Uranium toxicity

Advanced biochemical and biophysical effects

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Toxicity Regulations 1: Chemical

Uranium considered to be a ‘heavy metal’ poison, targetting the kidney and brain.

Limits are:

*US EPA <20μg /l drinking water

US NIOSH/OSHA <0.05mg/m^3 dust

US NRC (Nuclear) <0.2mg/m^3 inhalation

German BbodSchV <0.25mg/m^3 inhalation

** At well below these levels there is full saturation of DNAP*

Toxicity Regulations 2: Radiological

Uranium considered to be a low cancer risk because of its low activity; target organs are the kidney, lung and bone

U-238 has specific activity of about 12.4 MBq/kg so 10μg/l is 0.124Bq/l. (not counting the daughter beta-emitters)

ICRP68 gives dose coefficients for inhalation of Fast Medium and Slow dissolving forms of Uranium:

F: 4.4 E-7; M: 2.6E-6; S: 7.3E-6 Sieverts per becquerel

For ingestion the ICRP68 dose coefficients are:

Any form: 4.4E-8 and UO2: 7.6E-9

Therefore in the worst case, based on these coefficients doses from Uranium below 0.5mg/l are microSieverts.

This is why the Royal Society and WHO and their physicists dismiss the fears of the Gulf War veterans.

But there are problems with the IRCP radiological risk methods (ECRR2003, IRSN 2006)

- ICRP assumes that absorbed dose (energy per unit mass) is an accurate measure of risk. The decays from particulate uranium are short range and doses near micron sized particles can be large for local tissue volumes within range of the decays
- This was pointed out in ECRR 2003, CERRIE 2004, by IRSN 2006 and many others (including me) in the last 50 years (the hot particle problem, the second event problem).

There are new results from laboratory research

Because of interest in the health effects of Uranium weapons new research has shown that there are anomalous genotoxic effects at low concentrations:

1. Uranium causes genomic and genetic damage in cell cultures at concentrations where there are no significant alpha emissions (AC Miller et al, 98-05 and other teams also.)
2. Uranium (and tungsten) particles cause genetic changes in cell culture elements and cause cancer in laboratory animals (AC Miller teams 2000-2005)
3. Uranium causes anomalous inflammation in lung, kidney, brain and other living tissue in rats and causes chromosome damage in miners and Gulf War Veterans (French researchers, Zaire et al (1998), Schroeder et al (2003).
4. These effects are puzzling on basis of conventional risk models and have been ascribed to ‘heavy metal toxicity’ or ‘chemical effects’ or ‘synergy between radiation and chemistry’.

What are chemical ‘heavy metal’ effects in the cell? Some proposed mechanisms from the literature

1. Enzyme poisoning by binding to S-H groups inhibits a critical reaction (e.g. Pb, Hg, Cd)
2. Binding to DNA phosphate (Mg, Ca, Sr, Ba, UO_2^{++}) deforms the DNA tertiary conformation and alters folding or unfolding in some way.
3. Binding to some critical ‘receptors’ antagonise normal binding by agonists (e.g. zinc finger proteins and DNA replication)
4. Inflammatory responses at tissue level (brain, intestine, kidney, lung). Mechanism described as ‘Oxidative Stress’ and ‘Genotoxicity’ since associated with hydrogen peroxide and antioxidant responses and/or various other markers and end points (e.g. ENVIRHOM report references). But why?
5. Conclusions are usually given as a combination of CHEMICAL and RADIOLOGICAL effects that are greater than either alone, i.e. a multiplicative synergy. But how does this work?

What do heavy metals have in common chemically?

Answer:

Nothing

They have different chemistry, valency, affinity, redox equilibria, normal ionisation states, reactivity, Lewis acidity, ionic radii, energy levels, colour, work functions, solubility, melting points, boiling points, etc. etc.

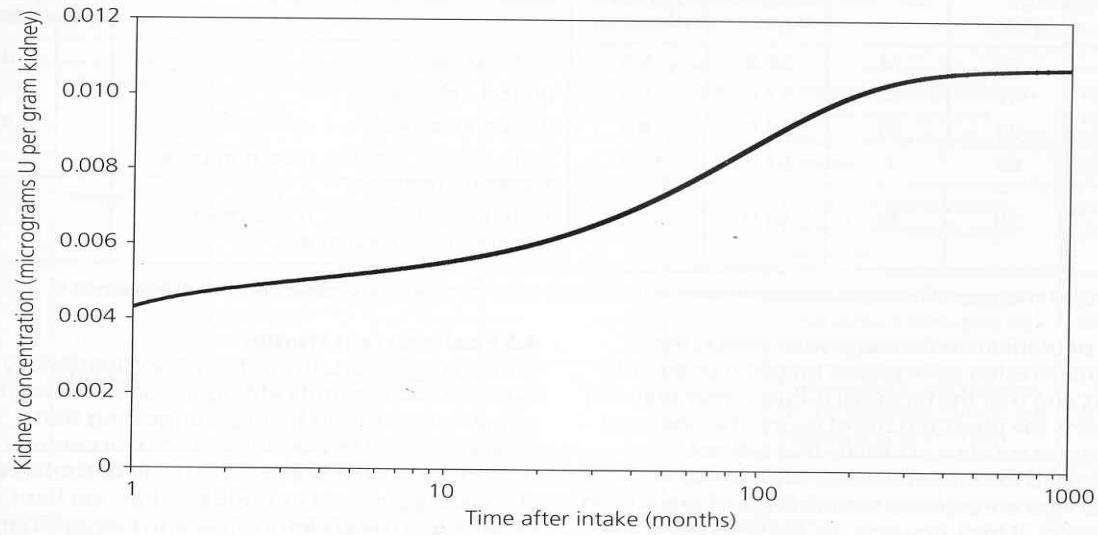
No physical chemist would understand the concept of a ‘heavy metal’.

