1 **I. Tower's Experience with Arthroprosthetic Cobaltism**

2

3   I am a practicing orthopedic surgeon with 30 years experience in primary and revision hip, shoulder, and knee arthroplasty. I

4 have a 30-year association with Dartmouth Biomedical Engineering Center, one of the world's foremost nonpartisan, academic,

5 arthroprosthetic explant research facilities, including multiple collaborative peer-reviewed publications.[1-4] My 40-year medical research

6 experience (onset 1975, CDC)[5] combined with my Internal Medicine Internship (1983-4, Dartmouth Hitchcock), 4 years of research,[6]

7 general-medical, and surgical practice (Orthopedic and General) predating my orthopedic residency in the Alaskan Indian Health Service

8 (1984-8), my 4 years of Orthopedic Residency training (OHSU) with peer reviewed publications (1988-92),[7-9] and my 27-year private

9 practice career in Anchorage (1992-2019) with a focused interest with the systemic (cobalt poisoning)[1,10-15] and periarticular failure

10 (histopathologic and mechanical) mechanisms of joint replacement designs and materials [1-4,7,8,11-16] along with multiple peer-reviewed

11 publications focused on cobalt-chrome metallosis complications,[1-4,7,8,11-18] and additional publications and presentations touching on the

12 topic of societal-harm related to the American-Medical-Industrial-Complex wherein market forces can drive research and medical

13 education, medical practice, and government regulation rather than science,[12,17,19] would seem to qualify me as an "expert" on the topic of

14 the metallosis complications of prosthetic joints yet I was denied membership on the FDA Expert Panels addressing these complications

15 in 2010 and 2019.

16   My personal (as patient), professional (as surgeon), and scientific (as researcher), qualifications directly bearing on

17 arthroprosthetic cobalt-chrome metallosis and my education and experiential foundation that allowed for publication primacy (2010), [3,10,16]

18 in the discovery that systematic cobalt poisoning (cobaltism) is a complication of primary (first-time) hip replacement, modern (since the

19 archaic Mckee-Farrah metal-on-metal hip of the 1970s)[20] hip replacements utilizing cobalt-chrome as an arthroprosthetic material with

20 multiple peer-reviewed publications over the past decade based on focused study of my patients and the peer-reviewed publications of

21 other investigators.[1,2,11-13,15,17-19]

22

2. Cobalt-Chrome is inherently unsafe for arthroprosthetics compared to proven alternatives

23

24   Modern hip, shoulder, and knee joint replacements employ metal, ceramic, or plastic materials to replace one or both articular surfaces. Iron

25 (FeCrNi), Cobalt (CoCr), and Titanium (TiAlV) are the base metals of arthroprosthetic alloys. Of the three base metals (Cobalt, Iron, Titanium), only

26 cobalt is notably toxic in the laboratory and in humans to the cells of periprosthetic tissues (hip capsule, ligaments, synovium, tendons, muscle, and

27 bone)[20-22] and multiple organ cell types (white blood cells,[23-26] myocardial,[23,27-38] neurons,[23,39,40] thyroid[23]). Cobalt has been know to result in systemic

28 metal poisoning (encephalopathy, cranial and peripheral neuropathy, cardiomyopathy, and thyroid failure) since the 1950s and is carcinogenic.[13,20,41-47]

29   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.[23,43]

30 Element cobalt is not essential to human-life.[41,43] Cobalt-deficiency occurs in beef-cows[48] not in humans.[41,43] Industry funded retrospective anti-science

31 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

32 was thought to be salubrious for anemic patients and was widely used to treat anemic children and adults with anemia related to kidney failure.[41,49-59] By

33 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,

34 heart, and thyroid gland, by the 1970s the practice of treating anemia with cobalt-chloride was abandoned due to this toxicity.[23,60-64] Exposure of workers

35 to cobalt ores and powders resulted in same syndrome sometimes resulting in death or heart transplantation.[23,41-43,65-73] Low-grade, long-term, industrial,

36 or arthroprosthetic cobalt exposure is linked to cognitive decline,[23,74] thyroid dysfunction,[41,43,75,76] cardiomyopathy,[41,77] and cancer.[41,45,47,65,78-81]

37   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

38 stem is more determined by its dimensions than its composition. The rare fatigue failures of Charnley's historically peerless FeCrNi stem[82] were solved

39 by upsizing its shape rather that switching to the potentially toxic CoCr alternative.[83]

40   Industry argues that Cobalt-Chrome (CoCr) is a superior prosthetic material to stainless steel (FeCrNi) for use in cemented polished stems

41 such as Zimmer's Heritage and CPT stems: they appear to confuse popularity with efficacy and their assertion is not supported by a 50-year experience

42 with cemented femoral stems. The "state-of-the-art" material for any cemented polished femoral stem is indisputably FeCrNi based on its superior

43 survivorship (comparative to cemented CoCr stems and uncemented TiAlV stems) in tens of millions of patients that have benefited from the matt-

44 finished FeCrNi Charnley femoral stem or the polish-finished finished FeCrNi Exeter stem.[82-93] This is not just my opinion: new hip designs and materials

45 are generally benchmarked against the FeCrNi Charnley Low-Friction-Arthroplasty,[92] because of its common use, long history (50-years), and its seldom

46 surpassed safety and survivorship, particularly for geriatrics.[82,93] In the Mayo series of 2000 patients with FeCrNi Charnley arthroplasties now followed >

47 40 years the annual risk of failure (revision) for geriatric patient to a material or design problem is < 0.5% per annum.[93] The failure of my own Zimmer

48 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

49 gross corrosion at the stem-cement interface is both concerning and exceptional.

50
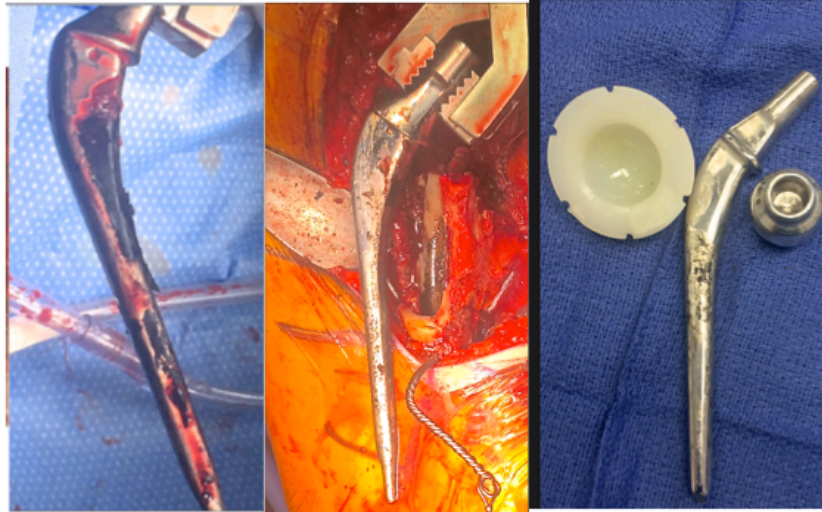
Patient A (polished Zimmer Heritage CoCr stem) revised 8/18 urine cobalt 10.6, composite FDG PET score -54, 5 hypometabolic cluster areas at 11 years post first cobalt exposure.

