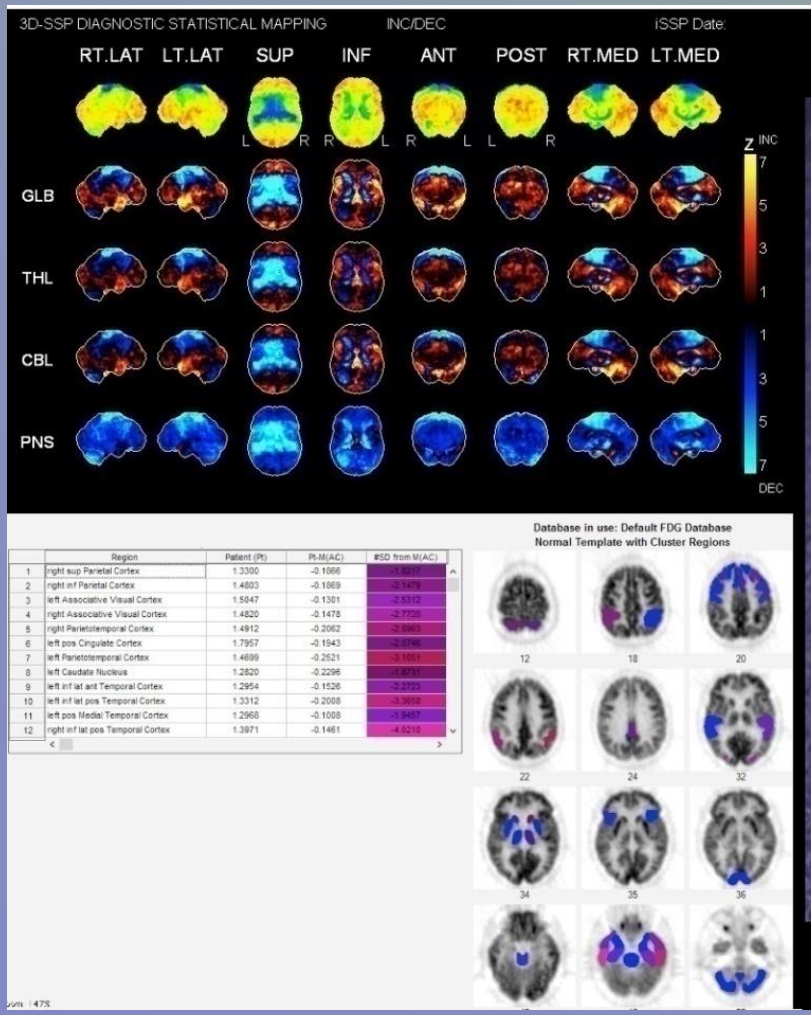
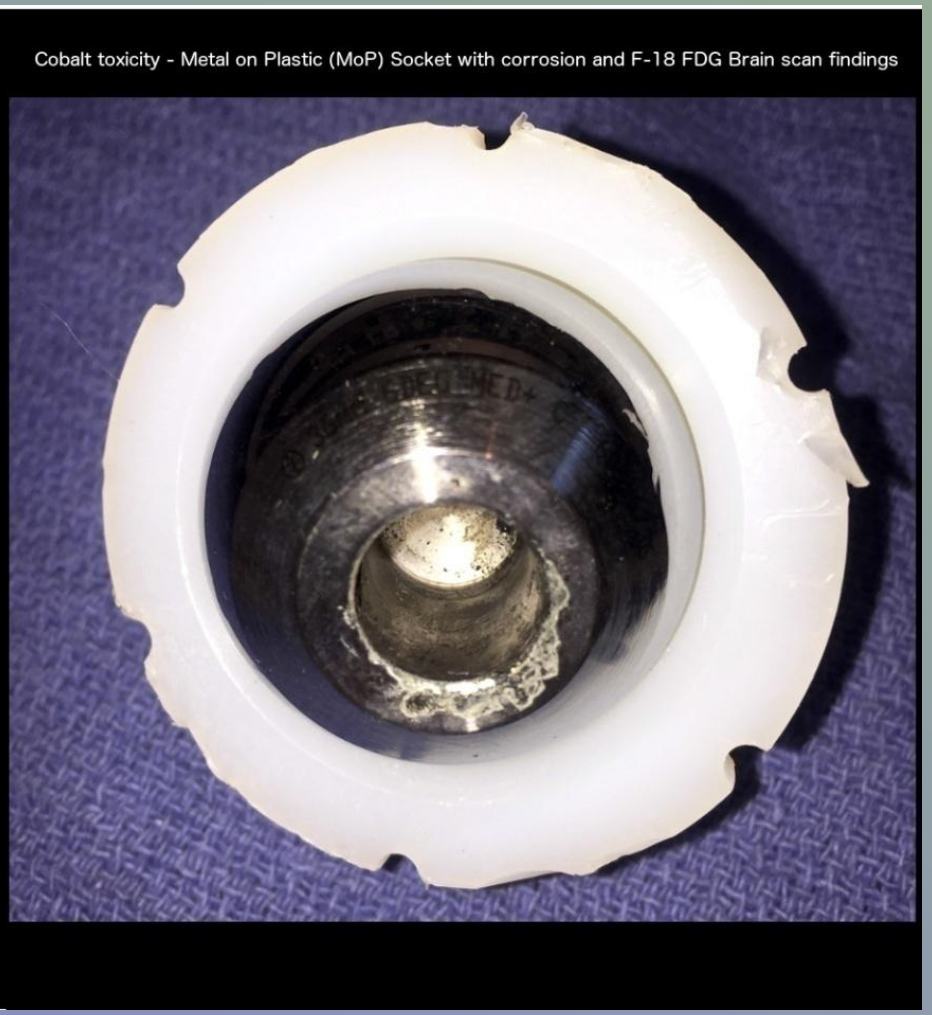
PET Brain Imaging in Cobalt Induced Chronic Toxic Encephalopathy Associated With Chromium Cobalt Hip Implants





Clarke's Three Laws

1. When a distinguished but elderly scientist states that something is possible, he is almost certainly right. When he states that something is impossible, he is very probably wrong.

2. The only way of discovering the limits of the possible is to venture a little way past them into the impossible.

3. Any sufficiently advanced technology is indistinguishable from magic.

Today we will focus on the last two of Arthur C. Clarke's laws, especially the last. This echoes the sentiment by Charles Fort in *Wild Talents….* "...a performance that may some day be considered understandable, but that, in these primitive times, so transcends what is said to be the known that it is what I mean by magic."

Or…. From Muppet Labs and Dr. Honeydew… "where the future is being made today."

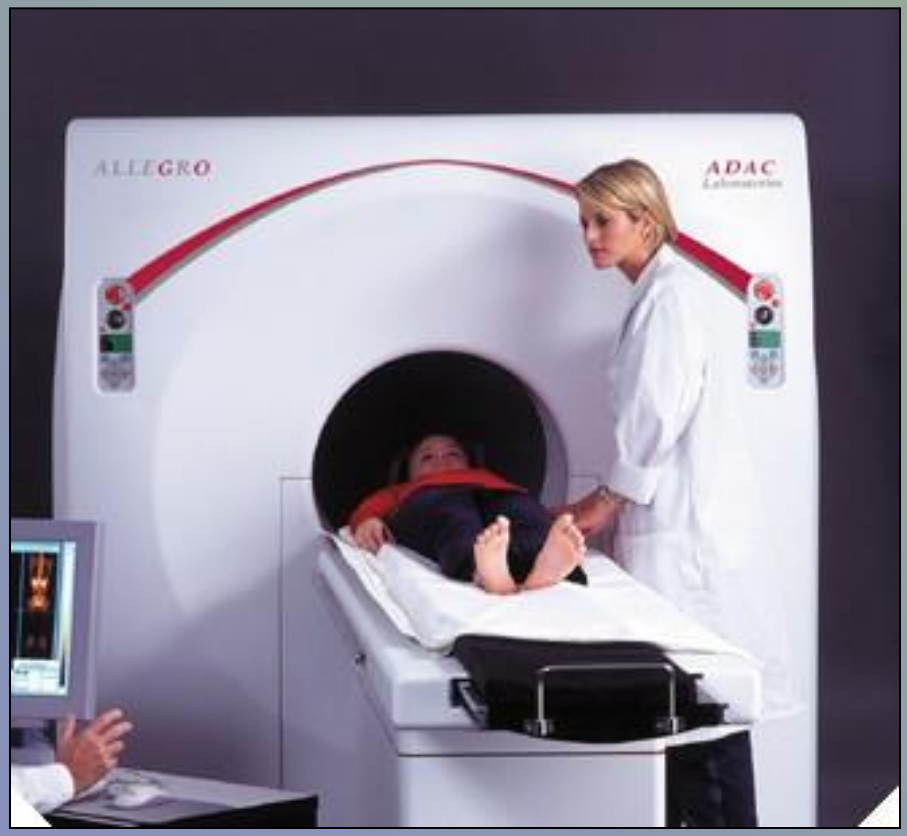
In 1966, NBC debuted a science fiction program called Star Trek.

This introduced the Starship Enterprise, a faster than light speed space craft, powered by the most efficient matter to energy conversion in the universe….. matter-antimatter reaction.

While the Starship Enterprise is still science fiction, its warp engines' power source is used daily throughout the world to diagnose cancer, heart and brain disease……

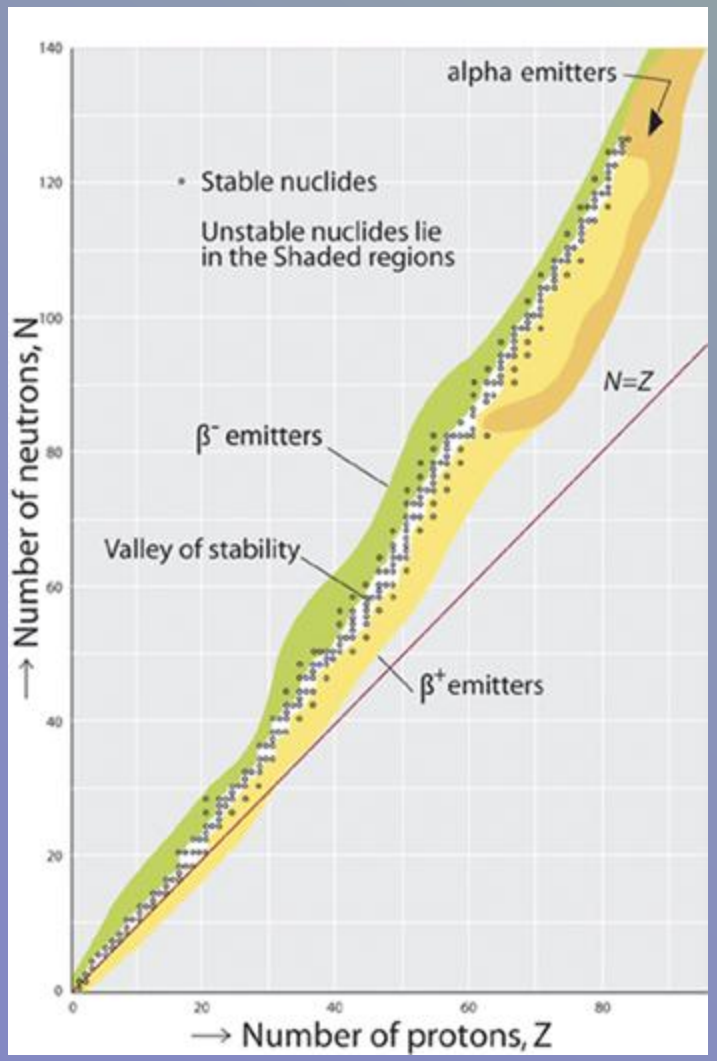
The Positron Emission Tomography (or "PET") Scanner