But the highest atomic number elements have catalytic activity when finely divided (e.g. Pt, Pd, U)

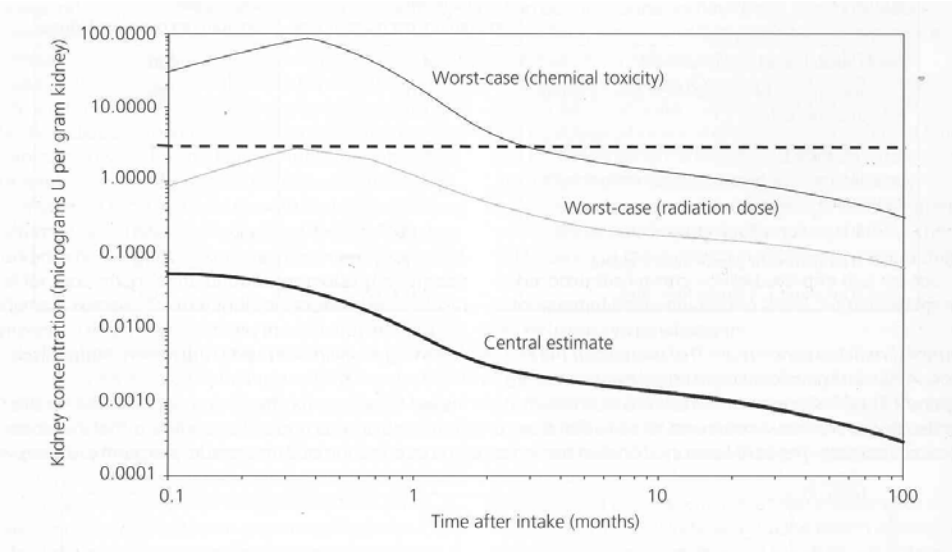
A new IDEA

Uranium is everywhere, and increasingly so due to DU and fertilisers. It builds up in humans and living systems due to its high affinity for tissue components, DNA and nervous system components. The graph below is from the Royal Society Report. It shows that a continuous daily ingestion of 1μg will result in kidney concentration of 12μg/l . At this concentration DNA will be saturated with UO_2^{++}.

Figure 2. Predicted concentration of uranium in the kidney from the constant uptake into the blood of 1μg uranium per day.



In the UK Depleted Uranium Oversight Board we were expecting to measure DU in veterans 13 years after exposures of 10 mg by acute inhalation. This shows how strongly Uranium is retained. The Veterans suffered from Gulf War Syndrome, a condition shown by Chaney et al (using phosphorus brain NMR) to be associated with loss of brain function in the lower brain and brainstem. Graph shows that DU excretion could still be measured (by ICPMS) following a 10mg inhalation intake.



Secondary Photoelectrons

- Since 2002 I have been drawing attention to the Photoelectric Enhancement (PE) of natural background radiation by elements of high atomic number Z. Uranium has the highest atomic number (Z=92) for all naturally occurring elements.
- This has led me to look at the idea of ‘heavy metal’ toxicity and carcenogenicity
- We need to consider what is really going on in the cell when the DNA is mutated by an agent. What is ‘Oxidative Stress’ and where else do we see it? We see it after radioactive exposure. But with Uranium, there is not enough intrinsic radioactivity. Is there?

Why do we call them ‘heavy metals?

- Because they are heavy: they are dense and have a high atomic mass
- The also have a high atomic number Z
- And their toxicity goes up with the atomic number Z
- For the Group II metals, which bind to the DNA phosphate strongly, the i.v. LD50 (soluble salts) in rats is:

Mg, Ca:	>2000	harmless
Sr:	540mg/kg;	some toxicity
Ba:	20mg/kg	high toxicity

But Fact (1) : Absorption of gamma and X-radiation is proportional to the fourth power of the atomic number Z

Material	Z	Z^4	$H_2O = 1$
H_2O	3.33	123	1.0
DNAP	5.5	915	7.4
Ca	20	0.15E6	1220
Sr	38	2.1E6	17,073
Ba	56	9.8E6	79,675
Au	79	38E6	308,943
U	92	72E6	585,365

