainless Steel (FeCrNi) alloy is iron which biologically benign compared to cobalt with is the primary element in the CoCr alloy used for Zimmer’s polished CoCr Heritage stem.

The harm to patients with polished CoCr cemented “force closed” stems such as Zimmer’s CPT and Heritage models and J&J’s Ultima stems (gross corrosion at the interface of the polished CoCr stem surface and the poly-methyl-methacrylate (PMMA)) is magnified by most all currently marketed bone cements which contain 10% (by weight) barium sulfate\textsuperscript{119} which is an abrasive and magnifies the documented corrosion than occurred at the cement-stem interface of polished “force-closed” stems. Industry’s assertion that CoCr metallosis produced by arthroprosthetic implants, when it does occur, only “rarely” produces periprosthetic Adverse Reaction to Metallic Debris (ARMD) is countermanded by both the literature,\textsuperscript{100,103,107,108,120-143} and by my experience as patient,\textsuperscript{3,10,11,16} arthroprosthetic revision surgeon and published authority on the periprosthetic and systemic toxicity of CoCr metallosis,\textsuperscript{2,13-15,144} and as an advocate for reform of the American Medical-Industrial-Complex.\textsuperscript{12,17,19} The proclivity of DePuy’s metal-on-metal ASR implant to produce CoCr metallosis and ARMD by wear of its articulation resulted it its formal recall of the marketplace including a systematic monitoring program including blood cobalt determinations and cross-sectional imaging of the hip.\textsuperscript{133,142,143-166}

The Styker (Kalamazoo, USA) ABG and Rejuvenate hips and ESKA (Lubeck, Germany) hip have a modular CoCr neck prone to corrosion producing CoCr metallosis at both ends resulting in formal recall from the market of the Styker products with a systematic monitoring program of blood cobalt and cross-sectional imaging at the hip for clinical and sub-clinical pseudotumors.\textsuperscript{107,108,167-184}
Zimmer’s VerSys 12/14 taper modular CoCr femoral heads and Stryker’s V40 taper CoCr heads are proven to be problematic regardless of whether they are mated to a CoCr stem trunnion or a TiAlV stem trunnion. Professional awareness that CoCr metallosis is a significant problem that can result in ARMD and systemic toxicity and therefore mandates orthopedic surgeon awareness, monitoring, and if indicated revision surgery is demonstrated by the following tables from the joint recommendations of the American Academy of Orthopedic Surgeons (AAOS), the American Hip and Knee Surgeon Society (AHKSS), and the Hip Society that was published January 2014. The consensus opinion was specific to cobalt exposure from Metal-on-Metal hips: but, we have learned from the taper corrosion of Metal-on-Plastic and even Ceramic-on-Plastic hips that both ARMD and cobaltism occur at much lower blood cobalt levels if the systemically circulated cobalt is produced by corrosion as opposed to the wear mechanism seen in Metal-on-Metal hip replacement and hip resurfacing.

A blood cobalt of $\geq 3$ ppb places a patient with a Metal-on-Metal hip in the moderate-risk category for a complication of CoCr metallosis whereas the threshold blood cobalt for concern is $\geq 1$ ppb for patients with a metal-on-plastic or ceramic-on-plastic hip with a taper joining one or more CoCr components. The reason that arthroprosthetically-produced, systemically-circulated cobalt produced by corrosion is more toxic peritrophically and systemically that that produced by wear of the articular surfaces of a metal-on-metal hip resurfacing relates to the much smaller particle size and more reactive nature of CoCr corrosion byproducts as opposed to much larger CoCr wear particles. Critical literature regarding thresholds of blood cobalt for concern for metal-on-metal hips or hips with metal-on-plastic or ceramic-on-plastic articulations prone to corrosion of modular CoCr parts are both by Kwon. At blood cobalt level of $3$ ppb is considered to place a patient with a metal-on-metal hip at-risk for ARMD, a lower blood cobalt threshold of $1$ ppb is considered concerning with metal-on-plastic or ceramic-on-plastic hip with modular CoCr component. As noted above this reflects the fundamental increased toxicity of CoCr metallosis produced by corrosion at CoCr modular junctions compared to that created by wear of CoCr articular surfaces.
Risk Stratification for monitoring and revision of patients with Metal-on-Metal hips at-risk for ARMD and Cobaltism (Kwon, JBJS, 2014)