Patient B (polished Zimmer Heritage CoCr stem) revised 9/18 urine cobalt 55.4, composite FDG PET score -78, 9 hypometabolic cluster areas at 17 years post first cobalt exposure.

Patient C (polished Zimmer Heritage CoCr stem) revised 12/18 urine cobalt 14.4, composite FDG PET score -172, 20 hypometabolic cluster areas at 20 years post first cobalt exposure.
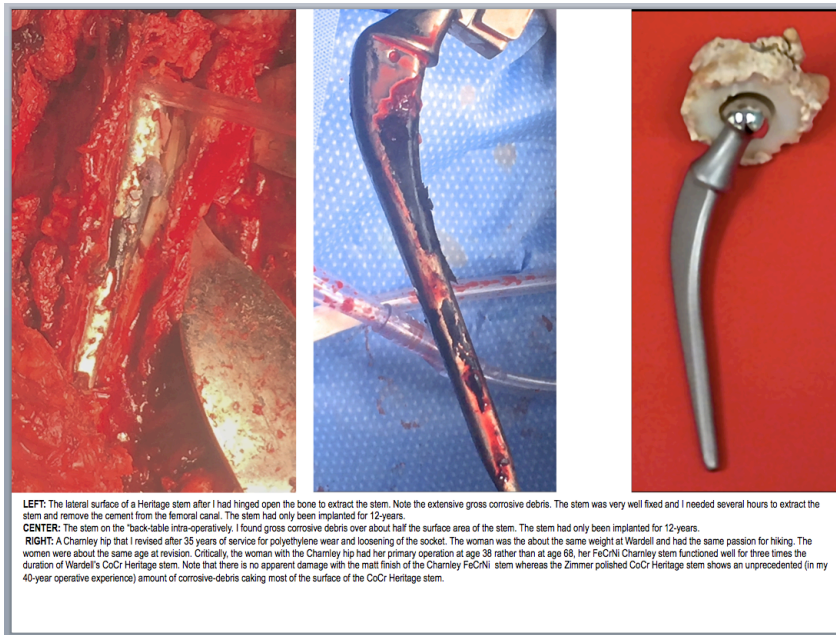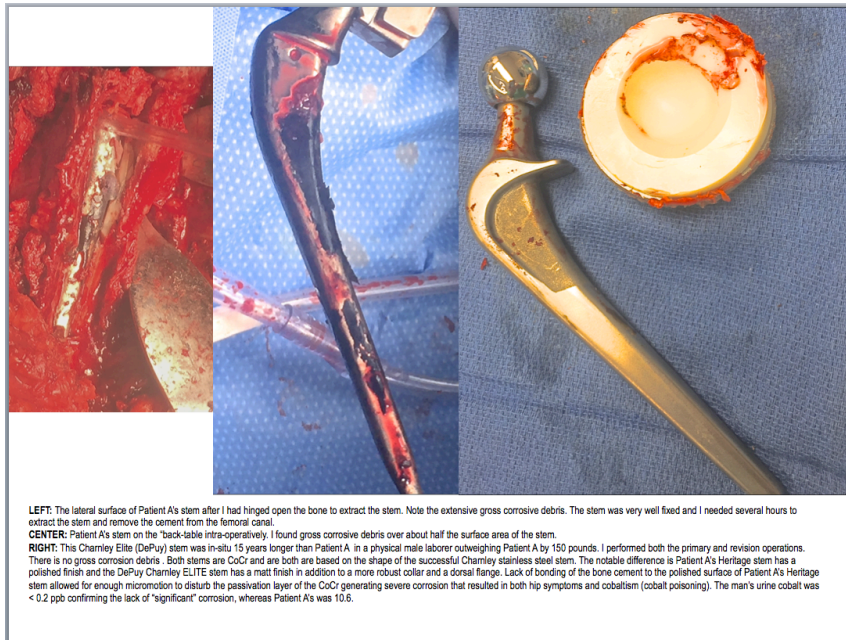
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52   Industry "experts" argue that corrosion is inevitable at the interface between a metallic femoral stem regardless of alloy and that corrosion

53   when it does occur is only "clinically significant" in "rare" cases. Both assertions are unsupported by the medical literature and are counter to my

54   extensive hip revision experience. Millions of Charnley's cemented FeCrNi stems have been implanted. Early in the evolution of Charnley's stem design

55   fatigue fracture of the early "flat-back" variant stem with coincident corrosion of the 316L or EN58J stainless steel alloys were occasionally described.[94]

56   This infrequent complication was remedied by beefing-up the stem, making it stiffer and stronger, and thereby less prone to fatigue failure.[95] Even in the

57   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

58   uncovered when I revised Patients A-C's well fixed CoCr Zimmer Heritage polished stems.[94]

59   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,

60   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

61   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

62   premature implant failure compared to the 4.0% for the Heritage (polished CoCr) at 7-years in a low-demand, elderly, population.[96] The DePuy Charnley

63   Elite CoCr stem (matt finished, robust collar, proximal dorsal flanges) is a "shape-closed" design that limits the micro-motion at the stem-cement

64   interface, the Zimmer Heritage stem (CoCr alloy, polished finish, minimal collar, no dorsal flanges) is a "force-closed" design which allows for stem-

65   cement micro-motion.[97-99] Micro-motion is sine qua non of Mechanically-Assisted-Crevice-Corrosion (MACC), the phenomena that I observed in spades

66   at the time of multiple revisions of Zimmer Heritage stems revised for periprosthetic and systemic cobalt toxicity. Femoral stems with an effective "shape-

67   closed" design (matt-finish, robust collar, dorsal flanges) rarely exhibit "significant" corrosion at the stem-cement interface,[85,96,97] "force-closed" femoral

68   designs such as Zimmer's CoCr Heritage and CPT, DePuy CoCr Ultima stem, Stryker's FeCrNi Exeter stem, and several abandoned TiAlV femoral

69   stems predictably corrode in patients and on the bench.[100-106]

70

4

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

71

LEFT: The lateral surface of a Heritage stem after I had hinged open the bone to extract the stem. Note the extensive gross corrosive debris. The stem was very well fixed and I needed several hours to extract the stem and remove the cement from the femoral canal. The stem had only been implanted for 12-years.
CENTER: The stem on the "back-table intra-operatively. I found gross corrosive debris over about half the surface area of the stem. The stem had only been implanted for 12-years.
RIGHT: A Charnley hip that I revised after 35 years of service for polyethylene wear and loosening of the socket. The woman was the about the same weight at Wardell and had the same passion for hiking. The women were about the same age at revision. Critically, the woman with the Charnley hip had her primary operation at age 38 rather than at age 68, her FeCrNi Charnley stem functioned well for three times the duration of Wardell's CoCr Heritage stem. Note that there is no apparent damage with the matt finish of the Charnley FeCrNi stem whereas the Zimmer polished CoCr Heritage stem shows an unprecedented (in my 40-year operative experience) amount of corrosive-debris caking most of the surface of the CoCr Heritage stem.