And Fact (2): Uranium, as UO_2^{++} (uranyl) binds strongly to DNAP

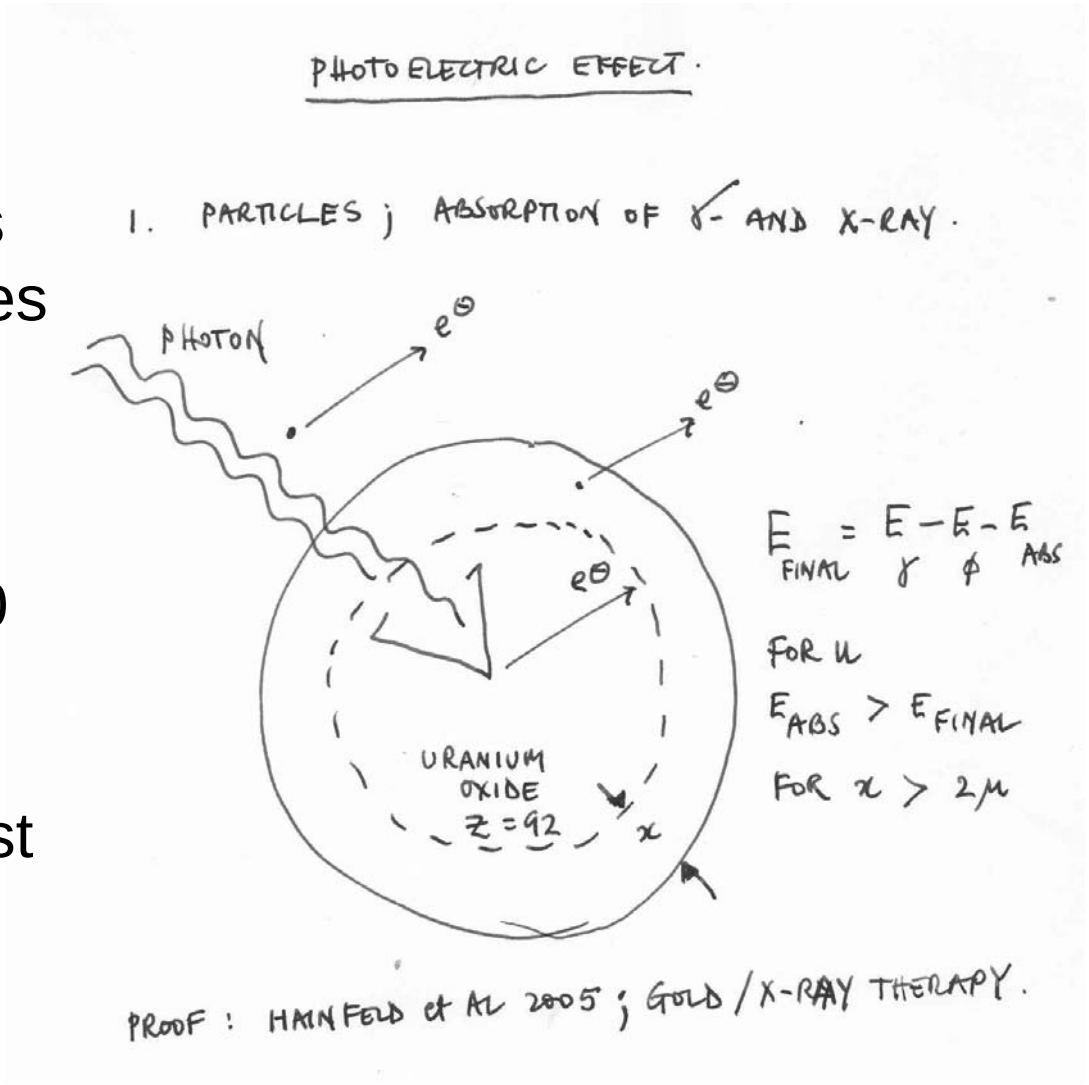
- The affinity constant is $10^{10}M^{-1}$ measured by Nielsen et al (1992)
- This means that at a concentration of

10^{-10}M (23.6ng/l) the DNAP will be half-saturated at a stoichiometry of 1 mole uranium to 2 moles PO_4^{--} .

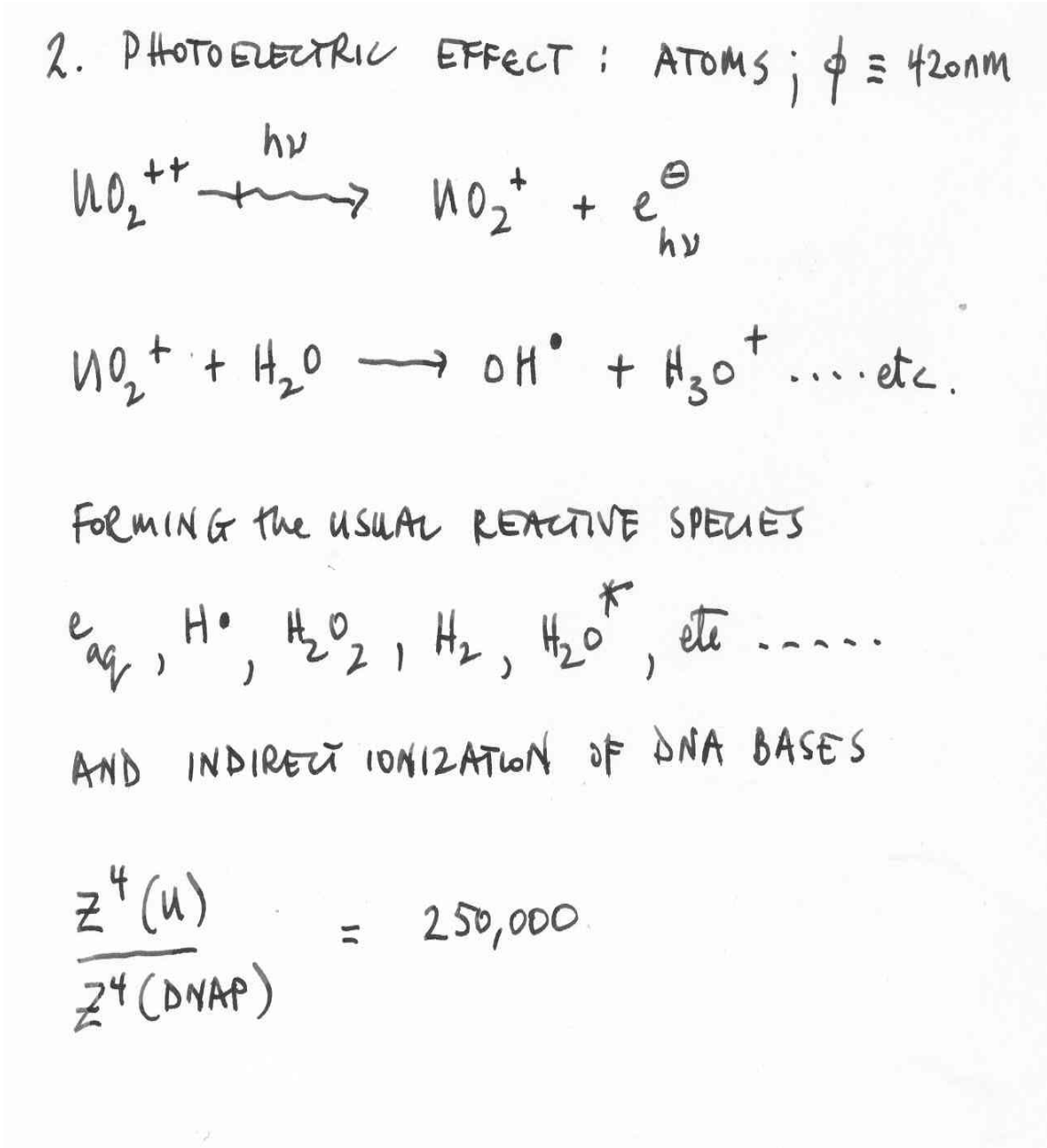
The affinity for DNAP was first pointed out in 1961 when it began to be used as an electron microscope stain:

Huxley and Zubay (1961) stated that DNA takes up its own dry weight in uranium from a 2% fixing solution

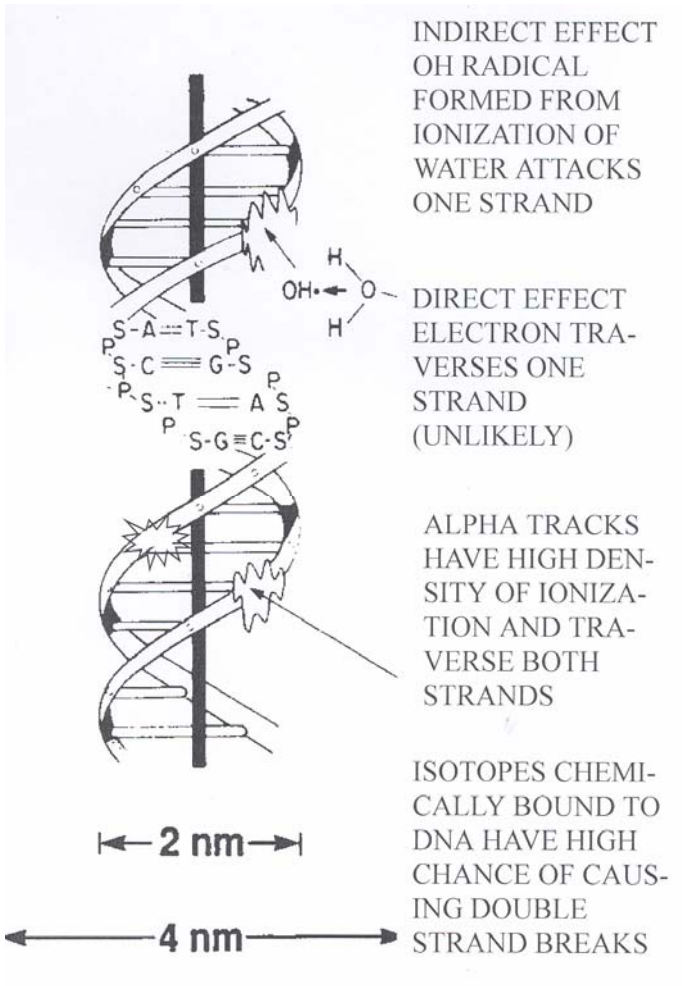
Taken together, this means that uranium bound to the DNA has more than 55,000 times more absorption of natural background gamma radiation than the DNA, and 500,000 than water. Uranium oxide **particles** from weapons will emit most of the absorbed the energy as photoelectrons into local tissue.