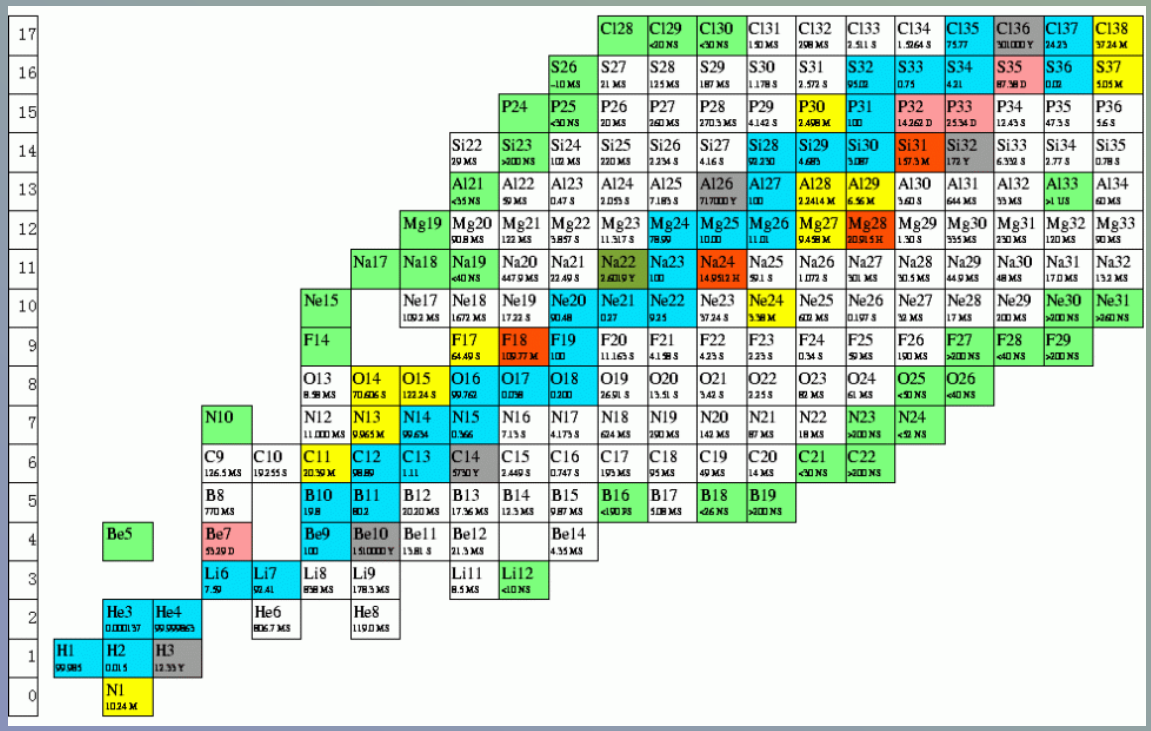
- PET images are essentially CT images of tissue metabolism.
- Like conventional nuclear medicine, PET involves radioisotopes, but ones based on positron emitting radiopharmaceuticals.
- Imaging can be of the specific isotope (such as F-18), the isotope attached to a drug or the isotope incorporated into the drug to see where it goes or how it interacts.



A Brief Exploration of Physics – Magic 101

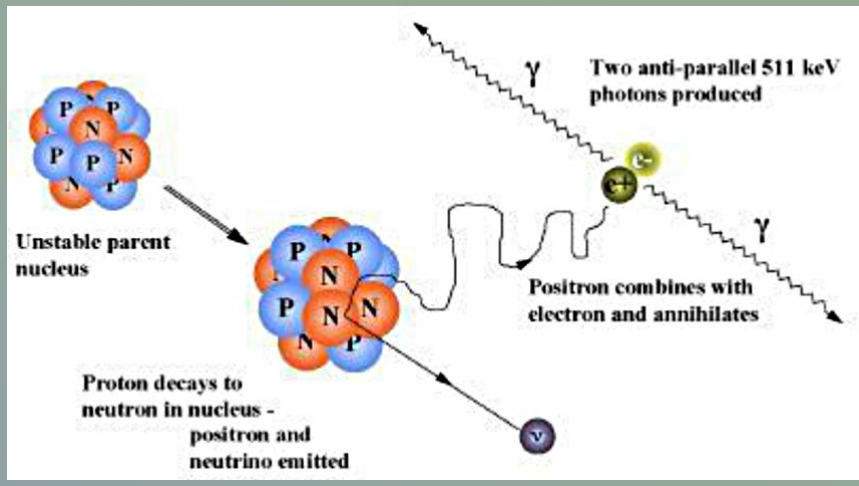
Radioactive isotopes are unstable because the nucleus has either too many neutrons or protons. The bigger the atom the more neutrons are needed to stabilize the nucleus. Radioisotopes decay toward the “valley of stability”.

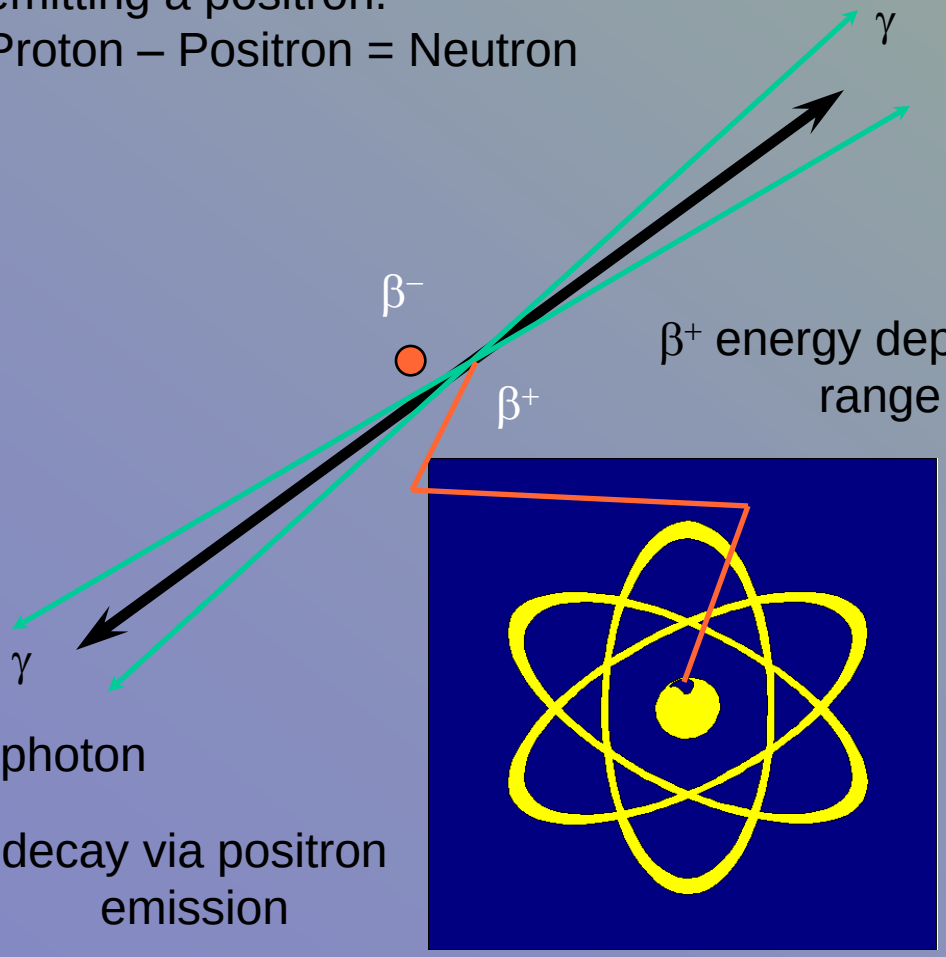




If too many protons in an atom, a neutron can be formed by grabbing a passing electron and adding to a proton or by the proton expelling a positively charged electron, a positron (anti-electron) from the nucleus.

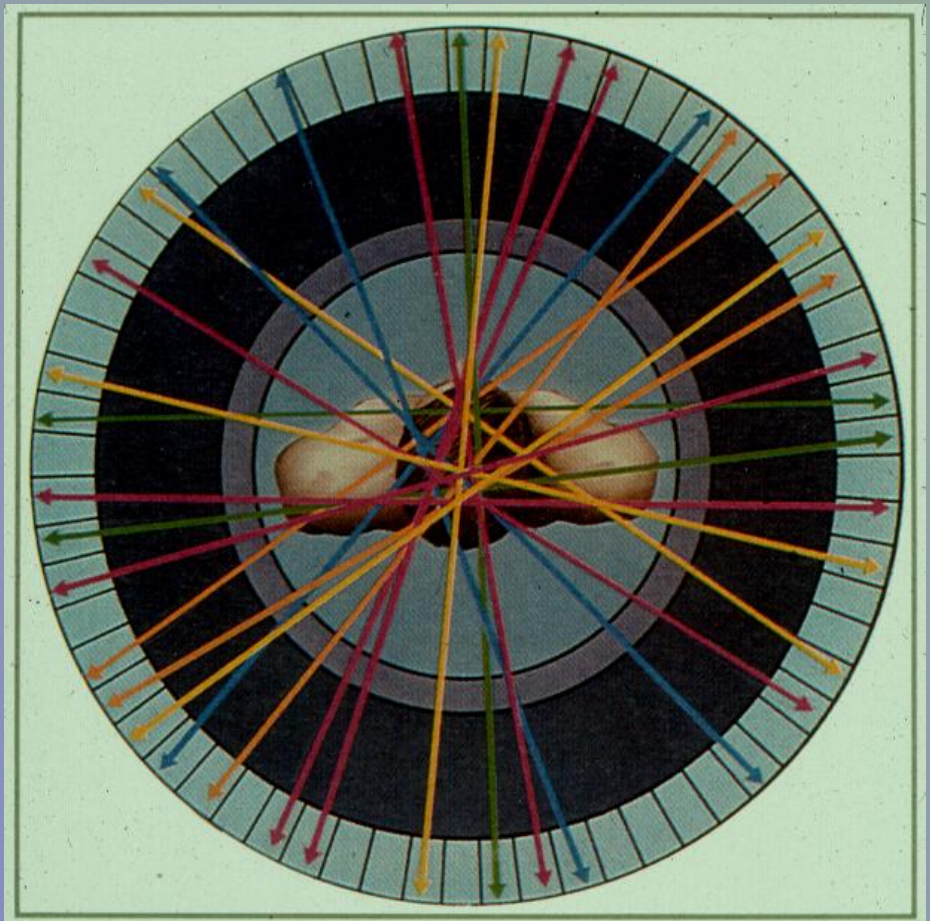
F-18 is produced in a cyclotron (atom smasher) by adding a proton to Oxygen-18. The unstable F-18 atom will get rid of the extra proton by emitting a positron.
Proton – Positron = Neutron





By Einstein's equation $E=MC^2$, matter and energy interchangable. The mass of an electron or a positron at rest is equal to 511 thousand electron volts (KeV).