LEFT: The lateral surface of Patient A's stem after I had hinged open the bone to extract the stem. Note the extensive gross corrosive debris. The stem was very well fixed and I needed several hours to extract the stem and remove the cement from the femoral canal.
CENTER: Patient A's stem on the "back-table intra-operatively. I found gross corrosive debris over about half the surface area of the stem.
RIGHT: This Charnley Elite (DePuy) stem was in-situ 15 years longer than Patient A in a physical male laborer outweighing Patient A by 150 pounds. I performed both the primary and revision operations. There is no gross corrosion debris . Both stems are CoCr and are both are based on the shape of the successful Charnley stainless steel stem. The notable difference is Patient A's Heritage stem has a polished finish and the DePuy Charnley ELITE stem has a matt finish in addition to a more robust collar and a dorsal flange. Lack of bonding of the bone cement to the polished surface of Patient A's Heritage stem allowed for enough micromotion to disturb the passivation layer of the CoCr generating severe corrosion that resulted in both hip symptoms and cobaltism (cobalt poisoning). The man's urine cobalt was < 0.2 ppb confirming the lack of "significant" corrosion, whereas Patient A's was 10.6.

72

73

74   The Exeter femoral stem (Stryker, Kalamazoo MI) is made of FeCrNi and has a polished finish and is shaped to encourage micro-motion

75 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

76 magnitude that I witnessed in my patients A-C with polished CoCr Zimmer Heritage stems.[101] The Exeter hip outperforms even the Charnley hip in

77 National Joint Registry 15-year survivorship data indicating that although corrosion can occur at the stem-cement interface of a polished FeCrNi stem it

78 is of limited periprosthetic or systemic consequence because the byproducts of FeCrNi corrosion are fundamentally less toxic than those liberated by
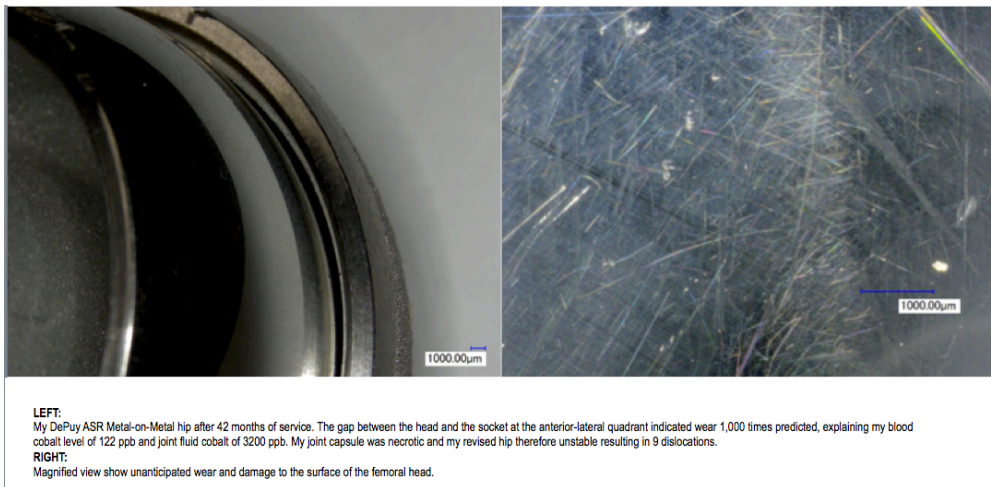
79 corrosion of a CoCr implant.[22,107-116]

80   **CoCr should never be used for a force-closed (polished) femoral stem because cobalt, in excess, is fundamentally toxic to the periprosthetic tissues**

81 **and to distant human organs (central and peripheral nervous system, heart, and thyroid).[20,41,43] It was know at the time of the design and promotion of the**

82 **Heritage CoCr stem[98,117] that polished (force-closed) femoral stems, regardless of alloy, were at risk for corrosion at the stem-cement interface.[106] It was also**
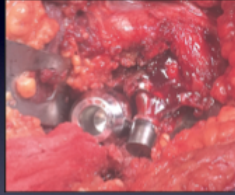
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83 **know then that cobalt is fundamentally toxic to the periprosthetic tissues[20,22,23] and systemically toxic to the human brain, nerves, heart, and thyroid**

84 **gland.[20,41]Although corrosion has been reported with the smooth finished classic Charnley FeCrNi "flat-back" stem[94] and polished FeCrNi dual taper Exeter**

85 **stem[118] it is rarely periprosthetically or systemically toxic because the major constituent the Stainless Steel (FeCrNi) alloy is iron which biologically benign**

86 **compared to cobalt with is the primary element in the CoCr alloy used for Zimmer's polished CoCr Heritage stem.**

87 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

88 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%

89 (by weight) barium sulfate[119] which is an abrasive and magnifies the documented corrosion than occurred at the cement-stem interface of polished "force-closed" stems.

90 Industry's assertion that CoCr metallosis produced by arthroprosthetic implants, when it does occur, only "rarely" produces periprosthetic *Adverse Reaction to*

91 *Metallic Debris* (ARMD) is countermanded by both the literature,[100,103,107,109,120-143] and by my experience as patient,[3,10,11,16] arthroprosthetic revision surgeon and published

92 authority on the periprosthetic and systemic toxicity of CoCr metallosis,[2,13-15,144] and as an advocate for reform of the American Medical-Industrial-Complex.[12,17,19] The

93 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

94 systematic monitoring program including blood cobalt determinations and cross-sectional imaging of the hip.[133,142,145-166]

LEFT:
My DePuy ASR Metal-on-Metal hip after 42 months of service. The gap between the head and the socket at the anterior-lateral quadrant indicated wear 1,000 times predicted, explaining my blood cobalt level of 122 ppb and joint fluid cobalt of 3200 ppb. My joint capsule was necrotic and my revised hip therefore unstable resulting in 9 dislocations.
RIGHT:
Magnified view show unanticipated wear and damage to the surface of the femoral head.