Conclusions: Although metal ion levels alone should not be relied on as the sole parameter to determine revision surgery, serum cobalt level of >1 ng/mL (1 ppb) and Co/Cr ratio >2 thresholds provide evidence based practical information for surgeons when interpreting metal ion levels in MoP THA patients for clinically relevant head-neck taper corrosion.

Between 2010 and 2015 Dr. Thomas Mego (chair Providence Alaska Medical Center Department of Pathology) and I reviewed the histopathology of 48-failed Metal-on-Metal and Metal-on-Plastic hips that were revised because of periprosthetic and systemic complications of CoCr metallosis. Histopathologic findings typically show metallosis in the form of inclusions in macrophages and in a “slate-blue” staining of the cytoplasm. Variable degrees of synovial-necrosis were the most common finding. We only found ALVAL lesions (focal lymphoid infiltrates around small blood vessels) in a minority of patients, generally those patients with a hyper-acute presentation (severe symptoms at the hip within months of hip implantation). The literature on the histopathology of ARMD supports Dr. Mego’s and my experience, the histologic picture of ARMD is highly variable; metallosis and necrosis are generally the most consistent microscopic findings. Prominent ALVAL lesions appear in a minority of cases, generally those patients that respond in an allergic fashion chrome-cobalt metallosis.
My clinical series indicated and “at-risk” hips extend beyond those with a modular cobalt-chrome neck stem or a hip with a metal-on-metal articulation. My first appreciation of this was February of 2013 when I revised a series of patients with severe corrosion the Zimmer’s 12/14 taper junctions when a CoCr VerSys head or Durom CoCr head was used. I was finding this problem throughout Zimmer’s product line including Zimmer’s popular ML Taper, Kinnectiv, or ZMR TiAlV stems when mated to a VerSys CoCr head articulating with a Longevity Plastic Liner or a Durom CoCr acetabular component. Multiple surgeons including my mentor Dr. Paul Duwelius were reporting this problem of corrosion with Zimmer’s 12/14 tapers when a VerSys CoCr or Durom CoCr heads were used. The case illustrated below is typical of the approximate 30 cases of Zimmer’s hips that I have revised due to ARMD since that index case early 2013, all revisions were for symptomatic ARMD, with severe periprosthetic tissue damage, and all were because of defective design of stems or tapers combined with a poor choice of alloy. The reason that patients with elevated cobalt levels are closely followed with cross-sectional imaging is that the damage from the metallosis to the periprosthetic tissues can be severe with minimal clinical symptoms resulting in an unsalvageable problem.

My index patient (revised February 2013) for the realization that Zimmer’s 12/14 tapers were extremely problematic when mated to a CoCr head is illustrated below. The loss of material from the bore of the CoCr taper adaptor for the Durom head was so severe that I could toggle the modular TiAlV Kinnectiv modular neck back and forth.
My appreciation that arthroprosthetically generated cobalt is neurotoxic has passed peer review muster many times, and even passed conflict-of-interest problematic peer review (most orthopedic surgeons that do peer-review for hip prosthetic related topics for presentation at the annual AAOS meeting are industry consultants allowing for our work using the Cobalt-Symptom-Inventory screen at-risk patients for arthroprosthetic cobaltism and FDG-PET-CT-Brain-imaging to confirm the diagnosis to be presented at the annual meeting of the AAOS in 2018 (appendix A).