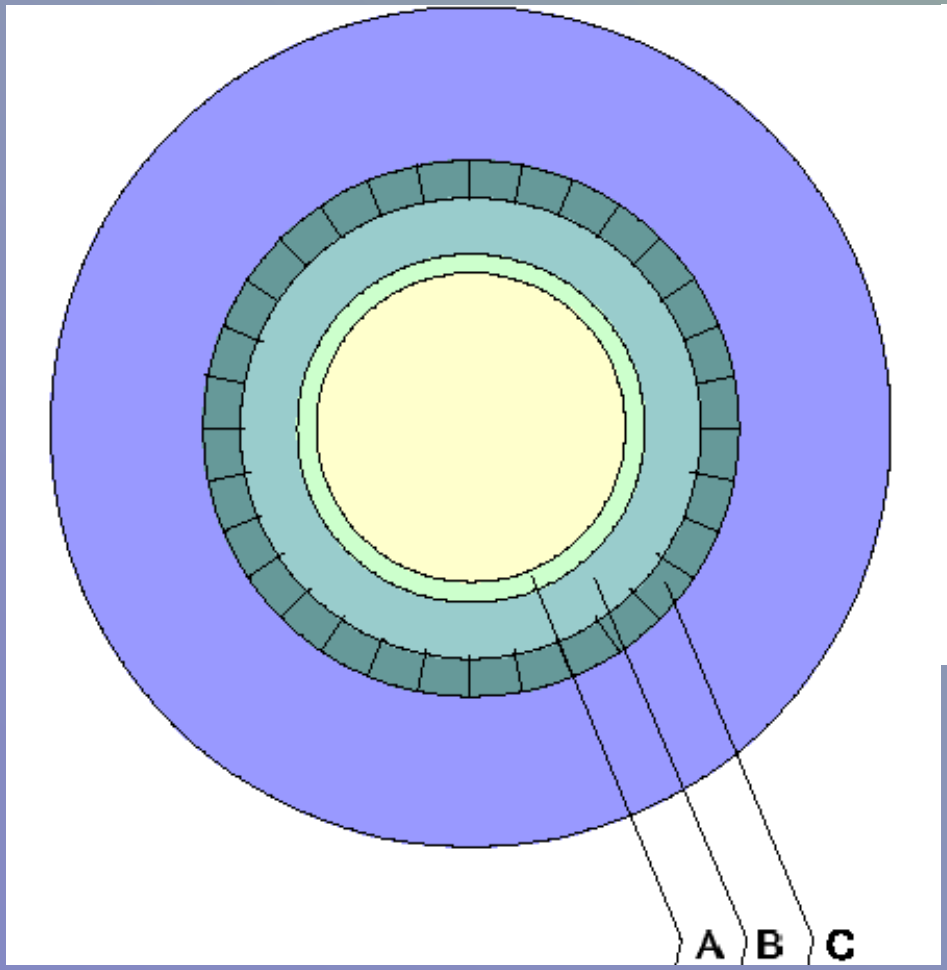
Lines of response

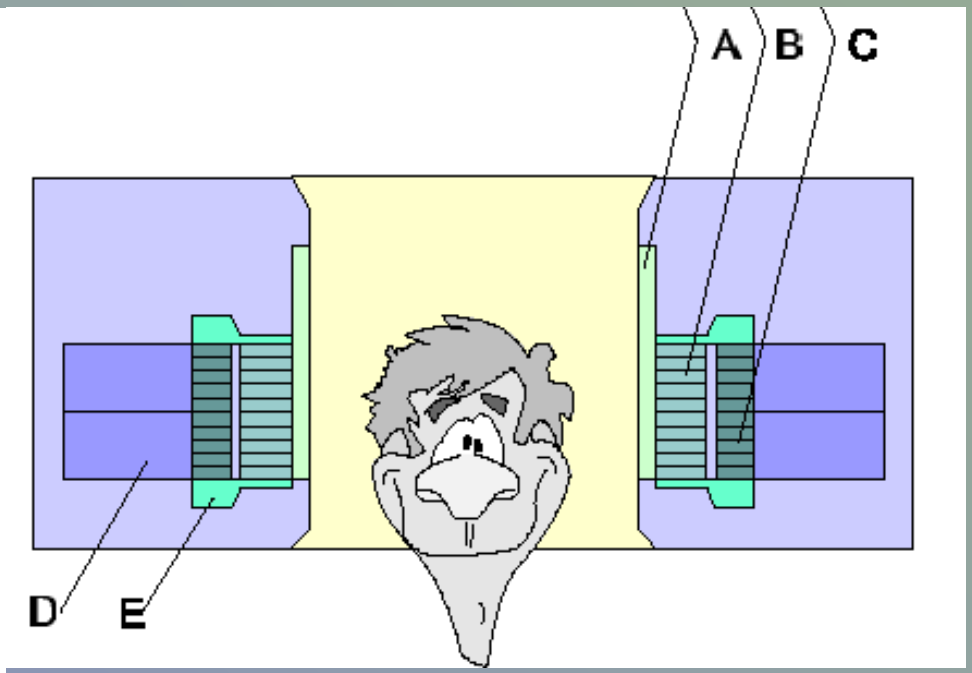


6. The multiple LORs through multiple points.

When opposing detectors simultaneously trigger, an electron-positron conversion happened on a line between the two detectors.

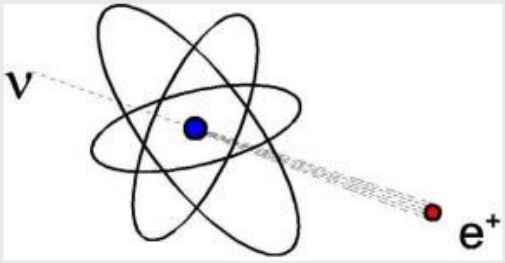
Inside the PET Scanner

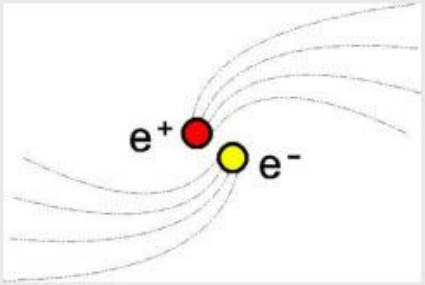


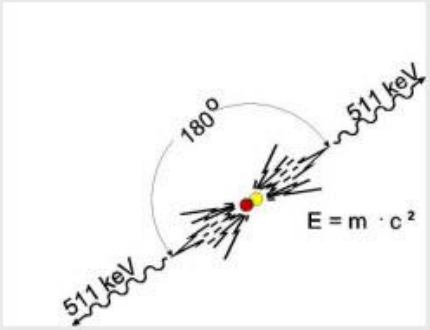


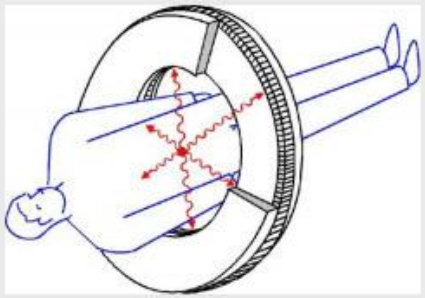
B-- Septa (2-D)
C- Crystals (not di-lithium!)
D- Optical – electronic detectors

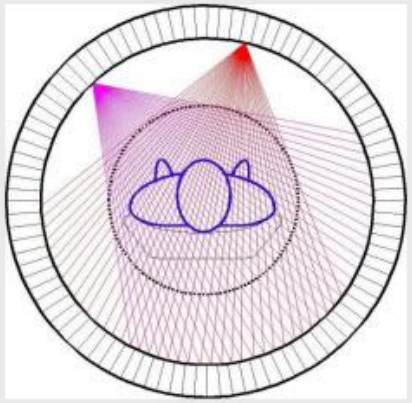
In Summary

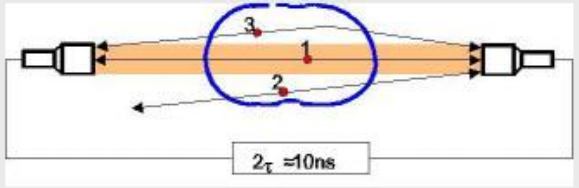






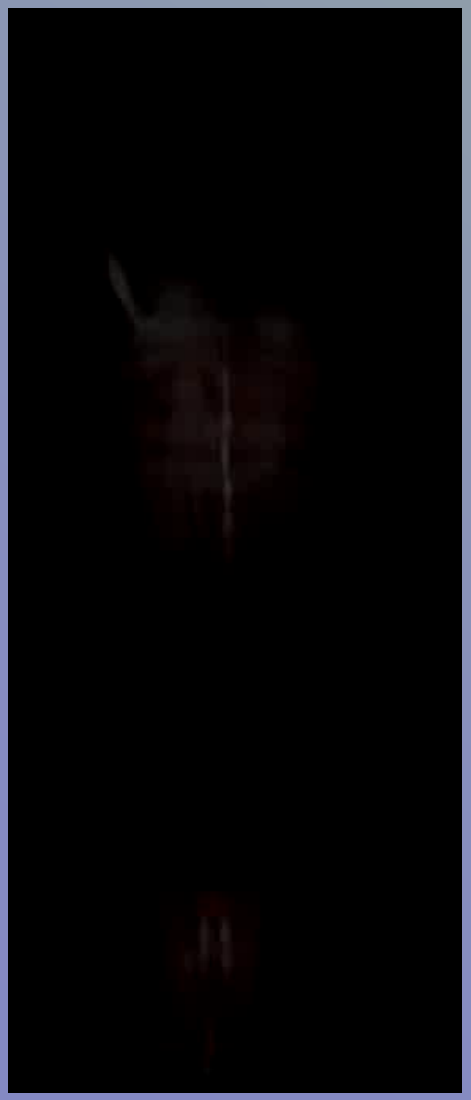




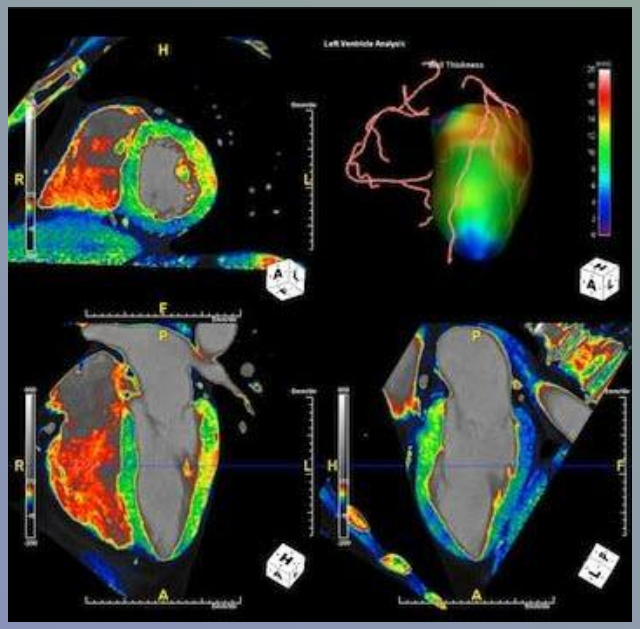


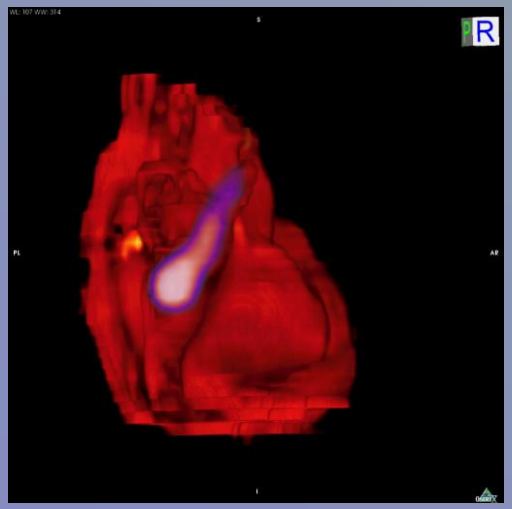
What is Positron Emission Tomography good for?