95

96 The Styker (Kalamazoo, USA) ABG and Rejuvenate hips and ESKA (Lubeck, Germany) hip have a modular CoCr neck prone to corrosion producing CoCr

97 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

98 the hip for clinical and sub-clinical pseudotumors.[107,108,167-184]

99

100

101   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

102   mated to a CoCr stem trunnion or a TiAlV stem trunnion.[109-115,180]

103

104

105   Professional awareness that CoCr metallosis is a significant problem that can result in ARMD and systemic toxicity and therefore mandates orthopedic surgeon

106   awareness, monitoring, and if indicated revision surgery is demonstrated by the following tables from the joint recommendations of the *American Academy of Orthopedic*

107   *Surgeons* (AAOS), the American Hip and Knee Surgeon Society (AHKSS), and the Hip Society that was published January 2014.[185] The consensus opinion was specific to

108   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

109   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

110   hip replacement and hip resurfacing.[110,113,115,169,185] A blood cobalt of ≥ 3 ppb places a patient with a Metal-on-Metal hip in the moderate-risk category for a complication of

111   CoCr metallosis[185] whereas the threshold blood cobalt for concern is ≥ 1 ppb for patients with a metal-on-plastic or ceramic-on-plastic hip with a taper joining one or more

112   CoCr components.[169] The reason that arthroprosthetically-produced, systemically-circulated cobalt produced by corrosion is more toxic periprosthetically and systemically

113   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

114   byproducts as opposed to much larger CoCr wear particles.[21,22,46,186-189] Critical literature regarding thresholds of blood cobalt for concern for metal-on-metal hips or hips

115   with metal-on-plastic or ceramic-on-plastic articulations prone to corrosion of modular CoCr parts are both by Kwon.[185,190] At blood cobalt level of 3 ppb is considered to

116   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

117   with modular CoCr component.[185,191] As noted above this reflects the fundamental increased toxicity of CoCr metallosis produced by corrosion at CoCr modular junctions

118   compared to that created by wear of CoCr articular surfaces.[21,43,46,47,186-189]

119

120

121   Risk Stratification for monitoring and revision of patients with Metal-on-Metal hips at-risk for ARMD and Cobaltism (Kwon, JBJS, 2014)

122

'Low' Risk Group Stratification	
Patient factors	Patient with low activity level
Symptoms	Asymptomatic (including no systemic or mechanical symptoms)
Clinical examination	No change in gait (i.e., no limp, no abductor weakness)
	No swelling
Implant type	Small-diameter femoral head (<36 mm) modular MoM THA; hip resurfacing in males <50 with osteoarthritis
Radiographs (2 views ± serial for comparison when available)	Optimal acetabular cup orientation (40° ± 10° inclination for hip resurfacing)
	No implant osteolysis/loosening
Infection work-up (ESR, CRP, ± hip aspiration)	Within normal limits
Metal ion level test (if available)	Low (<3 ppb)
Cross-sectional imaging (if available): these studies include MARS MRI; ultrasound or CT when MRI contraindicated or MARS protocol not available	Within normal limits
Treatment recommendation	Annual follow-up

'High' Risk Group Stratification	
Patient factors	Female with dysplasia (for hip resurfacing)
	Patient with high activity level
Symptoms	Symptomatic
	Severe local hip and/or mechanical symptoms
	Systemic symptoms
Clinical examination	Change in gait (i.e., limp)
	Abductor weakness
	Swelling
Implant type	Large-diameter femoral head (≥36 mm) modular or nonmodular MoM THA
	Recalled MoM implant
Radiographs (2 views ± serial for comparison when available)	Suboptimal acetabular cup orientation
	Implant osteolysis/loosening
Infection work-up (ESR, CRP, ± hip aspiration)	Within normal limits
Metal ion level test	High (>10 ppb)
Cross-sectional imaging (MARS MRI; ultrasound or CT when MRI contraindicated or MARS protocol not available)	Presence of abnormal tissue reactions with involvement of surrounding muscles and/or bone
	Solid lesions
	Cystic lesions with thickened wall
	Mixed solid and cystic lesions
Treatment recommendation	Consider revision surgery

123

Sensitivity and Specificity of Metal Ion Level in Predicting Adverse
Local Tissue Reactions Due to Head-Neck Taper Corrosion in
Primary Metal-on-Polyethylene Total Hip Arthroplasty

Young-Min Kwon, MD, PhD [*], John MacAuliffe, MEng, Paul G. Arauz, PhD,
Yun Peng, PhD

Department of Orthopaedic Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

124

125 **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**
126 **Co/Cr ratio >2 thresholds provide evidence based practical information for surgeons when interpreting metal ion levels in MoP THA patients for clinically relevant**
127 **head-neck taper corrosion.[191]**
128

129   Between 2010 and 2015 Dr. Thomas Mego (chair Providence Alaska Medical Center Department of Pathology) and I reviewed the histopathology of 48-failed

130 Metal-on-Metal and Metal-on-Plastic hips that were revised because of periprosthetic and systemic complications of CoCr metallosis. Histopathologic findings typically

131 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

132 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

133 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

134 histologic picture of ARMD is highly variable; metallosis and necrosis are generally the most consistent microscopic findings. Prominent ALVAL lesions appear in a minority

135 of cases, generally those patients that respond in an allergic fashion chrome-cobalt metallosis. [20,148,192-195]

COBALT TOXICITY AFTER McKEE HIP ARTHROPLASTY

136 D. ANTHONY JONES, H. KEITH LUCAS, MICHAEL O'DRISCOLL, C. H. G. PRICE and
B. WIBBERLEY, BRISTOL, ENGLAND

Results of histological examination
Tissues removed from the hip joints of Cases 1, 2, 3, 4
and 6 were studied. The only constant feature of note
was widespread necrosis of bone, joint capsule and
adjacent muscle, usually but not invariably without any
137 diffuse or focal inflammatory reaction (Figs. 22 to 25),

and accompanied by a great deal of granular fibrinoid
or collagen debris.
    These changes are by no means specific, and apprecia-
tion of their extent, which when wide may suggest a
cytotoxic effect, must depend upon the range of tissues
sampled by the operating surgeon and the zeal of the
examining pathologist. Minor unremarkable inflamma-
tory changes were noted and in two cases scattered tiny
138 round or oval birefringent particles of an unknown nature

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140

8

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141   My clinical series indicated and "at-risk" hips extend beyond those with a modular cobalt-chrome neck stem[108,171-174,176,178,179,183,184,196,197] or a hip with a metal-on-

142   metal articulation.[3,20,25,26,124,138,139,165,166,193,194,198-216] My first appreciation of this was February of 2013 when I revised a series of patients with severe corrosion the Zimmer's

143   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

144   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

145   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

146   used.[109-111,113-115,217] **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**

147   **early 2013, all revisions were for symptomatic ARMD, with severe periprosthetic tissue damage, and all were because of defective design of stems or tapers**