Cobalt encephalopathy is not my invention; I was just the first to recognize it as a complication of modern metal-on-metal hip arthroplasty because I experienced it as a patient. Cobalt encephalopathy manifesting as cognitive decline was first described by Jordan in 1997 from chronic cobalt industrial exposure. Since the 1960s we have known that iatrogenic deafness, blindness, thyroid abnormalities, and heart failure results when cobalt chloride is taken by mouth, as it was to treat anemia, a practice abandoned by 1980 because of its adverse risk to benefit ratio. Acute industrial cobalt exposure results in death, heart failure, deafness, blindness, and thyroid abnormalities. The fatigue and disabling mood disorder I experienced when my blood cobalt was 80X that considered safe in industry has now been described to be a common early feature of those suffering from arthroprosthetic cobaltism.

3. Industry’s Misinformation Campaign is confounding remediation of Arthroprosthetic Cobaltism

Industry financed retrospective anti-science argues that a blood cobalt level of 6 ppb (6X that thought safe in industry) from arthroprosthetic cobalt-chromium metallosis cannot result in systemic toxicity is based on a house of cards of misinformation, the foundation of which is Cardno ChemRisk LLC’s (San Francisco, CA) study of blood cobalt levels in 10 generally young, well, men and woman were dosed by mouth with the cobalt-laced dietary supplement (Mineralife, Colorado Springs, CO) for study period of 15, 30, and 90 days with monitoring of blood cobalt, blood counts, hearing, sight, cardiac and thyroid function. Cardno ChemRisk LLC fused this study with their theoretical model to calculate blood cobalt levels of 11 dialysis patients treated 8 weeks with oral cobalt-cladride for anemia in one study (Bowie, 1975), and 6 patients treated for 90 days (Duckham, 1976). Then Cardno ChemRisk treated 10 subjects with an oral cobalt laced dietary supplement for 90-days, at 90-days the 5 men had an average blood cobalt level of 20 ppb and the 5 women had a mean blood cobalt level of 53 ppd. With impenetrable logic Cardno ChemRisk states that blood cobalt of < 300 ppb should not cause toxicity in patients exposed to arthroprosthetically generated CoCr metallosis.

Neither Cardno ChemRisk’s 10 subjects nor the 17 dialysis patients treated a half century ago contribute any meaningful information concerning poisoning by CoCr periprosthetic metallosis. The 17 renal failure patients absorbed the cobalt from the gastro-intestinal tract, from there it is directly routed to the liver, the human body’s first line of defense against toxins and most all that is absorbed is excreted rapidly in the bile and urine, having little opportunity to enter the cells of the heart, brain, nerves, and thyroid gland which is where cobalt’s metabolic toxicity is expressed. Furthermore with 17 renal failure patients were dialyzed 3 times a week reducing their serum cobalt concentrations to nil. The CoCr metallosis produced by corrosion or wear of an orthopedic implant is nanoparticulate, bypasses the liver, and is directly presented the brain, nerves, heart, and thyroid gland in a form that more readily transverses the cell membrane than ionic cobalt absorbed through the gastrointestinal tract. Only 16 of the 27 dialysis patients reported to have tolerated large doses of oral cobalt completed a full 90-days of treatment. Cardno ChemRisk ignores that 3 of the 11 patients reported by Bowie developed deafness and one died shortly after the trial from heart failure. The duration of exposure to arthroprosthetically generated cobalt can span decades rather maximum 90-days endured by the 17-dialysis patients in 1975-6 or Cardno ChemRisk’s 10 subjects. Furthermore, the 17-dialysis patients that Cardno ChemRisk theorizes tolerated high blood cobalt (three actually developed deafness) underwent dialysis trice weekly and therefore were not exposed incessantly to cobalt as are patients exposed through a malfunctioning prosthetic implant.

Contradicting Cardno ChemRisk’s mercenary theoretical work there are now a plethora of arthroprosthetic cobaltism case reports showing that when blood cobalt exceeds 100 ppb extreme illness results in death, heart transplantation, psychiatric decompensation, blindness, deafness, thyroid failure, and severe peripheral neuropathy. Additionally, there are now multiple case series and case reports indicating that serious systemic illness can result once blood cobalt levels are ≥ 7 ppb from an arthroprosthetic source. These case reports likely represent a minute fraction of those patients actually experiencing arthroprosthetic cobaltism because awareness of the condition is so limited among medical providers and the public, a point reinforced by Umar et al in their 2019 review of arthroprosthetic cobalt myocardial pathology (CMP).
Umar’s conclusion is an echo of that of Gessner’s systematic review of the literature on Arthroprosthetic Cobaltism in 2015.