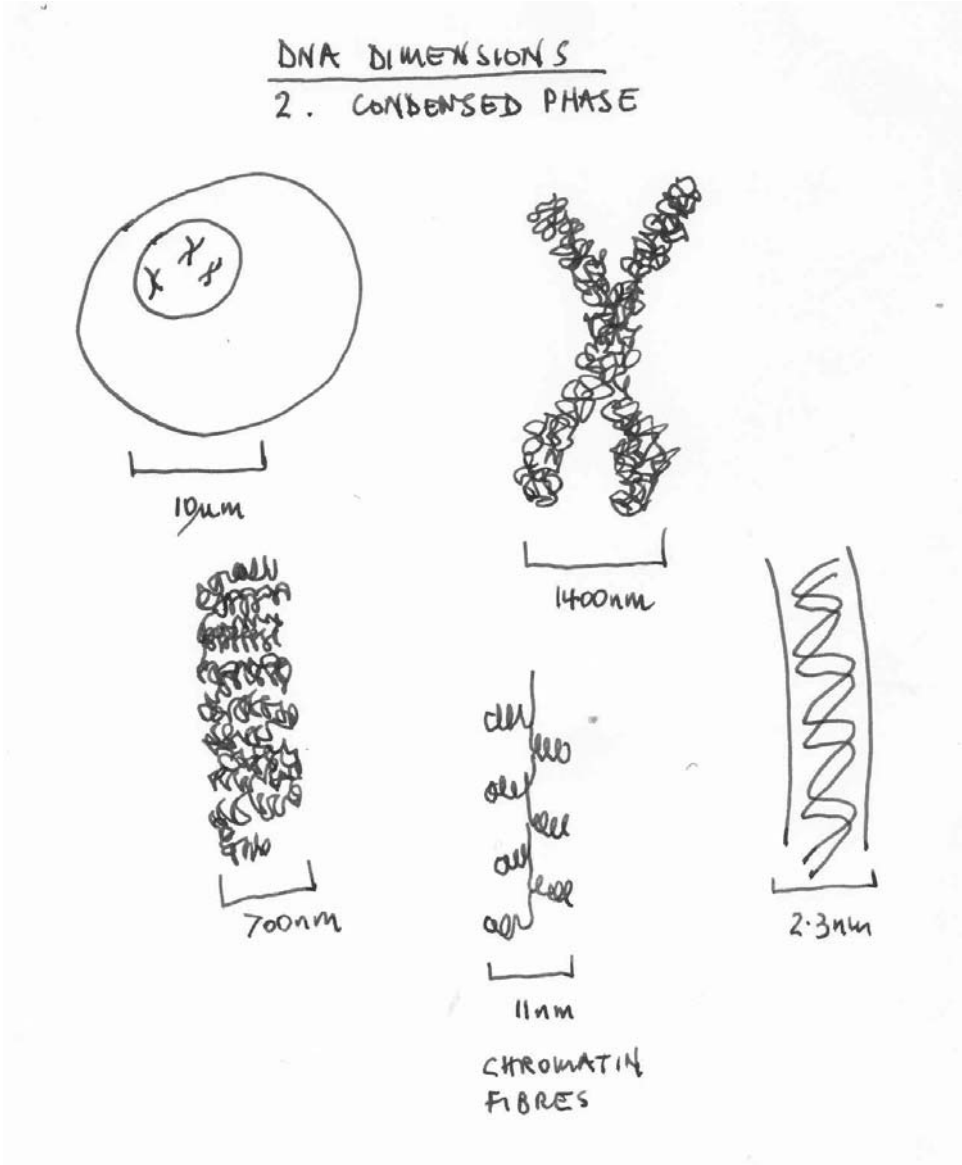


The DNA as the uranyl complex ion, will absorb natural background gamma and X-rays 55,000 times more effectively than solvent water and DNAP and even more than 450 times more than Ca++ ions which are the normal DNAP cations