148   **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

149   metallosis to the periprosthetic tissues can be severe with minimal clinical symptoms resulting in an unsalvageable problem.[191,218]
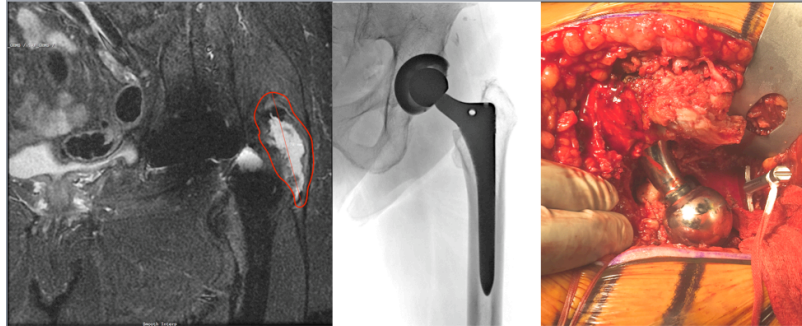
LEFT: MSRI of left hip of sedentary 71 year-old 132 woman with lateral hip pain and weakness 9 years post hip replacement with Zimmer TiAlV stem and 32 mm CoCr VerSys head with 12/14 taper. Her surgeon in New Jersey was treating her with cortisone injections and he did not check a cobalt level. She moved to Alaska and presented to my clinic with a severe limp because of left hip weakness. The image show a cobalt related pseudotumor with rupture of the hip abductor tendons. Her blood cobalt was 11.
CENTER: Her radiographs show well-positioned, stable, osteointegrated implants, no plastic wear, and no osteolysis.
RIGHT: Intra-operative revision photo, I have partially disengaged the taper to the show the gross corrosive debris. The trochanter is "bald" because of rupture of the hip abductor tendons. The appearance of the periprosthetic tissues is similar to Wardell. Fortunately for Wardell we revised her hip before her hip abductor tendons ruptured.

150

151   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

152   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

153   and forth.