**4. FDA pre and post market maleficence is delaying the recognition and remediation of Arthroprosthetic Cobaltism**

In 2012 my clinical experience indicated that arthroprosthetic cobaltism was common in patients with metal-on-metal hips beyond the recalled J&J ASR. I was surprised that the FDA at that time ignored this problem and excluded me from its expert panel addressing growing public concern of premature failure of this class of hip that was placed in about a million Americans. My 2012 manuscript on the frequency of the problem in Alaskans with metal-on-metal hips (appendix B) was submitted to the docket of the 2012 expert panel and was ignored. The FDA did not mandate a monitoring program for patients with metal-on-metal hips and the companies that made them were allow to silently remove them from the market. Three AAOS nominated surgeons that were allowed to participate on the 2012 panel soon thereafter wrote a review article in a AAOS-supported journal suggesting that metal-on-metal hips were safe. It was not until 2014 that a consciences opinion of the AAOS, Hip and Knee society, and the American Association of Knee and Hip Surgeons recommended a monitoring suggestion for the million Americans implanted with no longer marketed metal-on-metal hips. These recommendations are seldom systematically followed by American orthopedic surgeons and the FDA continues to post only vague recommendations for monitoring patients with no longer marketed metal-on-metal hips. Delayed inaction by the FDA concerning the now well documented periprosthetic and systemic cobalt-chromium metallosis has harmed hundreds of thousands of Americans. Systematic literature review by Gessner indicates that arthroprosthetic cobaltism is likely a spectrum illness with a large American at-risk population. My exclusion from the 2019 expert panel gives me cause for concern that the FDA’s pattern of placing the health of the arthroprosthetic industry above that of 20 million Americans with implanted CoCr hip, shoulder, and knee parts continues. My interactions with the FDA, the AAOS, Orthopedic Journals, and the committees that accept presentations for Orthopedic meetings confirms that conflict-of-interest is the driving force of commercial, academic, and regulatory malfeasance leading to the under-recognition, propagation, and delayed remediation of a silent epidemic of periprosthetic and systemic complications of arthroprosthetically generated cobalt-chromium metallosis with an American at-risk population of 20 million.

**5. Industry’s willful blindness to Arthroprosthetic Cobaltism is compounding the problem**

Rather than recognizing and remediating its CoCr metallosis liabilities industry appears to be intent on a cover-up, at least that was the approach of J&J during its bellwether trial Kransky v J&J concerning DePuy ill-starred MoM ASR hip … per Bloomberg:

**$5 Million**

Paustenbach said his firm ChemRisk Inc. has billed DePuy at least $5 million over the past 16 months. He was part of a team of 49 people who spent thousands of hours studying medical literature and found virtually no research on the effects of cobalt prior to the ASR recall.

“What systemic health effects have you found?” J&J attorney Alexander Calfo asked Paustenbach.

“I saw none,” Paustenbach said.

Paustenbach’s prior retrospective “pseudoscience” concerning asbestos and his mercenary behavior to his critics has resulted in the resignation of the entire editorial board of a respected Occupational and Environmental Toxicology Journal. It appears that Paustenbach’s companies Cardno ChemRisk LLC and Exponent exist for the sole purpose to manufacture misinformation “proving” that substances well known to be toxic are not for the purpose of defending industry, work for which Cardno ChemRisk LLC and Exponent are paid exorbitant fees. Most concerning is that the medical journal publishing behemoth Francis & Taylor appears to willing to legitimize Cardno ChemRisk LLC and Exponent’s “research” by strong-arming editorial boards to publish Exponent’s and Cardno ChemRisk’s work:


Any legitimate research effort into the known deleterious effects of arthroprosthetically generated cobalt could not have missed the 1981 US government commissioned tome on Cobalt toxicity edited by Smith and Carson and the seminal 1975 report of periprosthetic and systemic cobalt toxicity in a series of patients with periprosthetic CoCr metallosis from McKee-Farrar Metal-on-Metal hip replacement. The mercenary literature produced by Paustenbach and his co-conspirators fails to cite either.
Dr. Tower’s Briefing to Dr. Raj Rao, Chairperson FDA Medical Devices Advisory Committee
Expansion of Dr. Tower’s 8.5 minutes of Open Public Testimony, November 13 2019

Alone and ill, without force multiplier of $5 million and 40 confederates, I found both in December 2007 (6 years before Paustenbach’s, Exponent’s, and Cardno ChemRisk LLC’s mercenary exercise) after 3 months of disability from my first cobalt-toxic decompensation for my own right ASR XL.\(^3\),\(^10\),\(^11\),\(^16\)

It was apparent enough to me, then, based only on these two general and specific seminal publications on arthroprosthetic cobalt toxicity that I was cobalt poisoned.\(^23\),\(^41\) The psychiatric nature of my decompensation made it impossible at that time to convince my family, friends, and medical providers that I was suffering from metal poisoning rather than mood disorder not otherwise specified.\(^41\) My blood-cobalt level then was 122 times that indicating unsafe industrial exposure,\(^3\),\(^10\),\(^11\),\(^16\) yet was only a fraction of what Paustenbach and his confederates theorize to be a toxic blood-cobalt threshold of 300 ppb.\(^188\),\(^224\),\(^226\),\(^233\),\(^237\)

At the same time Cardno ChemRisk employed 40 confederates and charged DePuy 5 million dollars to show that the medical literature indicated that a blood cobalt level of < 300 ppb from arthroprosthetically generated CoCr metallosis is safe,\(^239\) Gessner and two rising second-year-medical-students found 25 well-documented cases of arthroprosthetic cobaltism.\(^239\)
Exceptional to Cardno ChemRisk’s claim that a blood cobalt of < 300 ppb is safe, Gessner et al found 4 cases reports of neurologic and cardiac toxicity in subjects with a blood cobalt level of < 20 ppb from arthroprosthetic. Gessner et al also noted that the severity of neurologic and cardiac illness correlated with the degree of elevation in blood cobalt level.219 My clinics ongoing work screening patients with any CoCr arthroprosthetic implant indicates that sensitive individuals exposed to arthroprosthetically generated cobalt may develop neurologic symptoms and significant brain hypometabolism by FDG-PET-Brain-Scan once their blood cobalt level equals or exceeds the 95 percentile blood-cobalt level (0.4 ppb) of subjects without exposure to cobalt through industry, by ingestion, or by having an CoCr arthroprosthetic implant.

Also counter to Cardno ChemRisk’s mercenary conclusions is a study of brain MRIs in 29 patients with asymptomatic hip resurfacing implants with mean blood cobalt of 1.72 ppb (1.1-6.0) compared with 29 patients with hip replacements with mean blood cobalt of 0.38 ppb (0.33-0.50), the groups were matched and studied at a mean period of 8 years post arthroplasty.247 The group with modest blood cobalt elevation showed significantly diminished brain volume in the optic pathways and the basal ganglia compared to the control group with normal blood cobalt level.247 The same subjects’ heart function was compared by echocardiography, the patients with modest blood elevation show significantly diminished heart function compared to the group with normal blood levels.248 It is critical to note that the 29 patients with resurfaced hips, abnormal brain volumes, and abnormal heart function, had a mean blood cobalt level 170 times247 lower than Paustenbach’s safety threshold of 300 ppb.228