Cancer

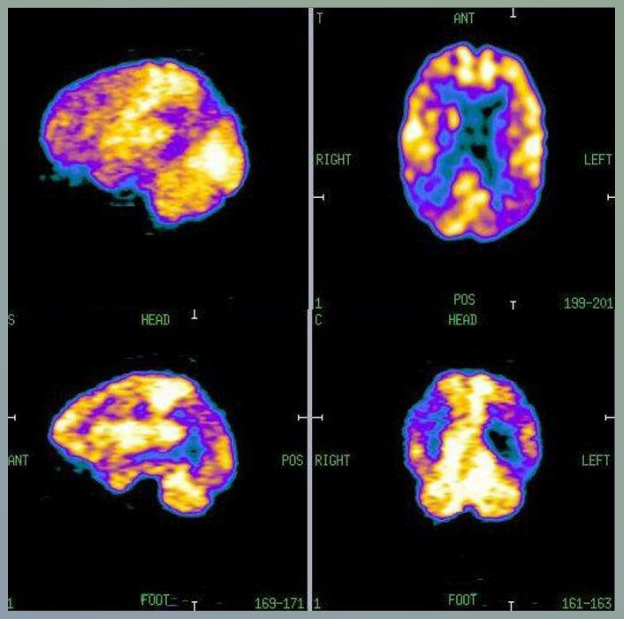


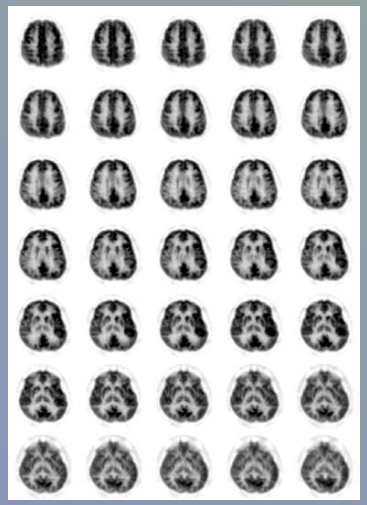
Heart Disease





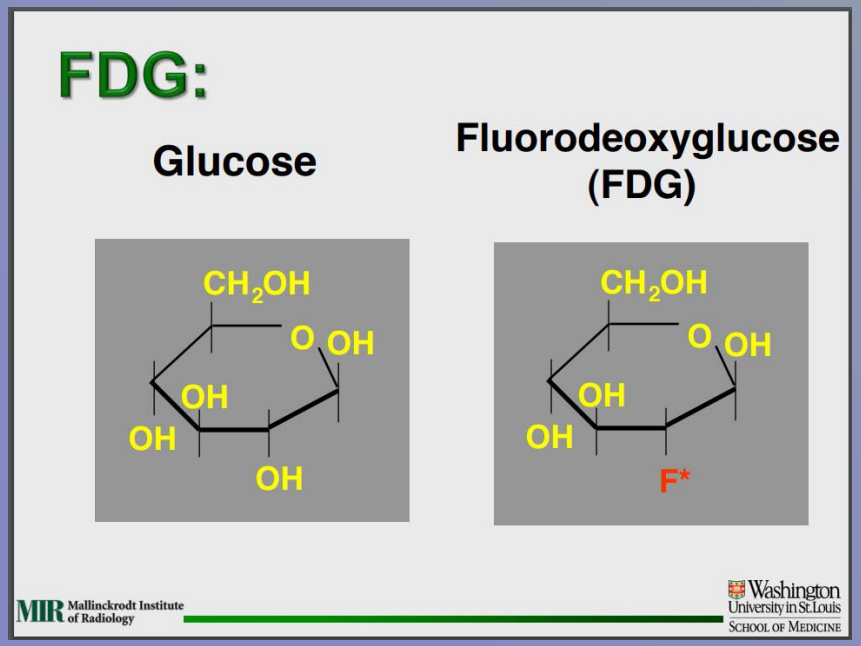
Brain Disease

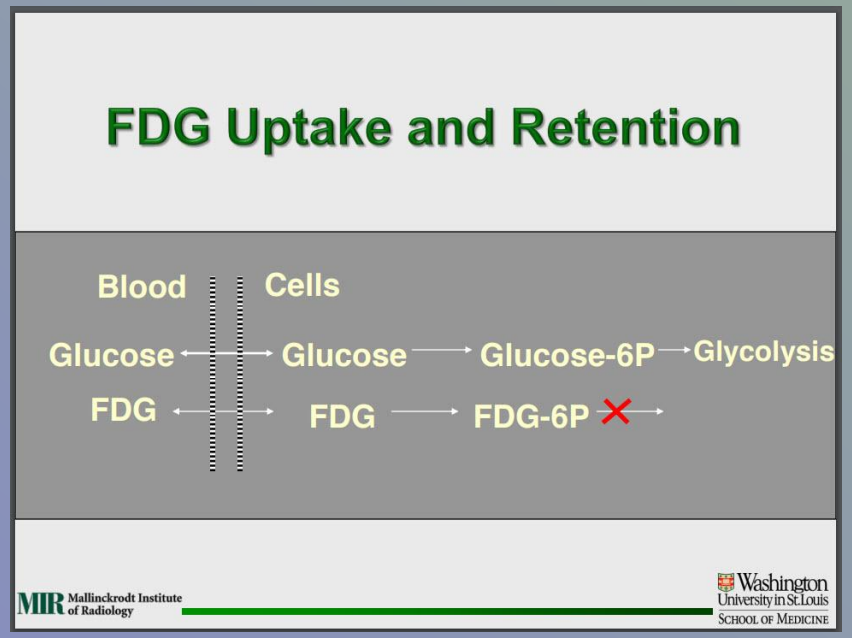




F-18 FDG PET Brain Imaging

- The brain uses only the sugar glucose for energy
- The positron emitter F-18 Fluorine can be attached to the glucose molecule
- The body will treat the F-18 labeled glucose as real sugar until it gets into the cell
- Once in the cell the labeled glucose is trapped as the enzymes can tell not glucose
- Because it acts like sugar at uptake the PET scanner can be used to detect,
- measure, and create 3-D image of the metabolism.
- F-18 FDG PET brain scans can detect dementias and other brain damage two
- years before clinical findings evident.





Chronic Toxic Encephalopathy

Chronic persistent diffuse injury to the brain with clinical manifestations involving cognitive impairment. Toxins include organic solvents (with high blood-brain permeability) and metals (with sometimes poorly understood mechanisms of neural uptake).

Cobalt(II) may become cobalt chloride or bind to proteins.

Three grades of severity in CTE

Type 1: Subclinical or subjective symptoms related to memory, concentration and mood. “Reversible”[1]

Type 2: Early objective evidence of memory and attention deficits, learning deficits and decreased psychomotor function on neurocognitive testing. Potentially still sub-clinical. “Reversible”??[1]

Type 3: Neurological deficits and/or neuroradiology findings. Type 1 and 2 neuro-imaging is usually normal and imaging used to exclude other issues. Irreversible.

[1]“Subclinical deficits usually recover after the exposure ceases, whereas clinical disorders usually do not recover. Finally, neurotoxins may reduce the functional reserves of the brain, potentially making the cells more vulnerable to the effects of aging and leading to accelerated senescence. Deterioration may continue for many years, even after exposure has ceased”[2]

[2]Kim y and Kim Jae Woo, Toxic Encephalopathy , SH@W, http://dx.doi.org/10.5491/SHAW.2012.3.4.243

Metals in Chronic Toxic Encephalopathy

Mercury: Minamata disease (methyl-) (Japan 1971). Cerebellar ataxia, visual impairment (concentric constricted fields), hearing impairment, smell and taste, somatosensory impairment. Memory loss, affect changes. ”Mad Hatter” (from felt hat making – “Erethism”). Gold dissolved into mercury painted on metal and heated to vaporize the mercury leaving gold plating (fire gilding as in the gold gilding of the iron dome of St. Isaac’s Cathedral where 60 workers died and hundreds injured from mercury fumes).

Photo By W. Eugene Smith Life Magazine 1972

Minamata Japan

St. Isaac’s Cathedral, St. Petersburg, Russia

Kim y and Kim Jae Woo, Toxic Encephalopathy , SH@W, http://dx.doi.org/10.5491/SHAW.2012.3.4.243

Metals in Chronic Toxic Encephalopathy

Lead: Tiredness, insomnia, delirium, cognitive deficits, tremor, hallucinations, and convulsions. When present in toxic amounts when mercury also present, 10 fold increase in symptoms.

Manganese: Parkinsonism. Psychiatric issues - asthenia, apathy, Irritability, lability, and locura manganica. Progresses to a reversible parkinsonism with dystonia. Final stage is irreversible symptoms even after cessation of exposure. Manganese Parkinsonism is PET negative with F-18 Fluoro-dopa and SPECT Dat-scan.

Cobalt: Tremor, parkinsonism, decreased processing and motor speed, memory impairment, loss of fine motor co-ordination,affect changes,cardiomyopathy, constricted optic fields, optic nerve damage, hearing loss, neuropathy. OSHA/EPA toxicity : 1 ppb. US Dept HHS anticipates cobalt to be carcinogenic. Derived from German – “Kobald” which were evil spirits in mines. “Cobalt Blues”.

Kim y and Kim Jae Woo, Toxic Encephalopathy , SH@W, http://dx.doi.org/10.5491/SHAW.2012.3.4.243

BanerjeeS, MontM, CherianJJ. Systemic cobalt toxicity from total hip arthroplasties: review of a rare condition Part 1 -history, mechanism... , Bone and Joint Journal. January 2016.

ClarksonT, Metal Toxicity in the Central nervous System, Environmental Health Perspectives, Vol.75, 59-64, 1987

Surgical Implant Alloys by Percent Composition

Alloy	Iron	Chromium	Cobalt	Moly	Mn	Nickel	Tungsten	Titanium
Stainless F55	59-70	17-20		2-4	2	10-14		
Co-Cr F75	0.75	27-30	57-65	5-7	1	2.5		
Co-Cr F90	3	19-21	46-53		2	9-11	14-16	
Stainless 296	62-72	16-18		2-3	2	10-14		
Titanium	0.5							99+
Titanium F136	0.25							88-92

Co-Cr alloys generally have high strength, are non-magnetic, and have been thought , until recently, to have favorable resistance to wear, corrosion, and tarnish with high modulus of elasticity without heavy cross-sections and thus reduced weight.

Rae T (1981): “It appears, therefore, that potentially the most harmful components are cobalt from cobalt-chromium alloy, nickel from stainless steel, and vanadium from titanium alloy. As far as can be estimated, the only combination of materials which is likely to give rise to toxic levels of metal under clinical conditions, is cobalt-chromium alloy articulating against itself to produce relatively high levels of cobalt.”[1]

1. RaeT, The Toxicity of Metals Used in Orthopeadic Prostheses, British Editorial Society of Bone and Joint Surgery. Vol 63-B, No. 3, 1981, pp 435-440.

Arthroplasty Joint Failure - History

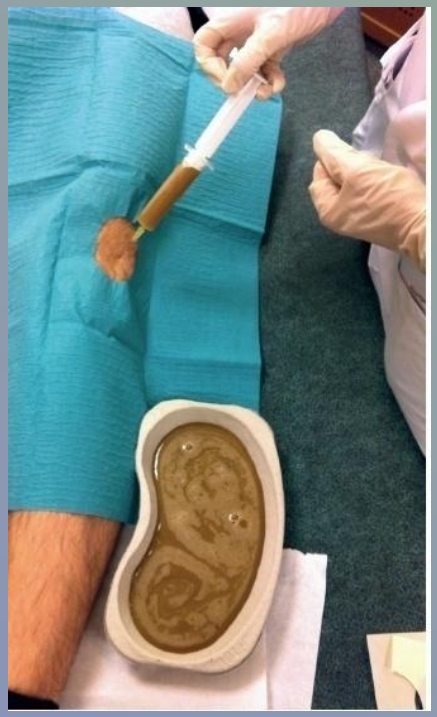
Jones DA, Lucas HK, O'Driscoll M, et al. Cobalt Toxicity after McKee Hip arthroplasty. The Journal of Bone and Joint Surgery. Vol.57-B, No. 3, August 1975, pp 289-296.

1. Progressive pain, feeling of instability, dislocation
2. Fracture, bone resorption, loosening
3. Nickel and chrome negative on patch test
4. Histology: Bone, joint capsule and muscle necrosis
5. Referenced earlier 1973 article on total hip failures (Charosky)

Recognition of local intra-articular pathology with passing reference to systemic toxicity.

Primarily focused on Metal-on-Metal joint replacements

1. Metallosis
2. ARMD: Adverse Reaction to Metal Debris
3. Pain, tissue necrosis and pseudotumor formation
4. About 5 million Cr-Co hip arthroprostheses in U.S.A. alone

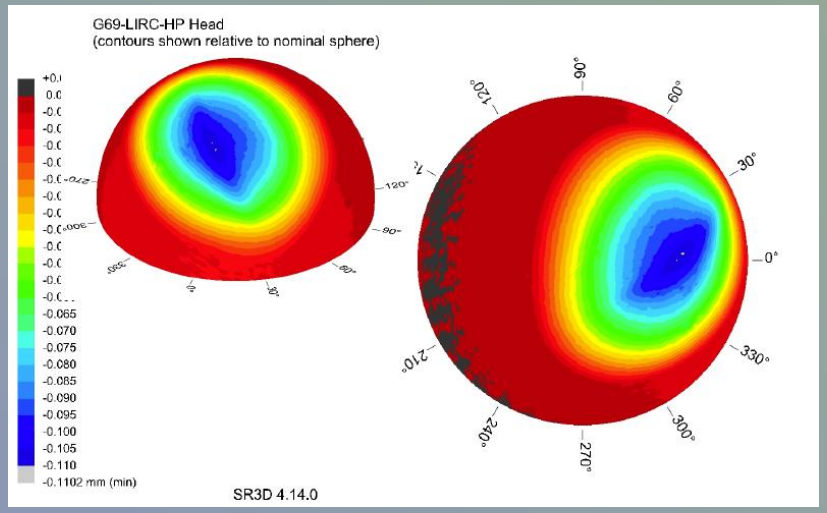


Images by permission from： Minna L, Jyrki N, Aleksi R, et al. High blood metal ion levels in 19 of 22 patients with metal-on-metal hinge knee replacements, Acta Orthopaedica, DOI: 10.1080/17453674.2017.1283846

Forms of Metal Alloy Loss of Hip Prostheses

Fretting: Mechanical wear and degeneration into metal particles

1. Contact between intended bearing surfaces (Metal-on-Metal – “MoM”)
2. Third body wear – surface contamination with abrasive debris
3. Wear from one intended and one non-intended surface- modularity