Final Diagnosis
```
    RIGHT HIP JOINT REVISION TISSUE:
    -- DISEASE PROCESS: Detritic synovitis.
    -- ACUTE INFLAMMATION: Focal, maximum four neutrophils per hpf.
    -- CHRONIC INFLAMMATION: Present, mild-moderate, lymphohistiocytic.
      - ALVAL (Aseptic Lymphocytic Vasculitis-Associated Lesion): Not identified.
    -- MONONUCLEAR HISTIOCYTES: Present, patchy, mild-moderate.
      - METAL PARTICLES: Present, mild.
    -- MULTINUCLEATED GIANT CELLS: Present, focal.
      - FOREIGN MATERIAL: Present, focal.
    -- NECROSIS: Present, fibrinoid, focally calcified.
    -- BONE CHIPS: Not identified.
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LEFT TOP: Explanted Zimmer Durom CoCr head and CoCr Head socket and modular Zimmer Kinnectiv TiAlV femoral neck.
CENTER TOP : The bore of the CoCr Durom 12/14 taper shows severe damage with loss of material and corrosive debris that resulted in symptomatic ARMD and brain atrophy by MRI with symptoms of imbalance, peripheral neuropathy and cognitive decline. The patient was male, moderately physically active, and was 65 and 170 pounds at time of revision surgery. The hip failed because of CoCr metallosis with ARMD and cobaltism after only ten years of service.
RIGHT BOTTOM: This patient's histopathologic, ALVAL is not an common histopathologic finding in clinically significant CoCr related ARMD. It is present in my experience in only a minority of cases and my experience is mirrored in the literature.

154
155

156 My appreciation that arthroprosthetically generated cobalt is neurotoxic has passed peer review muster many times,[3,11-13,15-18,144] and even passed conflict-of-

157 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

158 consultants [17] allowing for our work using the Cobalt-Symptom-Inventory screen at-risk patients for arthroprosthetic cobaltism and FDG-PET-CT-Brain-Imaging to confirm

159 the diagnosis to be presented at the annual meeting of the AAOS in 2018 (appendix A).

160 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

161 experienced it as a patient.[3,10,11,16,219] Cobalt encephalopathy manifesting as cognitive decline was first described by Jordan in 1997 from chronic cobalt industrial

162 exposure.[74] Since the 1960s we have known that iatrogenic deafness, blindness, thyroid abnormalities, and heart failure results when cobalt chloride is taken by mouth, as

163 it was to treat anemia, a practice abandoned by 1980 because of its adverse risk to benefit ratio.[41,42,60-64,220,221] Acute industrial cobalt exposure results in death, heart failure,

164 deafness, blindness, and thyroid abnormalities.[41,73,222] The fatigue and disabling mood disorder I experienced when my blood cobalt was 80X that considered safe in

165 industry has now been described to be a common early feature of those suffering from arthroprosthetic cobaltism.[128,132,133,146]

166 ### 3. Industry's Misinformation Campaign is confounding remediation of Arthroprosthetic Cobaltism

167 Industry financed retrospective anti-science argues that a blood cobalt level of 6 ppb (6X that thought safe in industry)[223] from arthroprosthetic cobalt-chromium

168 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) 2013

169 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)

170 for study period of 15, 30, and 90 days with monitoring of blood cobalt, blood counts, hearing, sight, cardiac and thyroid function.[224-234] Cardno ChemRisk LLC fused this

171 study with their theoretical model to calculate blood cobalt levels of 11 dialysis patients treated 8 weeks with oral cobalt-chloride for anemia in one study (Bowie, 1975),[235]

172 and 6 patients treated for 90 days (Duckham, 1976)[62]. Then Cardno ChemRisk treated 10 subjects with an oral cobalt laced dietary supplement for 90-days, at 90-days the

173 5 men had an average blood cobalt level of 20 ppb and the 5 women had a mean blood cobalt level of 53 ppd.[228] With impenetrable logic Cardno ChemRisk states that

174 blood cobalt of < 300 ppb should not cause toxicity in patients exposed to arthroprosthetically generated CoCr metallosis.[228]

175 Neither Cardno ChemRisk's 10 subjects[228] nor the 17 dialysis patients treated a half century ago[62,235] contribute any meaningful information concerning

176 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

177 human body's first line of defense against toxics and most all that is absorbed is excreted rapidly in the bile and urine, having little opportunity to enter the cells of the heart,

178 brain, nerves, and thyroid gland which is where cobalt's metabolic toxicity is expressed. [41,43] Furthermore with 17 renal failure patients were dialyzed 3 times a week

179 reducing their serum cobalt concentrations to nil.[62,235] The CoCr metallosis produced by corrosion or wear of an orthopedic implant is nanoparticulate, bypasses the liver,

180 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

181 gastrointestinal tract.[21,43,46,47,186,188,189] Only 16 of the 27 dialysis patients reported to have tolerated large doses of oral cobalt completed a full 90-days of treatment, Cardno

182 ChemRisk ignores that 3 of the 11 patients reported by Bowie developed deafness and one died shortly after the trial from heart failure.[228,235,236] The duration of exposure to

183 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.[62,188,224-

184 235,237] Furthermore, the 17-dialysis patients that Cardno ChemRisk theorizes tolerated high blood cobalt (three actually developed deafness) underwent dialysis trice weekly

185 and therefore were not exposed incessantly to cobalt as are patients exposed through a malfunctioning prosthetic implant.[62,235]

186 Contradicting Cardno ChemRisk's mercenary theoretical work there are now a plethora of arthroprosthetic cobaltism case reports showing that when blood

187 cobalt exceeds 100 ppb extreme illness results in death, heart transplantation, psychiatric decompensation, blindness, deafness, thyroid failure, and severe peripheral

188 neuropathy.[3,126-132,134,238-241] Additionally, there are now multiple case series and case reports indicating that serious systemic illness can result once blood cobalt levels are

189 ≥ 7 ppb from an arthroprosthetic source.[3,15,107,133,146,147,242-244] These case reports likely represent a minute fraction of those patients actually experiencing arthroprosthetic

190 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

191 cobalt myocardial pathology (CMP): [244]

> Cobalt-related CMP has been reported in a relatively very low number of cases of metal hip arthroplasty. However, it may be the tip of the iceberg, as for every published case report, there are likely hundreds of similar severity unrecognized or recognized and not reported cases. A delay in diagnosis may lead to significant morbidity

192

193

194   Umar's conclusion is an echo of that of Gessner's systematic review of the literature on Arthroprosthetic Cobaltism in 2015:[13]

DISCUSSION

Our study identified 25 cases of reported arthroprosthetic cobaltism that occurred since the initial report during 2001. Case reports have accelerated recently and have occurred from 8 countries. Despite the relatively widespread distribution, all but 2 US cases have originated from Alaska, suggesting the true scope of the problem has gone largely unreported. This likely has resulted from a combination of several factors including the slow onset, the protean symptoms that may mimic many different conditions, lack of uniform screening strategies for at-risk patients, and lack of awareness of arthroprosthetic cobaltism among surgeons and primary care physicians.

195

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

197   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

198   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

199   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

200   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

201   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

202   article in a AAOS-supported journal suggesting that metal-on-metal hips were safe.[245] It was not until 2014 that a consciences opinion of the AAOS, Hip and Knee society,

203   and the American Association of Knee and Hip Surgeons recommended a monitoring suggestion for the million Americans implanted with no longer marketed metal-on-

204   metal hips.[185] These recommendations are seldom systematically followed by American orthopedic surgeons and the FDA continues to post only vague recommendations

205   for monitoring patients with no longer marketed metal-on-metal hips.[246] Delayed inaction by the FDA concerning the now well documented periprosthetic and systemic

206   cobalt-chromium metallosis has harmed hundreds of thousands of Americans.[12] Systematic literature review by Gessner indicates that arthroprosthetic cobaltism is likely a

207   spectrum illness with a large American at-risk population.[13] My exclusion from the 2019 expert panel gives me cause for concern that the FDA's pattern of placing the

208   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

209   AAOS, Orthopedic Journals, and the committees that accept presentations for Orthopedic meetings confirms that conflict-of interest is the driving force of commercial,

210   academic, and regulatory malfeasance leading to the under-recognition, propagation, and delayed remediation of a silent epidemic of periprosthetic and systemic