5. Frequency and Severity of Corrosion at modular junctions of CoCr parts relates to taper design and tolerance

In my 40-year surgical experience with hip arthroplasty, surgery; clinically significant, gross corrosion, resulting in periprosthetic and systemic toxicity, is almost never seen in some implants yet is commonly seen in others. Clinically significant corrosion resulting in periprosthetic or systemic toxicity is a design and materials issue: Largely preventable by optimal material selection and prosthetic design. Systematic study for my practice over the past 4 years indicates that Zimmer’s 12/14 and Stryker’s V40 CrCo femoral heads commonly corrode over time. Many patients that experiencing this problem have periprosthetic and systemic morbidity sometimes severe enough to warrant revision hip surgery to replace corroding or wearing CrCo parts with safe plastic, ceramic, TiAlV, or FeCrNi alternatives.
The Y-axis is urine cobalt in ppb; the X-axis is years of hip implantation. The blue diamond data-points with urine-cobalt of < 1 ppb are nearly all Osteonics' C-Taper LFIT CoCr head on TiAlV alloy uncemented stem trunnions.

These Osteonics stems were both in situ for > 15 years in highly active young men. There is no apparent corrosion in the bores of the CoCr heads. This likely relates to robust design of the C-Taper, tight tolerance of taper angle match between the head-bore and stem-trunnion and the smooth finish of the trunnion.

Whether or not that corrosion will be periprosthetically or systemically adverse hinges on at least four factors: the toxicity of the corrosion byproducts (periprosthetically and systemically), the sensitivity of the patient to the corrosion byproducts (periprosthetically and systemically), the biomechanical consequences of corrosion, and the severity and extent of the process. Severe corrosion commonly occurs at the TiAlV stem-cement interfaces resulting in pain and early loosening of components that lead to the abandonment of that alloy for cemented stem application but I am not aware that either systemic toxicity or hypersensitivity has been reported from TiAlV corrosion debris but there has been at least one case of Vanadium neurotoxicity from wear of a TiAlV acetabular shell by ceramic.

Minor corrosion is commonly noted on the surface of explanted FeCrNi Exeter polished stems but this is generally without periprosthetic or mechanical consequence other than rare clinically significant immune reaction due to the nickel exposure. The severe corrosion I found the cement-stem interface of Zimmer polished CoCr Heritage stems in patients A-C did not result in radiographic or clinical loosening of the stems (the stems were difficult to extract) but the cobalt and chromium liberated by the corrosion resulted in symptoms at the hips and systemic poisoning of the patients confirmed by FDG-PET brain scans. A series of 13 failed Zimmer CPT polished CoCr stems revised for progressive hip symptom was recently reported, all had gross corrosion at the stem-cement interface.

DePuy’s polished CoCr Ultima stem frequently fails by the same mechanism, particularly when mated to a metal-on-metal articulation.
Periprosthetic CoCr metallosis produced by wear or corrosion of CoCr articular components (heads or sockets) or at the taper junctions (Figure 1) of articular and non-articular implants (stems, necks, or trays) may result in painful or painless periprosthetic tissue inflammation, necrosis and pseudotumor formation. Collectively, these radiographic findings and symptoms are called Adverse-Reaction-to-Metal-Debris (ARMD). Patients may also react in an immune fashion to CoCr implants by direct attack of leukocytes resulting in ARMD and systemically circulated cobalt in the absence of significant implant wear or taper corrosion. The histopathology of patients with CoCr symptomatic ARMD is highly variable. In my experience, and in that reported by others, patient with an hyper-acute presentation with months of implantation are more likely to have florid inflammatory infiltrates (ALVAL lesions) whereas the majority of patient that develop ARMD have an indolent presentation and generally a mixed histopathologic response of mild chronic inflammation, a macrophage response, varying degrees of tissue necrosis with ulcerations of the synovial membrane.