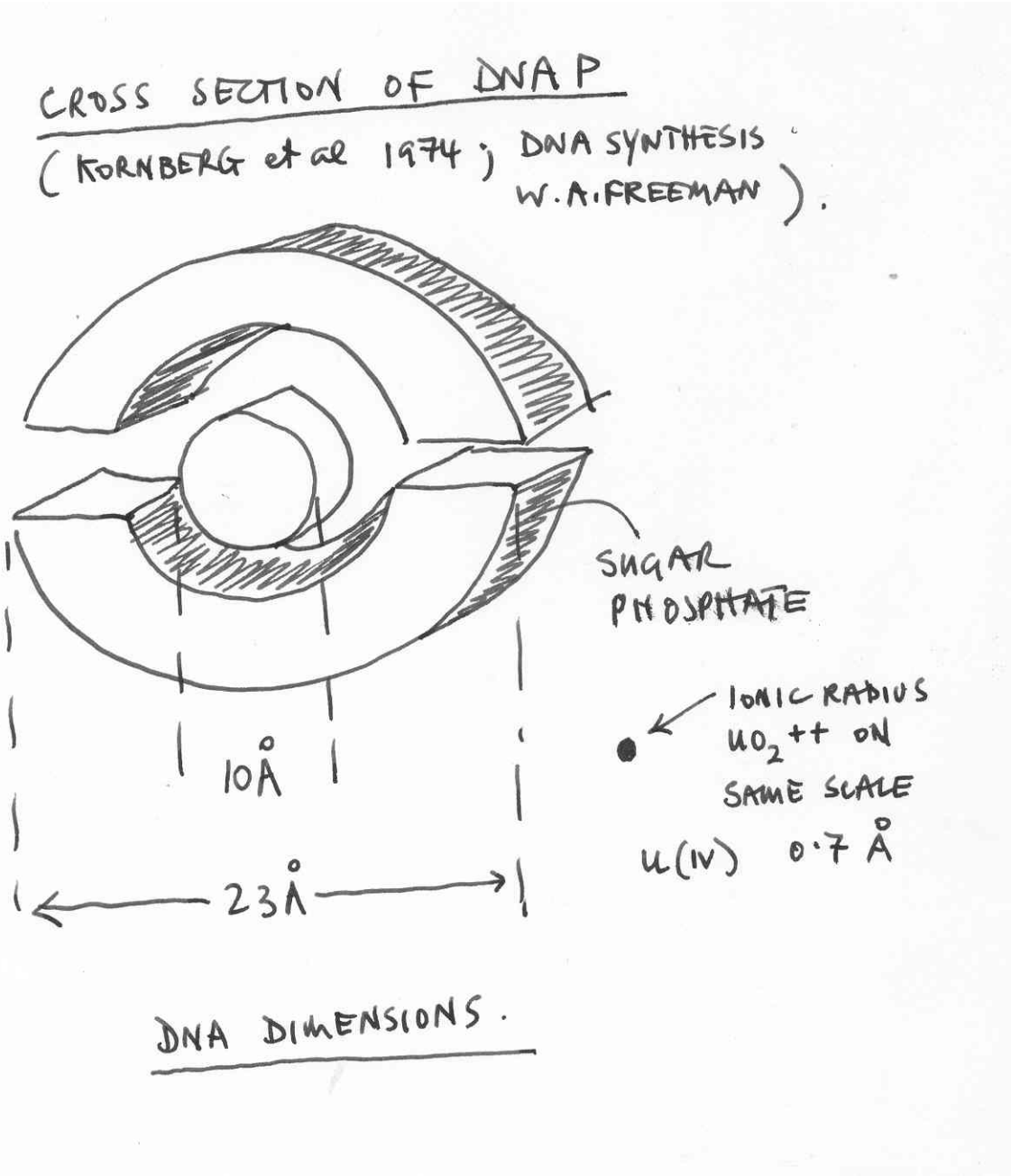


Some DNAP dimensions



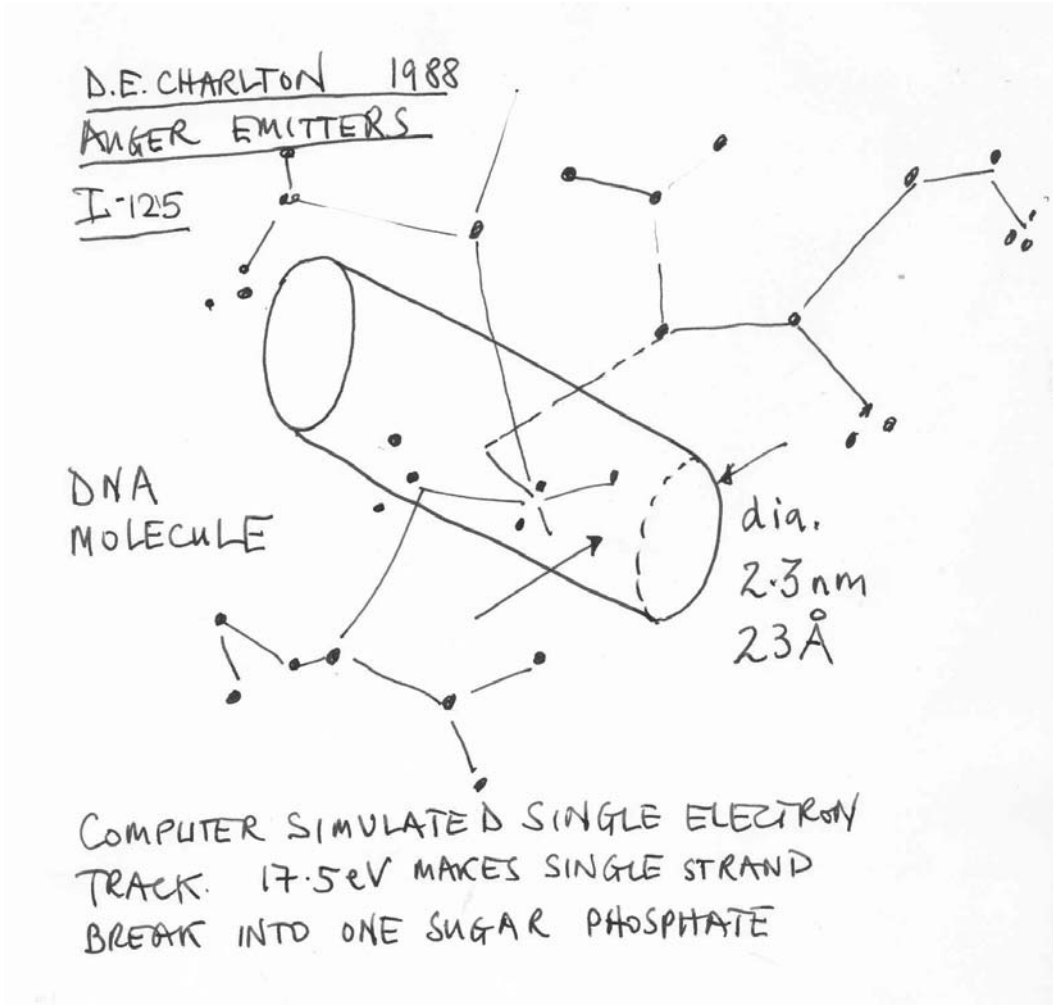


Uranium bound to the DNAP is within 2.3nm of the axis of the strands, but in the condensed chromatin, is buried deep within a mass of chromosomal genetic material. It will preferentially absorb gamma and X-ray background and re-emit the energy as short range photoelectrons



We know from experiments with Auger emitters bound to DNA (e.g.I-125) that DNA is the target for the effects of ionising radiation. BEIR V (1990) p 14 give the absorption of DNA by 1 Gray of radiation. Quoting Ward et al, (1988) they assume 6pg of DNA of which 1.2pg is phosphate.

This allows me to calculate that at half saturation (tissue concentration of 23.8ng/l) there is 0.7pg uranium per cell.