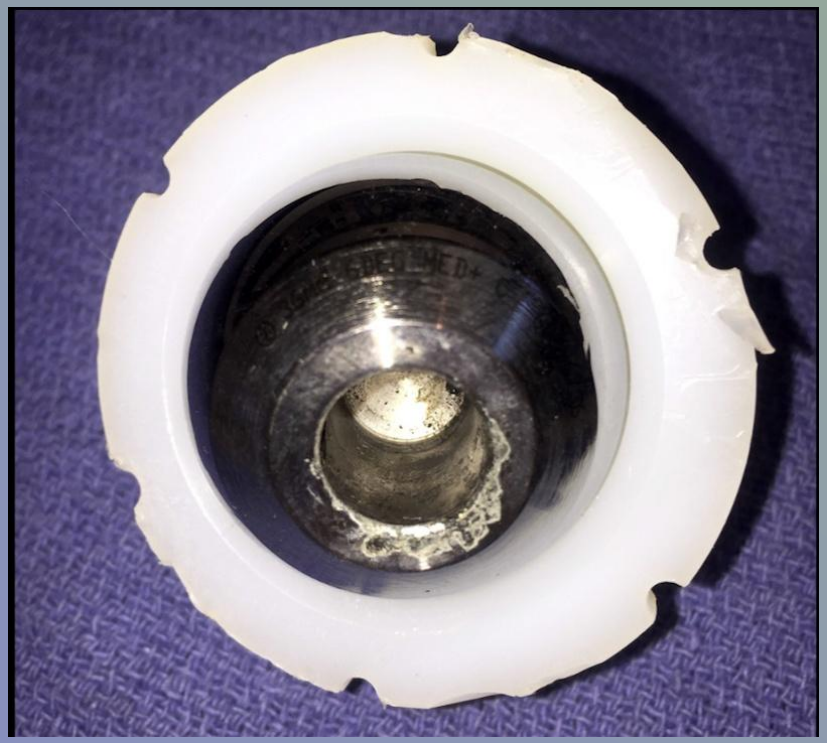
Hx: 57 y.o. male, time component implanted 52 months, “MoM”

1. Serum cobalt 65.3 ppb and Chromium 34.8 ppb
2. British MHRA “alert” - 7 ppb – limited to MoM - Soft Tissue only (2012)
3. Cobalt lost approx. 64 mm^3 or 5x6x2 mm over 52 months
4. One year following implant developed fatigue, confusion, irritability, memory loss, tinnitus and constricted optic fields.

Forms of Metal Alloy Loss of Hip Prostheses

Corrosion: Loss of surface matrix from electro-chemical reaction

1. Anodic surface erosion overcoming passivation shielding
2. Generation of acidic pH from interaction of metal with joint fluid



Corroded Explanted Metal on Plastic (MoP) Hip Prosthesis

Tribology: Mechanical wear and corrosion

1. In vivo: biotribology

Arthroplasty Cobalt Encephalopathy

Case reports in literature

Steens w, Loehr Jf, von Foerster G, et al. Chronic Cobalt Poisoning in Endoprothetcic replacement. Orthopade. Aug 2006;35(8): 860-4.

Rizzetti MC, Liberini P, Zarattini G, et al. Loss of sight and sound. Could it be the hip? Lancet. Mar 21 2009;373(9668):1052.

Ikeda T, Takahashi K, Kabata T, Sakagoshi D, Tomita K, Yamada M. Polyneuropathy caused by cobalt-chromium metallosis after total hip replacement. Muscle Nerve. Jul 2010;42(1):140-143.

Tower SS, Arthroprosthetic cobaltism: neurological and cardiac manifestations in two patients with metal-on-metal arthroplasty: a case report. J Bone Joint Surg [Am] 2010;92-A:2847–2851.

Steens W, Von Foerster, Katzer A. Severe cobalt poisoning with loss of sight after ceramic-metal pairing in a hip —a case report. Acta Orthopaedica 2006; 77 (5): 830-832

Mao X, Wong A, Crawford R. Cobalt toxicity — an emerging clinical problem in patients with metal-on-metal hip prostheses?: MJA. Vol. 194, No. 12 June 2011; 649- 651.

E Woelber, DW Van Citters, T Steck, et al. Explant Analysis from a Patient Exhibiting Rapid Acceleration of Parkinson Disease Symptoms and Hypercobaltemia Following Metal-on-Metal Total Hip Arthroplasty. J Invest. Med. 2015;63 (1): 163-164

Green B, Griffiths E, Almond S. Neuropsychiatric symptoms following metal-on-metal implant failure with cobalt and chromium toxicity. BMC Psychiatry (2017) 17:33.

Clinical presentation: Vision and hearing loss, Parkinsonism, polyneuropathy, cognitive decline, memory loss, tremor , cardiac dysfunction

Patient Selection

100 patients implanted with chrome-cobalt implants were screened with blood and urine cobalt levels over two-years after an extensive symptom inventory was performed.

Two-thirds were hypercobaltemic (B[Co] > 1 ppb)

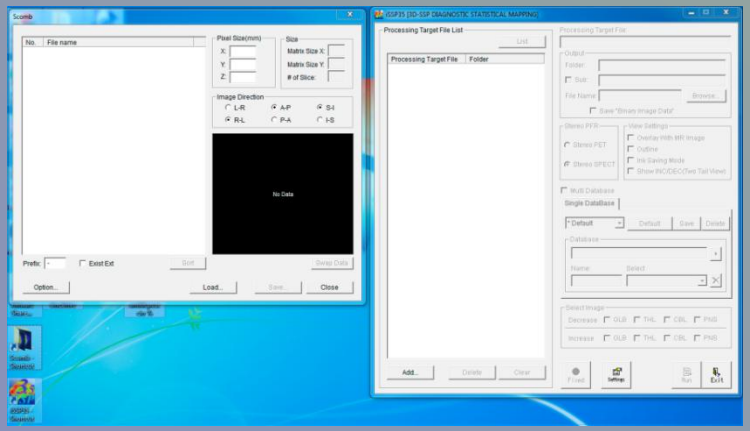
Of those with elevated serum cobalt , 25 had new onset of cognitive decline, a new neurologic or sleep disorder, or notable fatigue since their index arthroplasty.

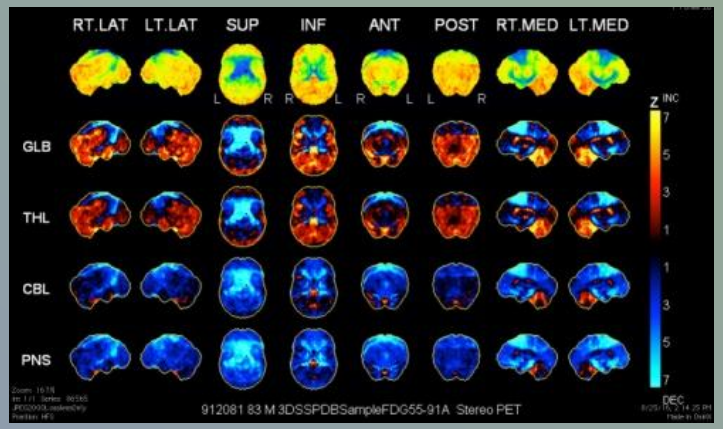
20 of these 25 patients were evaluated with FDG PET brain scans

Of the 20 who underwent FDG PET brain scans:

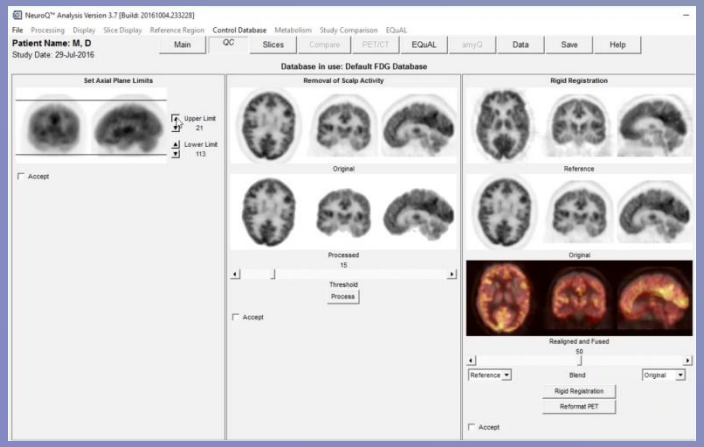
10 underwent formal neurocognitive testing by a neuropsychologist.
All had Global Assessment of Function (GAF) scoring.
Demographics:
Ages 51 to 83.
11 men / 9 women.
Duration of prosthesis of 4.6 to 27.1 years.
Serum cobalt levels 1.7 to 19.2 ppb.

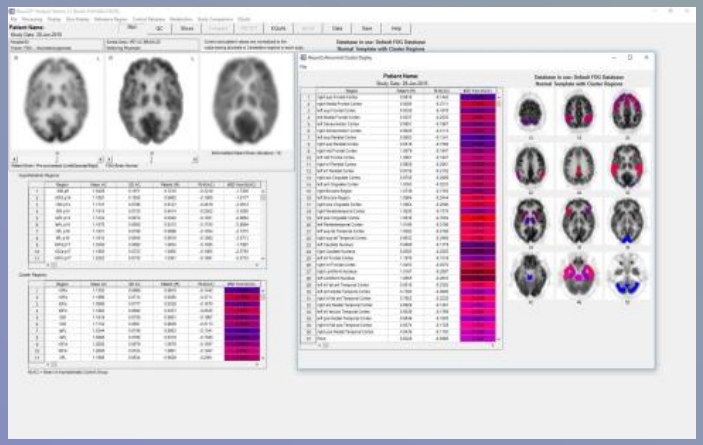
NeuroStat 3D-SSP: DICOM files converted to nifti by Scomb
(Univ. of Utah) NeuroStat run as both Windows GUI and Mac command format.
Default and Austin atlases of normal brains matched for age and sex..





NeuroQ: NeuroQ program running within Mirada Medical XD3 workstation
(Syntermed) Cranial-caudal limits selected
Scalp activity removal at default
Rigid fusion with default 10 iterations
Pons used as reference level
Scoring on aggregate of all areas of hypo-metabolism and number
of abnormal cluster regions (240 regions/47 clusters) Threshold: -1.65 SD





NeuroStat 3D-SSP

Metabolically mapping the brain.

First 16 patients with pons as base reference.