Most of the publications addressing the symptoms, laboratory abnormalities (elevated blood and urine cobalt levels), imaging findings, gross and histopathologic findings at revision surgery of CoCr periprosthetic metallosis report on hip resurfacings failed due to wear, or Metal-on-Metal total hips in which the CoCr metallosis may be generated by wear of the articular surfaces or corrosion at taper junctions. The notable failure of the Stryker Rejuvenate with its modular CoCr neck that was prone to corrosion at the distal junction were it dove-tailed into a TiAlV alloy stem, and at its proximal junction regardless of whether it was mated to a CoCr or ceramic head informed me that ARMD and cobaltism were not unique to Metal-on-Metal articulations. The Rejuvenate was a popular implant in Anchorage; fortunately I never implanted one but I revised many. Because the implant was formally recalled by Stryker July of 2012 and the recall program recommend a systematic screen program for cobalt levels and imaging of any symptomatic implant I became aware that the patients with failed Rejuvenate implants were experiencing the same problems as the patients with failed Metal-on-Metal hips. If anything the patient’s with failed Rejuvenates often had more florid ARMD than the MoM patients (by symptoms) although their blood and urine cobalt levels were generally an order of magnitude less that those MoM patients whose metallosis related to excess wear of their articular surfaces. Other investigators have confirmed that corrosion generated cobalt-chrome metallosis (tapers) being more toxic periprosthetically than wear generated cobalt-chrome metallosis (edge loading of metal-on-metal hip articulations).

Clinically, cemented FeCrNi stems with Monoblock or Modular FeCrNi heads articulating on polyethylene have superior survivorship in single institution series and in the National Joint Registry of England-Wales in the form of the matt finished Charley stem or the polished Exeter stem compared nearly all other contemporary bearing couples and femoral stem materials. The Charnley and Exeter hips utilizing FeCrNi stems and head articulating on either cross-linked or standard polyethylene are among the few contemporary hips that meet the NICE criteria of an annualized failure rate of < 0.5% per year.

Systemic cobalt-toxicity (cobaltism) most commonly affects the nervous, endocrine and cardiovascular systems. Profound deafness, blindness, peripheral neuropathy, thyropathy, polycythemia, cardiac failure, and death may result in extreme cases. Reports of such severe toxicity are limited to two circumstances: revision of a fractured ceramic hip implant to a CoCr femoral head, or when a CoCr ball and CoCr socket articulate (Metal-on-Metal-Hip). The incidence of the former is rare compared to the latter: about 2 million Metal-on-Metal-Hips were implanted. A subtler presentation of neurologic, psychiatric, and constitutional maladies, easily confused with aging, and similar to the vocational manganese toxicity, results from nominal cobalt exposure from wear or corrosion of modular CoCr implants, or CoCr articular surfaces. F11DG-PET-CT-Brain-Scan has become instrumental in early detection and monitoring of neurodegenerative disease and neurotoxin exposure. Visual interpretation of SPECT and PET imaging was described in 1991 to identify regions of brain injury...
resulting from vocational pesticide and solvent exposure. Subsequently, FDA approved software was developed that quantitatively compares patient FIDG-PET-CT-Brain-Scan data to age-gender norms assigning a T-score to 47 cluster-regions. Such software provides a reproducible and objective dataset without the inter-observer variability or basis inherent with the earlier technology.

**Patient Vignettes**

**Patient 1:** 83 year-old retired engineer with 6-year history of a 36 mm CoCr right Metal-on-Plastic-Hip (Stryker, Kalamazoo MI) presented with new onset hip pain and weakness, bilateral restless leg syndrome, difficulty sleeping, sleep apnea, fatigue, exertional-dyspnea, deafness, and retinopathy. Screening blood and urine cobalt were 4.8 and 49.1 ppb and his Cobaltism-Symptom-Inventory-Score was 5/14. Metal-Suppression-Hip-MRI confirmed ARMD including incomplete detachment of the gluteus medius tendon from the greater trochanter. Initial FIDG-PET-CT-Brain-Scan had a summed score for 90 regions of -228.4 with 22 hypometabolic-cluster-regions. CT showed mild symmetric prominence of sulci. At surgery there was marked corrosion at the trunnion of the stem and the bore of the head and the peri-prosthetic tissues were inflamed and thickened. Cobalt level of right joint fluid collected at time of surgery was 1,000 ppb. Repeat PET scan 17 months post revision showed a summed score for 34 regions of -88.7 with 6 hypometabolic-cluster-regions. Post-revision blood and urine cobalt fell to 0.5 and 2.5 ppb.