The enhancement of absorption

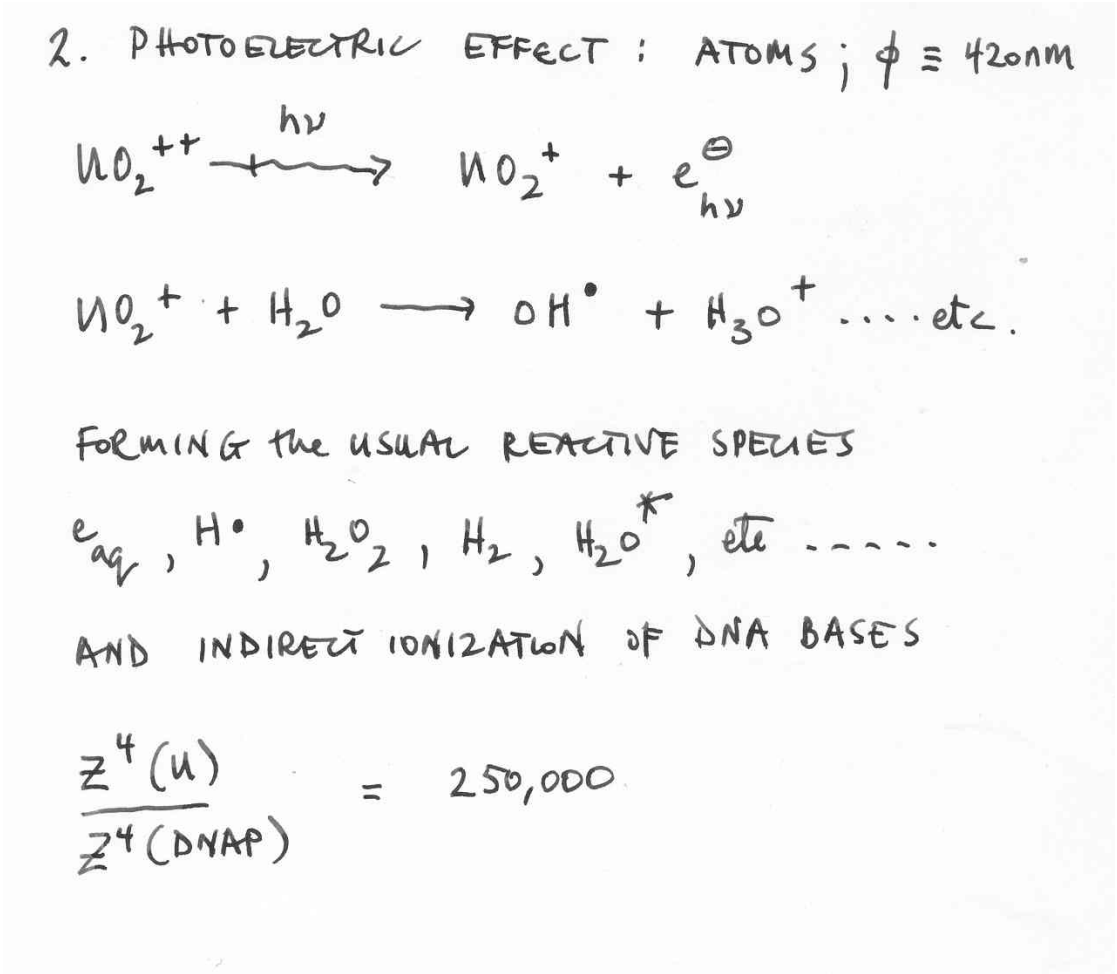
- Energy deposited by 1Gy in the DNAP of the cell is 36keV (BEIR V, 1990)
- Energy absorbed by the phosphate is 7.3keV (BEIR V 1990)
- At 50% saturation the uranium mass is 0.7pg from the stoichiometry, this is 12% of DNA by mass.
- Substituting Uranyl (Z^4 ratio 450) for calcium the absorption enhancement factor is 100-fold (3285keV/Gy)
- Where does the energy go?

(1) Into the DNAP as photoelectrons and their ionisations

(2) Into the DNA through catalytic balancing redox reactions

(3) Causing Oxidative Stress

The ionisation of a daughter element following beta emission is ignored by ICRP. Yet if the element is bound to DNAP (e.g Sr90, Ba140) it represents a serious hazard. For Uranium and photoelectrons there is continuous and repeating loss of the electrons, change of charge and reaction with solvent to generate hot species.



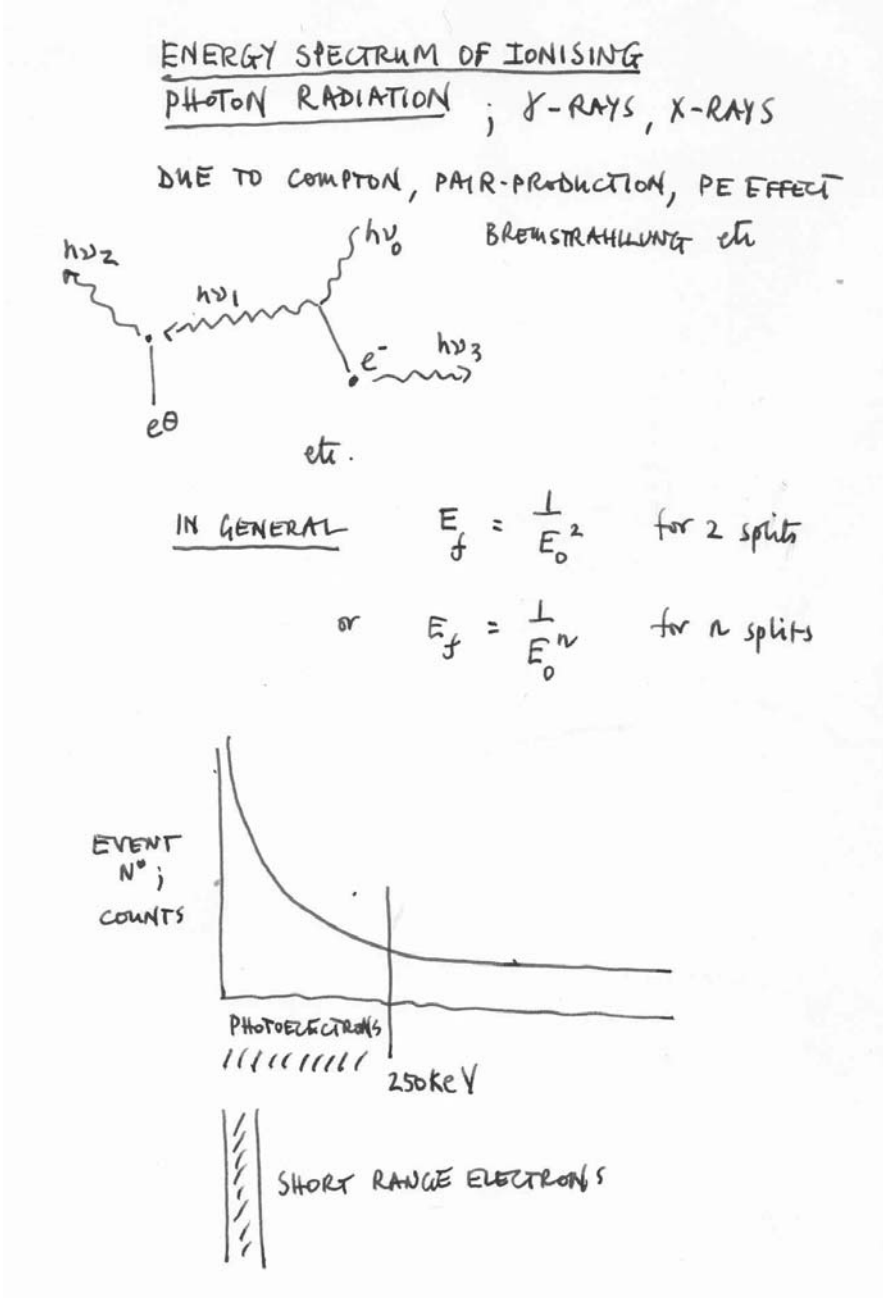
Evidence for this effect; it is not a new idea