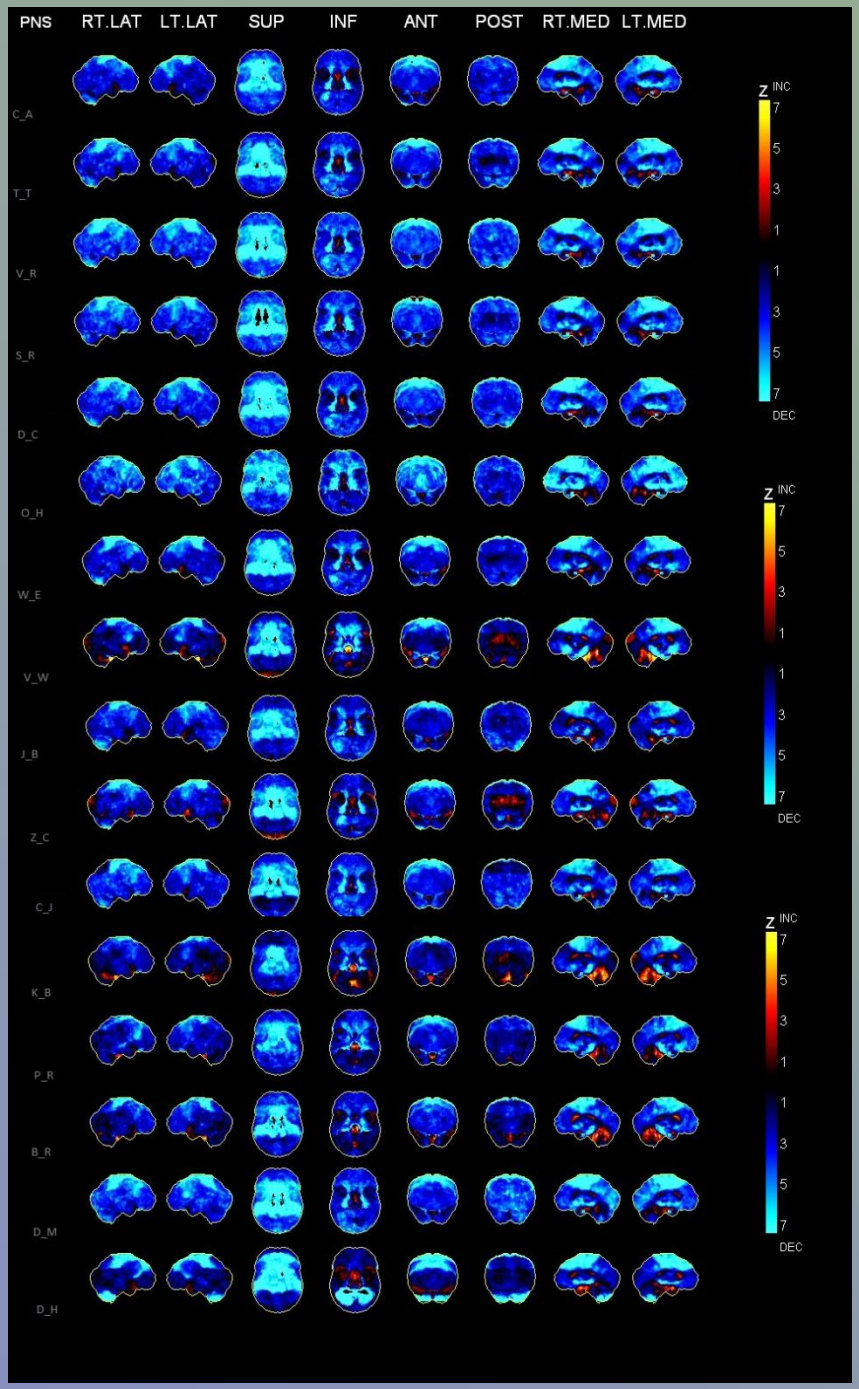
All show a global hypo-metabolism

NeuroStat allowed a frugal “first-look” at brain metabolism using global, thalamic, cerebellar and pontine reference regions.

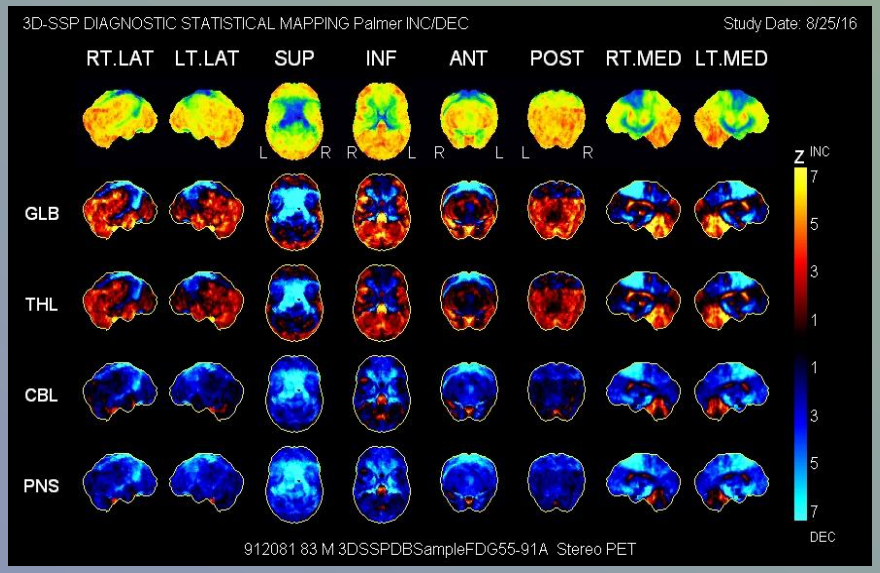
NeuroStat a “gateway” for determination of further investment in processing on a more granular level with NeuroQ.

Pons consistently the better reference region with the cerebellum second. In one patient pons more hypo-metabolic than cerebellum.

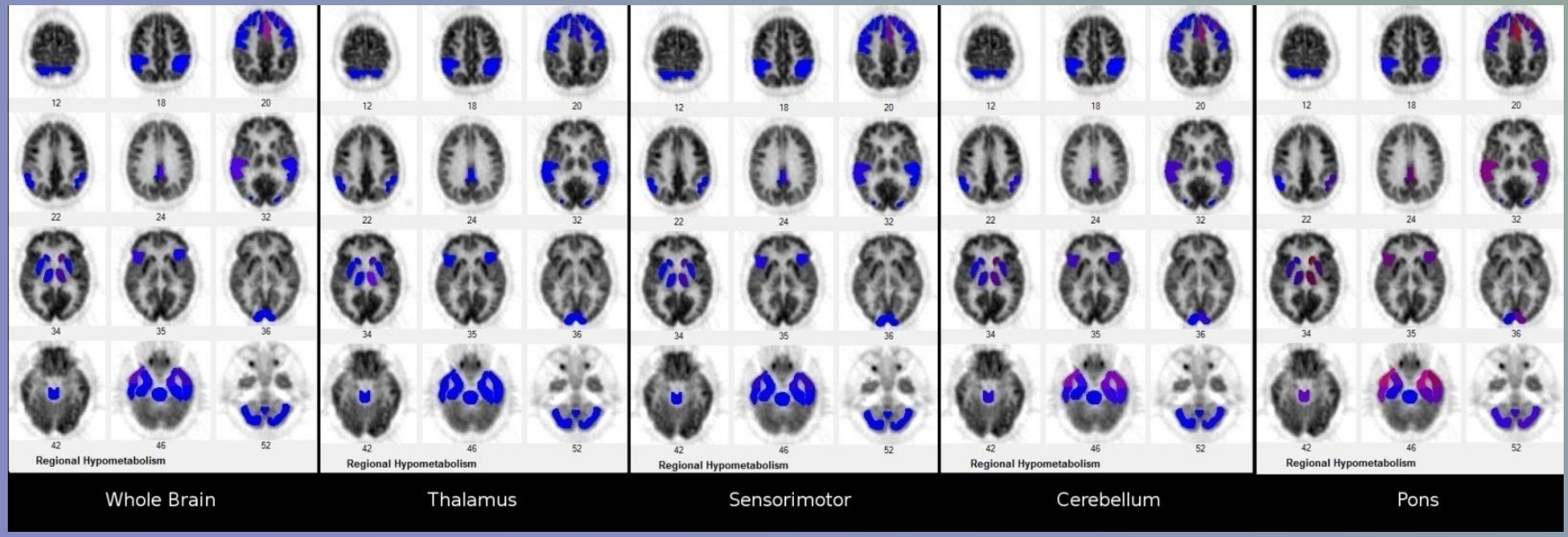
Both regions showed better, but not complete, resilience to cobalt toxicity.



How Metabolic Mapping is Displayed



3D SSP – Stereotactic Surface Projection



NeuroQ – Internal Regions with Standard Deviations Color Coded

Temporal Lobe Regions

Level	Patients	Cluster Regions	Right	Left	Clusters Spread (Standard Deviation)
Level 1	5/6	3/10	4/6	1/6	-1.94 to -3.55
Level 2	7/7	7/10	6/7	3/7	-1.65 to -4.26
Level 3	9/9	10/10	7/9	8/9	-1.61 to -5.06
Level 4	3/3	10/10	3/3	3/3	-1.75 to -5.31

Patient #	right sup lat Temporal Cortex	left sup lat Temporal Cortex	right inf lat ant Temporal Cortex	left inf lat ant Temporal Cortex	right inf lat pos Temporal Cortex	left inf lat pos Temporal Cortex	right ant Medial Temporal Cortex	left ant Medial Temporal Cortex	right pos Medial Temporal Cortex	left pos Medial Temporal Cortex
3										
23					-1.94					
13					-2.46					
8						-3				
15		-2.67				-2.06				
21					-2.92					
20			-2.52		-3.55					
27					-3.22					
26					-1.7					
18	-2.15		-1.92		-3.14			-2.32		
7			-2.68	-1.92	-3.68					
22					-4.26					
14		-3.06								
24		-1.92		-2.16			-1.65			
4	-1.84		-2.01		-5.06					
25			-2.14	-2.82	-1.66		-1.87			
9		-1.87		-2.92		-2.57		-1.94		
11				-2.2723	-4.021	-3.3658				-1.9457
28	-2.372	-1.6927	-3.2312	-2.6996	-1.7036					
6			-1.94	-2.49	-2.8			-1.83		-1.71
12	-2.6	-1.8	-2.42	-2.81	-2.08					
1						-1.83				
17	-2.02	-1.87	-3.14	-2.5	-3.9	-2.08	-2.04	-3.21	-1.72	-1.88
19	-2.4	-1.69	-2.72	-2.31	-4.96					
5		-1.76	-2.52	-2.72	-4.73	-2.99	-1.88	-2.23	-2.03	-1.82
16	-2.43	-2.05	-2.84	-2.73	-1.97	-1.85	-2.1	-3.71		-2.06
2	-1.84	-2.023	-1.7		-2.68	-1.75				
10	-2.76	-3.05	-3.17	-2.85	-5.31	-3			-2.34	-1.88

NeuroQ

Frontal Lobe Regions

Level	Patients	Cluster Regions	Right	Left	Clusters Spread (S.D.)
Level 1	4/6	1/6	1/6	0/6	-1.69 to -2.62
Level 2	4/7	4/6	1/7	3/7	-1.83 to -2.21
Level 3	8/9	6/6	8/9	6/9	-1.73 to -3.22
Level 4	3/3	4/6	3/3	3/3	-1.75 to -2.93

Patient #	right Medial Frontal Cortex	left Medial Frontal Cortex	right mid Frontal Cortex	left mid Frontal Cortex	right inf Frontal Cortex	left inf Frontal Cortex
3						
23						
13					-2.62	
8					-2.59	
15						
21					-2.3	
20					-1.69	
27						
26				-1.83		
18						-2.02
7						
22						
14					-2.21	
24		-1.9127				
4			-1.96		-2.95	
25	-1.85	-2.26			-1.86	
9		-2.27			-1.73	-2.22
11						
28	-2.1442	-1.8866			-1.9798	
6				-1.85	-1.99	-2.33
12	-2.18	-1.97			-1.99	
1		-2.77	-1.89	-2.83	-2.73	-2.63
17		-1.73		-2.14	-2.5	
19	-1.9		-2.27		-3.22	
5				-1.75	-2.47	-2.09
16		-2.83		-1.81	-1.92	-1.98
2	-1.75	-2.45	-2.16	-2.52	-2.93	-2.43
10		-2.37		-2.12	-2.13	-2.03

NeuroQ

Cingulate Regions

Anterior

Level	Patients	Cluster Regions	Right	Left	Clusters Spread (S.D.)
Level 1	0/6	0/2			
Level 2	1/7	2/2	1/2	1/2	-2.15 to -3.09
Level 3	5/9	2/2	4/9	5/9	-1.71 to -3.03
Level 4	3/3	2/2	2/3	3/3	-1.88 to -4.51

Posterior

Level	Patients	Cluster Regions	Right	Left	Clusters Spread (S.D.)
Level 1	0/6	0/2			
Level 2	2/7	1/2	0/9	2/9	-1.83 to -2.43
Level 3	5/9	2/2	4/9	4/9	-1.71 to -3.03
Level 4	2/3	2/2	1/3	2/3	-2.45 to -3.17

A	AQ	AR	AS	AT
Patient #	right ant Cingulate Cortex	left ant Cingulate Cortex	right pos Cingulate Cortex	left pos Cingulate Cortex
3				
23				
13				
8				
15				
21				
20				
27				-1.83
26				
18				-2.43
7				
22				
14				
24	-2.15	-3.09		
4	-1.71	-2.7		
25	-2.45	-3.52		
9	-1.73	-2.64		
11				-2.0746
28			-1.7182	-2.9993
6	-2.43	-3.28	-2.22	-2.5
12			-1.77	-3.03
1		-2.66	-1.79	
17				
19	-2.48	-2.52		
5		-2.34		
16	-1.88	-3.62		-2.52
2		-2.52		-1.8
10	-2.25	-4.51	-2.45	-3.17

NeuroQ

Broca's Regions

Level	Patients	Cluster Regions	Right	Left	Clusters Spread (S.D.)
Level 1	1/6	1/2	0/6	1/6	-1.97
Level 2	2/7	2/2	2/7	2/7	-1.76 to -2.96
Level 3	4/5	2/2	3/9	6/9	-1.75 to -3.65
Level 4	4/4	2/2	1/3	2/3	-1.77 to -2.61