**Patient 2:** 67 year-old retired businesswoman with 12-year history of left CoCr Pinnacle Metal-on-Metal-Hip (DePuy, Warsaw IN) presented with hip pain, forgetfulness, fatigue, and depression. Blood and urine cobalt were 0.9 and 1.6 ppb and her Cobaltism-Symptom-Inventory-Score was 3/14. Metal suppression MRI of hip confirmed ARMD. Initial FIDG-PET-CT-Brain-Scan showed no structural abnormalities with 134 hypometabolic regions with summed score of -381.7 with 28 hypometabolic cluster-regions. The patient was treated with oral OTC N-acetyl-Cysteine, and revision of the CoCr-socket-liner to plastic, and revision of the CoCr-head to ceramic. Corrosion was found at taper interface between the TiAlV stem and CoCr head at revision-surgery and the peri-prosthetic tissue was inflamed and thickened, joint-fluid-cobalt was 160 ppb. At 13 months post-revision repeat scan had 87 hypometabolic regions with score of -229.6 and 18 hypometabolic cluster-regions. Blood and urine cobalt declined to 0.2 and 0.4 ppb.

**Patient 3:** A 57 year-old retired-Army-Colonel with a left revision Ceramic-on-Plastic-Hip utilizing a modular CoCr-socket-liner for a “Modular-Dual-Mobility” (Stryker, Kalamazoo MI) articulation. These components replaced a recalled Rejuvenate stem (Stryker, MI) that utilized a modular CoCr neck, five years previously, because the patient had symptomatic cobaltism, ARMD, and blood-cobalt of 19 ppb. After initial resolution of hip and neurologic symptoms blood-cobalt and urine-cobalt climbed to 1.5 and 9.9 ppb, and the patient’s hip, neurologic, cardiac symptoms recurred. Cobaltism-Symptom-Inventory-Score was 7/14. CT imaging showed mild left temporal-parietal sulci prominence from an IED explosion that excluded him from the primary study group. Operative findings noted corrosion on the backside of CoCr Dual-Mobility-Acetabular-Liner, and peri-prosthetic fluid had cobalt of 220 ppb. Pre-revision FIDG-PET-CT-Brain-Scan found 40 hypometabolic regions with score of -96.6 and 4 hypometabolic cluster-regions. 8-months post-revision repeat scan showed 19 hypometabolic regions, a score of -42 and 2 hypometabolic cluster-regions. Blood-cobalt and urine-cobalt declined to < 0.2 and 0.2 ppb.

**Patient 4:** 77 year-old retired teacher with right Metal-on-Plastic-Hip (Zimmer, IN) of 9 years duration presented with progressive hip pain, fatigue, forgetfulness, retinopathy, and decreased reading speed and comprehension. Screening Cobaltism-Symptom-Inventory-Score was 5/10 and blood-cobalt and urine-cobalt were 4.9 and 10.6 ppb. Metal-suppression-hiMI showed a cystic ARMD. Initial FIDG-PET-CT-Brain-Scan revealed no structural abnormality with 25 hypometabolic regions with summed score of -54 and 5 hypometabolic cluster-regions, two years later a follow-up scan showed progression with 25 hypometabolic regions with summed score of -56.5 and 8 hypometabolic cluster-regions. Because of progression of hip pain, neurologic and constitutional symptoms, and progressive brain hypometabolism by FIDG-PET-CT-Brain-scan revision surgery was elected. The cemented CoCr Heritage stem (Zimmer, Warsaw IN) was highly corroded, and the peri-prosthetic tissues were inflamed and thickened, and peri-prosthetic fluid cobalt was 390 ppb. At 5-months post-revision blood-cobalt and urine-cobalt have declined to 0.7 and 1.0 ppb and the patient’s hip pain, neurologic and constitutional symptoms have resolved.

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Appendix

Cobalt Poisoning by Joint Replacement

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Manuscript submitted to FDA Expert Panel June 2012 addressing the safety of Metal-on-Metal Hip Replacements