211   complications of arthroprosthetically generated cobalt-chromium metallosis with an American at-risk population of 20 million.

212   5. Industry's willful blindness to Arthroprosthetic Cobaltism is compounding the problem

213   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

214   its bellwether trial Kransky v J&J concerning DePuy ill-starred MoM ASR hip … per Bloomberg:

215

$5 Million

Paustenbach said his firm ChemRisk Inc. has billed DePuy at least $5 million over the past 18 months. He was part of a team of 40 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.

216
217   Paustenbach's prior retrospective "pseudoscience" concerning asbestos and his mercenary behavior to his critics has resulted in the resignation of the entire

218   editorial board of a respected Occupational and Environmental Toxicology Journal. It appears that Paustenbach's companies Cardno ChemRisk LLC and Exponent exist

219   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

220   ChemRisk LLC and Exponent are paid exorbitant fees. Most concerning is that the medical journal publishing behemoth Francis & Taylor appears to willing to legitimize

221   Cardno ChemRisk LLC and Exponent's "research" by strong-arming editorial boards to publish Exponent's and Cardno ChemRisk's work:

222   https://www.propublica.org/article/sudden-shift-at-a-public-health-journal-leaves-scientists-feeling-censored
223

224   Any legitimate research effort into the known deleterious effects of arthroprosthetically generated cobalt could not have missed the 1981 US government

225   commissioned tome on Cobalt toxicity edited by Smith and Carson[41] and the seminal 1975 report of periprosthetic and systemic cobalt toxicity in a series of patients with

226   periprosthetic CoCr metallosis from McKee-Farrah Metal-on-Metal hip replacement.[20] The mercenary literature produced by Paustenbach and his co-conspirators fails to

227   cite either.[188,224-234,237]

228
229   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
230   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]
231
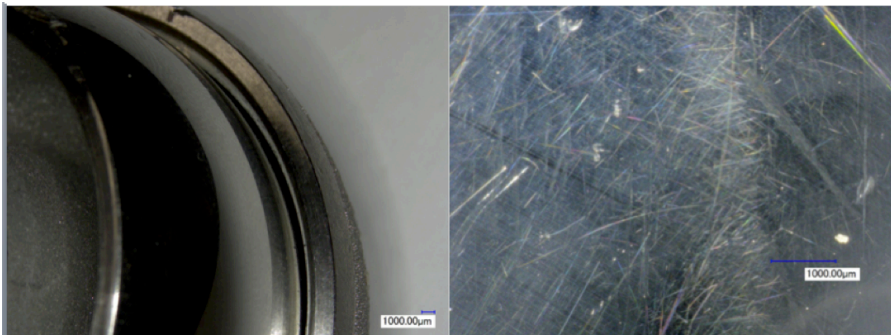
LEFT:
My DePuy ASR Metal-on-Metal hip after 42 months of service. The gap between the head and the socket at the anterior-lateral quadrant indicated wear 1,000 times predicted, explaining my blood cobalt level of 122 ppb and joint fluid cobalt of 3200 ppb. My joint capsule was necrotic and my revised hip therefore unstable resulting in 9 dislocations.
RIGHT:
Magnified view show unanticipated wear and damage to the surface of the femoral head.

232

233   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

234   poisoned.[20,41] 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

235   metal poisoning rather than *mood disorder not otherwise specified*.[11] My blood-cobalt level then was 122 times that indicating unsafe industrial exposure,[3,10,11,16] yet was

236   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]

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

238   cobalt level of < 300 ppb from arthroprosthetically generated CoCr metallosis is safe,[228,232] Gessner and two rising second-year-medical-students found 25 well-documented

239   cases of arthroprosthetic cobaltism:[219]

A Systematic Review of Systemic Cobaltism After Wear or Corrosion of Chrome-Cobalt Hip Implants

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240

Objectives: We sought to synthesize data on systemic arthroprosthetic cobaltism, a recently described syndrome that results from wear or corrosion of chrome-cobalt hip components.

Methods: We conducted a systematic literature review to identify all reported cases of systemic arthroprosthetic cobaltism. To assess the epidemiologic link between blood cobalt levels (B[Co]), we developed a symptom scoring tool that evaluated 9 different symptom categories and a category of medical utilization.

Results: We identified 25 patients reported between 2001 and 2014 with a substantial increase in case reports over the past 3 years. Symptoms were diverse and involved the hip (84%), cardiovascular system (60%), audiovestibular system (52%), peripheral motor-sensory system (48%), thyroid (48%), psychological functioning (32%), visual system (32%), and the hematological, oncological, or immune system (20%). The mean latency from implantation to presentation or revision was 41 months (range, 9–99 months). The mean B[Co] was 324 µg/L and 4 patients had levels less than 20 µg/L. The B[Co] but not blood chromium level was highly associated with a quantitative measure of overall symptom severity (r^2, 0.81; $P < 0.001$). Mean B[Co] and symptom scores were substantially higher in patients with revisions of failed ceramic-on-ceramic prostheses than those with primary metal-on-metal prostheses.

Conclusions: Systemic arthroprosthetic cobaltism is an increasingly recognized complication of wear or corrosion of chrome-cobalt hip implants, may involve a large number of organ systems, and may occur with relatively low B[Co]. There is an urgent need to better define the overall scope of the problem and to develop screening and management strategies.

Key Words: arthroplasty, cobalt, cobaltism, hip, hip replacement

(*J Patient Saf* 2015;00: 00–00)

241

242   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

243   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

244   elevation in blood cobalt level.[219] My clinics ongoing work screening patients with any CoCr arthroprosthetic implant indicates that sensitive individuals exposed to

245   arthroprosthetically generated cobalt may develop neurologic symptoms and significant brain hypometabolism by FDG-PET-Brain-Scan once their blood cobalt level equals

246   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

247   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

248   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

249   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

250   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

251   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,

252   abnormal brain volumes, and abnormal heart function, had a mean blood cobalt level 170 times[247] lower than Paustenbach's safety threshold of 300 ppb.[228]

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

254   In my 40-year surgical experience with hip arthroplasty, surgery; clinically significant, gross corrosion, resulting in periprosthetic

255   and systemic toxicity, is almost never seen in some implants yet is commonly seen in others. Clinically significant corrosion resulting in

256   periprosthetic or systemic toxicity is a design and materials issue: Largely preventable by optimal material selection and prosthetic

257   design. Systematic study for my practice over the past 4 years indicates that Zimmer's 12/14 and Stryker's V40 CrCo femoral heads

258   commonly corrode over time. Many patients that experiencing this problem have periprosthetic and systemic morbidity sometimes severe

259   enough to warrant revision hip surgery to replace corroding or wearing CrCo parts with safe plastic, ceramic, TiAlV, or FeCrNi

260   alternatives.

261
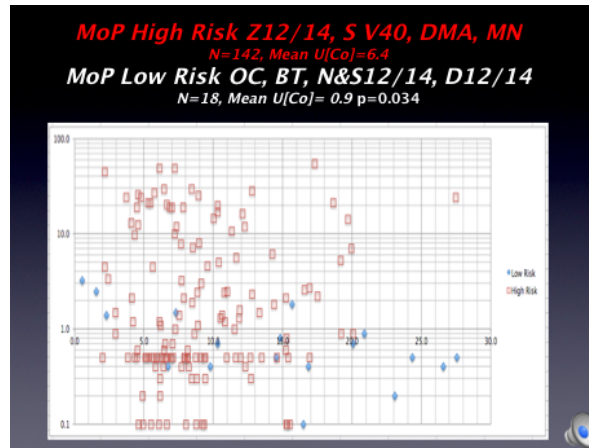
262 The Y-axis is urine cobalt in ppb; the X-axis is years of hip implantation. The blue diamond data-points with urine-cobalt of < 1 ppb are nearly all Osteonics' C-
263 Taper LFIT CoCr head on TiAlV alloy uncemented stem trunnions

264

265 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
266 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[249-251]
267

268 Whether or not that corrosion will be periprosthetically or systemically adverse hinges on at least four factors: the toxicity of the

269 corrosion byproducts (periprosthetically and systemically), the sensitivity of the patient to the corrosion byproducts (periprosthetically and

270 systemically), the biomechanical consequences of corrosion, and the severity and extent of the process. Severe corrosion commonly

271 occurs at the TiAlV stem-cement interfaces resulting in pain and early loosening of components that lead to the abandonment of that

272 alloy for cemented stem application but I am not aware that either systemic toxicity or hypersensitivity has been reported from TiAlV

273 corrosion debris but there has been at least one case of Vanadium neurotoxicity from wear of a TiAlV acetabular shell by ceramic.[105,106]

274 [252] Minor corrosion is commonly noted on the surface of explanted FeCrNi Exeter polished stems but this is generally without

275 periprosthetic or mechanical consequence other than rare clinically significant immune reaction due to the nickel exposure.[104,253] The

276 severe corrosion I found the cement-stem interface of Zimmer polished CoCr Heritage stems in patients A-C did not result in radiographic

277 or clinical loosening of the stems (the stems were difficult to extract) but the cobalt and chromium liberated by the corrosion resulted in

278 symptoms at the hips and systemic poisoning of the patients confirmed by FDG-PET brain scans. A series of 13 failed Zimmer CPT

279 polished CoCr stems revised for progressive hip symptom was recently reported, all had gross corrosion at the stem-cement interface.[100]

280 DePuy's polished CoCr Ultima stem frequently fails by the same mechanism, particularly when mated to a metal-on-metal articulation.[103]

281   Periprosthetic CoCr metallosis produced by wear or corrosion of CoCr articular components (heads or sockets) or at the taper