Patient #	right Broca's Region	left Broca's Region
3		
23		
13		
8		-1.97
15		
21		
20		
27		
26	-1.76	-2.96
18		
7		
22		
14	-2.44	-2.49
24		
4	-3.04	
25		
9		-2.15
11		
28		-1.751
6		-2.26
12		-1.95
1	-3.04	-3.65
17		-2.47
19	-1.8	
5		-2.37
16		-2.61
2	-3.33	-3.06
10	-1.77	

NeuroQ

Parietal Lobe Regions

Level	Patients	Cluster Regions	Right	Left	Clusters Spread (S.D.)
Level 1	1/6	2/6	1/6	1/6	-1.71 to -1.78
Level 2	2/7	4/6	2/7	2/7	-1.66 to -2.18
Level 3	5/9	5/6	5/9	5/9	-1.77 to -3.11
Level 4	2/3	2/6	1/3	1/3	-2.15 to -2.45

Patient #	right sup Parietal Cortex	left sup Parietal Cortex	right inf Parietal Cortex	left inf Parietal Cortex	right Parietotemporal Cortex	left Parietotemporal Cortex
3						
23						
13						
8			-1.71			-1.78
15						
21						
20						
27			-1.66	-1.92		-2.01
26						
18						
7						
22						
14						
24	-2.18			-1.94		
4			-2.21	-1.73	-1.82	
25	-1.82			-1.65		
9						
11	-1.8217		-2.1479		-2.8963	-3.1051
28						
6			-1.9			-1.77
12						
1						
17					-1.97	-2.1
19			-2.07	-2.01		
5						-2.45
16						
2			-2.02			-1.76
10			-2.15			

Basal Ganglia Regions

Level	Patients	Cluster Regions	Right	Left	Clusters Spread (S.D.)
Level 1	3/6	2/6	1/6	2/6	-1.7 to -1.87
Level 2	0/7	0/6			
Level 3	5/9	3/6	1/9	5/9	-1.7 to -2.09
Level 4	1/3	2/6	0/3	2/3	-2.03 to -2.45

A	BE	BF	BG	BH	BI	BJ
Patient #	right Caudate Nucleus	left Caudate Nucleus	right Thalamus	left Thalamus	right Lentiform Nucleus	left Lentiform Nucleus
3	0.27	-0.36	-1.41	-1.7	-0.27	-0.39
23	-0.53	-0.038	-0.37	-1.13	-0.77	-0.93
13	-1.04	-0.73	-0.74	-1.05	-0.71	-0.09
8	-0.21	-1.13	-0.85	-1.87	-0.85	-0.84
15	-0.9	-0.38	-0.96	-1.47	-0.75	-0.43
21	-1	-0.98	-1.03	-1.06	-1.72	-1.15
20	-0.23	-0.95	-0.62	-1.35	-0.89	-0.67
27	-0.19	-1.21	-0.56	-1.03	-0.33	-0.32
26	-0.27	-1.27	0.49	-0.04	0.52	0.03
18	-0.66	-0.86	-0.29	-0.56	-0.3	-0.32
7	-0.73	-1.65	-0.53	-1.34	-0.49	-0.35
22	1.27	0.87	-0.26	-0.87	1.16	0.8
14	-0.75	-0.48	-0.6	-0.86	-0.45	-0.34
24	-0.25	-0.94	-0.02	-0.56	-0.26	-0.34
4	-0.75	-1.08	-0.62	-1.29	-0.74	-0.34
25	-0.29	-0.67	-0.06	-0.33	0.01	-0.21
9	-1.35	-2.06	0.46	-0.61	-1.04	-1.18
11	-0.92	-2.09	-0.51	-1.44	-0.37	-0.36
28	-1.31	-0.69	0.37	-0.04	-1.84	-1.18
6	-0.45	-1.35	-10.5	-1.63	-0.21	-0.4
12	-0.98	-1.79	-0.63	-0.99	-1.32	-1.28
1	-0.6	-1.85	-0.99	-1.78	-0.03	-0.18
17	-0.97	-1.71	-0.67	-1.04	-1.13	-1.16
19	-0.24	-0.89	-0.37	-1.19	0.11	0.2
5	-0.56	-0.9	-0.36	-1.21	-0.6	-0.78
16	-0.94	-2.45	-1.2	-2.15	-1.03	-1.27
2	-1.16	-2.03	-0.77	-2.19	-0.04	-0.38
10	-1.19	-1.62	-0.1	-0.55	-1.29	-0.76

NeuroQ

Visual Cortex Regions – Primary and Associative

Level	Patients	Cluster Regions	Right	Left	Clusters Spread (S.D.)
Level 1	1/6	1/4	0/6	1/6	-2.08
Level 2	1/7	1/4	0/7	1/7	-2.18
Level 3	5/9	4/4	4/9	5/9	-1.68 to -2.77
Level 4	3/3	4/4	2/3	2/3	-1.75 to -6.29

Patient #	right Primary Visual Cortex	left Primary Visual Cortex	right Associative Visual Cortex	left Associative Visual Cortex
3		-2.08		
23				
13				
8				
15				
21				
20				
27				
26				
18				
7				
22		-2.18		
14				
24				
4	-1.68	-2.06		
25				
9				
11			-2.772	-2.5312
28				
6		-2.09		
12				
1	-1.93	-2.44		
17				
19	-2.48	-2.68		
5	-4.66	-6.29	-3	-2.41
16		-2.03		
2	-2.91	-3.85		
10			-1.75	

NeuroQ

Thalamic Regions

Level	Patients	Cluster Regions	Right	Left	Clusters Spread (S.D.)
Level 1	2/6	1/2	0/6	2/6	-1.7 to -1.87
Level 2	0/6	0/2			
Level 3	1/9	1/2	0/9	1/9	-1.78
Level 4	1/3	1/2	0/3	1/3	-2.15

Patient #	right Thalamus	left Thalamus
3	-1.41	-1.7
23	-0.37	-1.13
13	-0.74	-1.05
8	-0.85	-1.87
15	-0.96	-1.47
21	-1.03	-1.06
20	-0.62	-1.35
27	-0.56	-1.03
26	0.49	-0.04
18	-0.29	-0.56
7	-0.53	-1.34
22	-0.26	-0.87
14	-0.6	-0.86
24	-0.02	-0.56
4	-0.62	-1.29
25	-0.06	-0.33
9	0.46	-0.61
11	-0.51	-1.44
28	0.37	-0.04
6	-10.5	-1.63
12	-0.63	-0.99
1	-0.99	-1.78
17	-0.67	-1.04
19	-0.37	-1.19
5	-0.36	-1.21
16	-1.2	-2.15
2	-0.77	-2.19
10	-0.1	-0.55

NeuroQ

Synopsis of Neurocognitive Testing

Sub-Group 1: 10 patients

Dedicated neurocognitive testing by neuropsychologist
1 with 2 MoM , 1 with 1 MoM, 8 with MoP (just counting hips!)
Memory loss: 10/10 patients
Tremor: 7/10 patients
Executive function compromised: 4/10
Mood: 4/10

Sub-group 2: All 20 patients

General Assessment of Function testing
All but a few patients noted both fatigue and forgetfulness beyond what they could attribute to aging.
Half developed a new mood or sleep disorder, poor balance or a tremor.
A third developed executive dysfunction, deafness, or non-refractive blindness.
A quarter experienced generalized pain or peripheral neuropathy

"Affect": Subjectively from interaction with staff and technologists all patients had affect changes ranging from withdrawn, to labile, to gross inappropriateness, to finally "chiroptera guano crazy'.

Subjects with U[Co] < 1.0	45/105	Tremor or Dystonia % YES	Poor Balance or Myopathy % YES	Executive Dysfunction % YES	Poor Memory % YES	Disordered Mood % YES	Chronic Pain % YES	Sleep Disorder % YES	Fatigue or Exercise Intolerance % YES	Weight Loss > 10% % YES	Peripheral Neuropathy % YES	Audio-Vestibular Dysfunction % YES	Non-Refractive Blindness % YES
		25	9	4	9	9	2	2	9	0	0	4	0
FPBS Scanned Subjects U[CO]>1.0	24/60	Tremor or Dystonia % YES	Poor Balance or Myopathy % YES	Executive Dysfunction % YES	Poor Memory % YES	Disordered Mood % YES	Chronic Pain % YES	Sleep Disorder % YES	Fatigue or Exercise Intolerance % YES	Weight Loss > 10% % YES	Peripheral Neuropathy % YES	Audio-Vestibular Dysfunction % YES	Non-Refractive Blindness % YES
		63	58	33	92	42	29	63	83	13	21	38	29
Relative Risk		2.5	6.4	7.5	10.3	4.7	13.1	28.1	9.4	>13	>21	8.4	>29

Results:

All patients exhibited global hypometabolism when referenced to pons

Increasing aggregate score of S.D. of hypometabolism and number of abnormal clusters:

1. Demonstrated a progression of regional involvement. Temporal >Frontal > >Parietal > Occipital>Basal ganglia >Caudate>Thalamic > Visual Cortex.
2. PET brain scans usually “worse” than clinical presentation as some areas are probably sub-clinical in presentation. However if reference region damaged, true hypo-metabolism may be worse.

Also from aggregate hypometabolic scoring could be broken down into four levels:

1. 0-50 S.D. : with one to three abnormal cluster areas
2. 50-120 S.D. : with three to eight abnormal cluster areas
3. 120-225 S.D. : with ten to thirteen abnormal cluster areas
4. >225 S.D. : with twenty-two to twenty-nine abnormal cluster areas

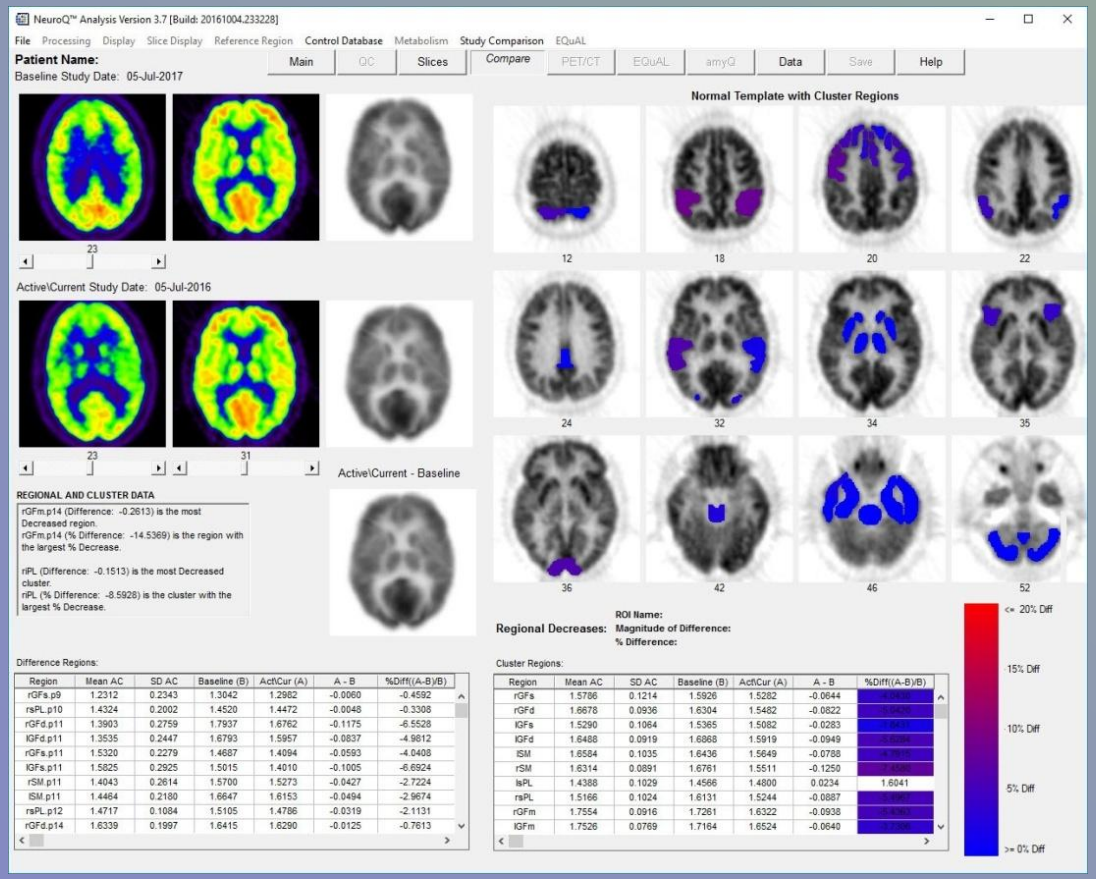
None of the patients’ CT imaging showed significant neuro-radiological changes

Metal-on-Plastic (MoP) no different than Metal-on-Metal for CTE presentation.

Results - 6 months post-revision for the four patients with pre/post scans

Patient 14: Reversible with aggregate -96.6 to -42 and cluster regions from 4 to 2
Patient 24: Mixed with aggregate -96.5 to -122.4 but cluster regions from 7 to 4
Patient 1: Worse with aggregate -173.8 to -230.4 and cluster regions from 14 to 20
Patient 11: Worse with aggregate -132 to -237 and cluster regions from 12 to 18.

For worsening symptoms, were the changes from irreversible toxicity from cobalt, progression of confounding issues or potentiation of combined processes? As shown, mercury and lead together are 10 times worse.



NeuroQ

Relevant Studies for Comparison with ACE

Callender T, Morrow L, Subramanian K, et al. [1]

- Clinical toxic exposure to neurotoxins (solvents/pesticides)
- 33 workers – ages 24 to 63 ; 29 underwent neuropsychological testing – type 2A/2B CTE
- SPECT (HMPAO) brain scans on all and two had FDG PET brain scans – visual assessment
- 93% had abnormal brain scans – two negative scans considered false negative
- Good correlation between brain scans and neuropsychology testing with findings of poor memory, tremor, ataxia, anxiety, depression, vertigo
- Temporal>frontal>basal ganglia>thalamus>parietal>motor strip>occipital>caudate

Clark M, Prentice N, Hoggard M,et al.[2]

- Chronic mildly elevated serum cobalt levels in patients with well functioning THAs.
- MRI scans for volume and gray matter attenution versus non-cobalt THA patients
- 29 patients with MoM THAs, serum cobalt 0.89-4.47
- MRI attenuation determined with PRIME/FIRST
- Subtle structural changes in visual pathways and basal ganglia in asymptomatic patients
- No significant differences in brain volumes for cobalt patients versus non-cobalt THA

Mito Y, Yoshido K, Yabe I,et al.[3]

- SPECT Brain analysis of Parkinson's disease by 3D-SSP
- 38 patients – mean age 68 years
- Perfusion decrease anterior cingulate cortex and occipital lobe.
- With gait disturbance – medial frontal lobe, lateral frontal, lateral temporal association

[1] Callender T, Morrow L, Subrmanian K, et al. Three-dimensional Brain Metabolic Imaging in Patients with Toxic Encephalopathy. Environmental Research 60, 295-0319 (1993)

[2]Clark M, Prentice J, Hoggard N, Brain Structure and Function in Patients after Metal-on-Metal Hip Resurfacing. AJNR , 2014 Sep:35(9):1753-8.

[3] Mito Yoshido K, Yabe I, et al. Brain SPECT analysis by 3-D SSP and clinical features of Parkinson's disease. Hokaido Igaku Zasshi. 2006 Jan:81()1): 15-23.

Comparison of ACE findings to Callender et al

	ACE	3D Brain Metabolic Imaging[1]
# of Patients	26	33

STUDY	# of Patients	Cerebellum	Caudate	Frontal	Motor	Occiptal	Parietal	Temporal	Thalamus	Basal Ganglia
Three-Dimentional Brain Metabolic Imaging in Patients with Toxic Encephalopathy	33	6.50%	3.20%	61.00%	9.60%	3.20%	13.00%	94.00%	29.00%	45% (visual)
PET/CT Brain Imaging of Cobalt Encephalopathy (ACE)	26	8.00%	23.00%	73.00%	4.00%	42.00%	42.00%	96.00%	12.00%	38.00%

Regions	Percentages of Patients with Deceased Metabolism	
Cerebellum	8.0%	6.5%
Caudate	23%	3.2%
Frontal	73%	61%
Motor	4%	9.6%
Occiptal	42%	3.2%
Parietal	42%	13 %
Temporal	96%	94%
Thalamus	12%	29%
Basal Ganglia	38%	45%[2]

3D: Temporal>Frontal>Basal Ganglia>Thalamus>Parietal>Motor strip>Occipital>Caudate

ACE: Temporal >Frontal>Parietal > Occipital>Basal ganglia >Caudate>Thalamic > Visual Cortex

[1] Callender T, Morrow L, Subrmanian K, et al. Three-dimensional Brain Metabolic Imaging in Patients with Toxic Encephalopathy. Environmental Research 60, 295-0319 (1993)

[2]Callender, et al – visual interpretation of abnormally decreased HMPAO perfusion of regions without quantification

Comparison of ACE findings to Clark M, Prentice N, Hoggard M, et al

No significant brain atrophy for cobalt patients in either study
Visual and basal ganglia involvement in both studies

Clark et al only looked at normal functioning hips prostheses with only marginally elevated serum cobalt levels

Required significant post-imaging computer analysis to tease out findings

Comparison of ACE findings to Mito Y, Yoshido K, Yabe I, et al

Perfusion decrease anterior cingulate cortex and occipital lobe on SPECT. ACE PET study showing similar findings for regions may be reason for Parkinsonism in ACE patients

With gait disturbance – medial frontal lobe, lateral frontal, lateral temporal association on SPECT. Similar findings on ACE PET may also suggest similar process with cobalt toxicity.

Clark M, Prentice J, Hoggard N, Brain Structure and Function in Patients after Metal-on-Metal Hip Resurfacing. AJNR , 2014 Sep:35(9):1753-8.

Mito Yoshido K, Yabe I, et al. Brain SPECT analysis by 3-D SSP and clinical features of Parkinson's disease. Hokaido Igaku Zasshi. 2006 Jan:81()1): 15- 23.

Conclusions:

FDG PET brain scans provide straightforward, quantifiable and reproducible data which may be helpful for the earlier detection and better quantification of arthroplastic cobalt encephalopathy when compared to present clinical and laboratory studies. ACE may be more prevalent than appreciated in the literature.[1]

All arthroprosthetic joint replacements containing cobalt alloy may be considered as a source of potential encephalopathy, not just Metal-on-Metal (MoM) prostheses.

Monitoring serum cobalt levels , while grossly helpful, may be insufficient to assess neurocognitive risk

The use of any CrCo alloy in prostheses is an area well overdue for further investigation and clinical guidance from molecular imaging to:

1) establish better thresholds for cobalt exposure
2) define monitoring protocols for patients with CrCo prostheses
3) identify reversible versus irreversible thresholds for cobalt toxicity
4) discriminate ACE from other age- and dementia-related illness
5) evaluate treatment options and timing for medical versus surgical interventions.

Lastly, with alternative safer materials commonly available such as ceramics, stainless steels, advanced plastics and titanium, further research may find that continued use of Cr-Co alloys for joint replacements may be unwarranted.

[1]Cheung A, Banerjee S, Cherian J, et al. Systemic cobalt toxicity from total hip arthoplasties. Bone Joint J 2016;98-B:6-13.

What If? - A Case Report based on clinical conjecture

Subject: 57 year old male

Athletic - history of playing basketball, as adult, pick up games
Artistic

Medical history:

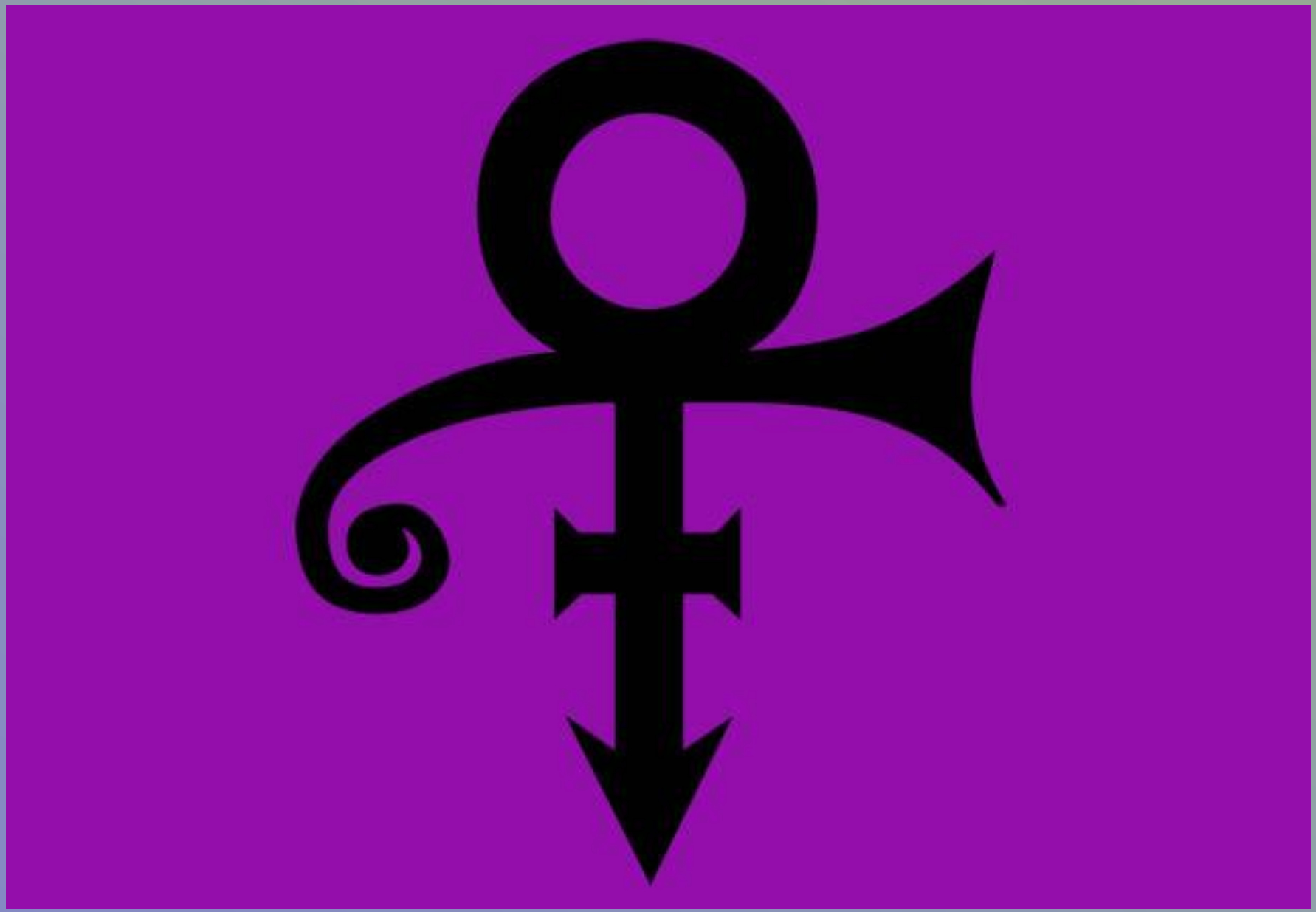
- Childhood epilepsy
- Reports of diagnosis of AIDS in last 6 months
- Orthopedic problems- hip pain with need for surgery 2005
  - Required cane to assist prior to surgery. ? From footwear?
- Hip surgery 2008 – Left hip (?both)
  - Recurrent pain in following years requiring cane
- Opioid addiction – seeking help with withdrawal
  - Died from accidental overdose of Fentanyl

Hip arthroplasty performed in England. At the time, recommendation would have been for MoM resurfacing for active individual of his age and professional requirements. This is not the same person as the MoM hip shown earlier, but possibly the same brand of hip prosthesis.

Reelz documentary May 2017 noted major concern for increasing “memory problems”

Other theory is of pain from fibromyalgia causing hip pain.

This discussion is retrospective conjecture without extensive review of medical history which is presently unavailable. There are confounding co-morbidities. However, taking into account present literature and preliminary research data, such an individual might have had the local and systemic effects from cobalt toxicity such as ARMD and cobalt induced CTE. Did this accentuate the need for pain medications? We will never know. Individual cremated. Knowledge now can not be used to judge the past, but hopefully aid patients in the future. All that can be said is…….



R.I.P. - Prince Rogers Nelson (June 7, 1958 – April 21, 2016)