282   junctions (Figure 1) of articular and non-articular implants (stems, necks, or trays) may result in painful or painless periprosthetic tissue

283   inflammation, necrosis and pseudotumor formation.[3,140,141,196,254,255] Collectively, these radiographic findings and symptoms are called

284   Adverse-Reaction-to-Metal-Debris (ARMD).[141] Patients may also react in an immune fashion to CoCr implants by direct attack of

285   leukocytes resulting in ARMD and systemically circulated cobalt in the absence of significant implant wear or taper corrosion.[256] The

286   histopathology of patients with CoCr symptomatic ARMD is highly variable.[124,203,257,258] In my experience, and in that reported by others,

287   patient with an hyper-acute presentation with months of implantation are more likely to have florid inflammatory infiltrates (ALVAL lesions)

288   whereas the majority of patient that develop ARMD have an indolent presentation and generally a mixed histopathologic response of mild

289   chronic inflammation, a macrophage response, varying degrees of tissue necrosis with ulcerations of the synovial

290   membrane.[20,192,194,195,257,259]

291   Most of the publications addressing the symptoms, laboratory abnormalities (elevated blood and urine cobalt levels), imaging

292   findings, gross and histopathologic findings at revision surgery of CoCr periprosthetic metallosis report on hip resurfacings failed due to

293   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

294   junctions.[141-143,258,260-268] The notable failure of the Styker Rejuvenate with its modular CoCr neck that was prone to corrosion at the distal

295   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

296   head informed me that ARMD and cobaltism were not unique to Metal-on-Metal articulations. The Rejuvenate was a popular implant in

297   Anchorage; fortunately I never implanted one but revised many. Because the implant was formally recalled by Stryker July of 2012 and

298   the recall program recommend a systematic screen program for cobalt levels and imaging of any symptomatic implant I became aware

299   that the patients with failed Rejuvenate implants were experiencing the same problems as the patients with failed Metal-on-Metal hips. If

300   anything the patient's with failed Rejuvenates often had more florid ARMD than the MoM patients (by symptoms) although their blood and

301   urine cobalt levels were generally an order of magnitude less that those MoM patients whose metallosis related to excessive wear of their

302   articular surfaces. Other investigators have confirmed that corrosion generated cobalt-chrome metallosis (tapers) being more toxic

303   periprosthetically than wear generated cobalt-chrome metallosis (edge loading of metal-on-metal hip articulations).[2,169,191]

304   Clinically, cemented FeCrNi stems with Monoblock or Modular FeCrNi heads articulating on polyethylene have superior

305   survivorship in single institution series and in the National Joint Registry of England-Wales in the form of the matt finished Charley stem

306   or the polished Exeter stem compared nearly all other contemporary bearing couples and femoral stem materials. The Charnley and

307   Exeter hips utilizing FeCrNi stems and head articulating on either cross-linked or standard polyethylene are among the few contemporary

308   hips that meet the NICE criteria of an annualized failure rate of < 0.5% per year. [82,90,269,270]

309   Systemic cobalt-toxicity (cobaltism) most commonly affects the nervous, endocrine and cardiovascular systems. Profound

310   deafness, blindness, peripheral neuropathy, thyropathy, polycythemia, cardiac failure, and death may result in extreme cases.[3,13,20,41-43]

311   Reports of such severe toxicity are limited to two circumstances: revision of a fractured ceramic hip implant to a CoCr femoral head, or

312   when a CoCr ball and CoCr socket articulate (Metal-on-Metal-Hip).[13] The incidence of the former is rare compared to the latter: about 2

313   million Metal-on-Metal-Hips were implanted.[12,13,271] A subtler presentation of neurologic, psychiatric, and constitutional maladies, easily

314   confused with aging, and similar to the vocational manganese toxicity, results from nominal cobalt exposure from wear or corrosion of

315   modular CoCr implants, or CoCr articular surfaces.[1,3,13,107,140,146,255,272]

316   F[18]DG-PET-CT-Brain-Scan has become instrumental in early detection and monitoring of neurodegenerative disease and

317   neurotoxin exposure.[273-278] Visual interpretation of SPECT and PET imaging was described in 1991 to identify regions of brain injury

318 resulting from vocational pesticide and solvent exposure.[278] Subsequently, FDA approved software was developed that quantitatively

319 compares patient F[18]DG-PET-CT-Brain-Scan data to age-gender norms assigning a T-score to 47 cluster-regions.[279] Such software

320 provides a reproducible and objective dataset without the inter-observer variability or basis inherent with the earlier technology.[278,279]

321 **Patient Vignettes**

322 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

323 new onset hip pain and weakness, bilateral restless leg syndrome, difficulty sleeping, sleep apnea, fatigue, exertional-dyspnea, deafness, and

324 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-

325 MRI confirmed ARMD including incomplete detachment of the gluteus medius tendon from the greater trochanter.   Initial F[18]DG-PET-CT-Brain-Scan

326 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

327 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

328 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

329 with 6 hypometabolic cluster-regions). Post-revision blood and urine cobalt fell to 0.5 and 2.5 ppb.

330 Patient 2: 67 year-old retired businesswoman with 12-year history of left CoCr Pinnacle Metal-on-Metal-Hip (DePuy, Warsaw IN) presented

331 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

332 3/14. Metal suppression MRI of hip confirmed ARMD.   Initial F[18]DG-PET-CT-Brain-Scan showed no structural abnormalities with 134 hypometabolic

333 regions with summed score of -381.7 with 28 hypometabolic cluster-regions. The patient was treated with oral OTC N-acetyl-Cysteine, [280] and revision of

334 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

335 head at revision-surgery and the periprosthetic tissue was inflamed and thickened, joint-fluid-cobalt was 160 ppb. At 13 months post-revision repeat

336 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.

337 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-

338 Dual-Mobility" (Stryker, Kalamazoo MI) articulation.[255] These components replaced a recalled Rejuvenate stem (Stryker, MI) that utilized a modular CoCr

339 neck, five years previously, because the patient had symptomatic cobaltism, ARMD, and blood-cobalt of 19 ppb.   After initial resolution of hip and

340 neurologic symptoms blood-cobalt and urine-cobalt climbed to 1.5 and 9.9 ppb, and the patient's hip, neurologic, cardiac symptoms reoccurred.

341 Cobaltism-Symptom-Inventory-Score was 7/14. CT imaging showed mild left temporal-parietal sulci prominence from an IED explosion that excluded

342 him from the primary study group. Operative findings noted corrosion on the backside of CoCr Dual-Mobility-Acetabular-Liner, and periprosthetic fluid

343 had cobalt of 220 ppb. Pre-revision F[18]DG-PET-CT-Brain-Scan found 40 hypometabolic regions with score of -96.6 and 4 hypometabolic cluster-regions.

344 8-months post-revision repeat scan showed 19 hypometabolic regions, a score of -42 and 2 hypometabolic cluster-regions. Blood-cobalt and urine-

345 cobalt declined to < 0.2 and 0.2 ppb.

346 Patient 4: 77 year-old retired teacher with right Metal-on-Plastic-Hip (Zimmer, IN) of 9 years duration presented with progressive hip pain,

347 fatigue, forgetfulness, retinopathy, and decreased reading speed and comprehension. Screening Cobaltism-Symptom-Inventory-Score was 5/10 and

348 blood-cobalt and urine-cobalt were 4.9 and 10.6 ppb. Metal-suppression-hip-MRI showed a cystic ARMD. Initial F[18]DG-PET-CT-Brain-Scan revealed no

349 structural abnormality with 25 hypometabolic regions with summed score of -54 and 5 hypometabolic cluster-regions, two years later a follow-up scan

350 showed progression with 25 hypometabolic regions with summed score of -56.4 and 8 hypometabolic cluster-regions. Because of progression of hip

351 pain, neurologic and constitutional symptoms, and progressive brain hypometabolism by F[18]DG-PET-CT-Brain-Scan revision surgery was elected. The

352 cemented CoCr Heritage stem (Zimmer, Warsaw IN) was highly corroded**,** and the periprosthetic tissues were inflamed and thickened, and

353 periprosthetic 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

354 pain, neurologic and constitutional symptoms have resolved.

355

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Dr. Tower's Briefing to Dr. Raj Rao, Chairperson FDA Medical Devices Advisory Committee
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932   # Appendix

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935   ## Cobalt Poisoning by Joint Replacement

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938   ## Stephen S. Tower, MD

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