- Photoelectron enhancement of dose has been examined since Speirs (1949) calculated that there is an enhancement of 10-fold near bones in X-raying
- Since then, Matsudeira *et al (*1980) used Iodine contrast media to enhance X-ray radiotherapy
- Castillo *et al* (1988) showed enhanced doses near mandibular reconstruction plates
- Regulla *et al* (1998) measured 100-fold photoelectron enhancements near gold foils
- Herold *et al* (1999) used 400nm gold particles to enhance X-ray doses in radiotherapy
- Hainfeld *et al* (2005) showed that gold 10-50nm nanoparticles (Z=79) could be successfully used to enhance X-ray radiotherapy for tumours in mice and **patented the method**.

The energy spectrum of natural background gamma rises sharply (as E^{-2} or E^{-n}) toward low energy.

Conversion to photoelectrons for elements of Z>30 occurs for photon energy below about 250kev

This means that most of the photoelectrons in tissue derived from natural background external radiation are short range



A thought: Evolution

- Evolution has had access to many elements to incorporate into living systems
- If I am right, use of elements of high atomic number will attract major disadvantages
- And it seems this is so: no element with Z> 30 is employed by living systems with one exception
- IODINE, Z=53
- Why? Why jump over Bromine?

PERIODIC TABLE OF THE ELEMENTS

2a	3b	4b	5b	6b	7b	8	1b	2b	3a	4a	5a	6a	7a	0	Orbit
	KEY TO CHART Atomic Number → 50 +2 ← Oxidation States Symbol → Sn +4 Atomic Weight → 118.69 18 18 4 ← Electron Configuration													2 0 He 4.00260 2	K
4 +2 Be 9.01218 2-2									5 +3 B 10.81 2-3	6 +2 +4 −4 C 12.011 2-4	7 +1 +2 +3 +4 +5 −1 N 14.0067 −2 −3 2-5	8 −2 O 15.9994 2-6	9 −1 F 18.998403 2-7	10 0 Ne 20.17₉ 2-8	K-L
12 +2 Mg 24.305 2-8-2	Transition Elements						Transition Elements		13 +3 Al 26.98154 2-8-3	14 +2 +4 −4 Si 28.0855 2-8-4	15 +3 +5 −3 P 30.97376 2-8-5	16 +4 +6 −2 S 32.06 2-8-6	17 +1 +5 +7 −1 Cl 35.453 2-8-7	18 0 Ar 39.948 2-8-8	K-L-M
20 +2 Ca 40.08 -8-8-2	21 +3 Sc 44.9559 -8-9-2	22 +2 +3 +4 Ti 47.90 -8-10-2	23 +2 +3 +4 +5 V 50.9415 -8-11-2	24 +2 +3 +6 Cr 51.996 -8-13-1	25 +2 +3 +4 +7 Mn 54.9380 -8-13-2	26 +2 +3 Fe 55.847 -8-14-2	27 +2 +3 Co 58.9332 -8-15-2	28 +2 +3 Ni 58.71 -8-16-2	29 +1 +2 Cu 63.546 -8-18-1	30 +2 Zn 65.38 -8-18-2	31 +3 Ga 69.735 -8-18-3	32 +2 +4 Ge 72.59 -8-18-4	33 +3 +5 −3 As 74.9216 -8-18-5	34 +4 +6 −2 Se 78.96 -8-18-6	35 +1 +5 −1 Br 79.904 -8-18-7	36 0 Kr 83.80 -8-18-8	-L-M-N
38 +2 Sr 87.62 -18-8-2	39 +3 Y 88.9059 -18-9-2	40 +4 Zr 91.22 -18-10-2	41 +3 +5 Nb 92.9064 -18-12-1	42 +6 Mo 95.94 -18-13-1	43 +4 +6 +7 Tc 98.9062 -18-13-2	44 +3 Ru 101.07 -18-15-1	45 +3 Rh 102.9055 -18-16-1	46 +2 +4 Pd 106.4 -18-18-0	47 +1 Ag 107.868 -18-18-1	48 +2 Cd 112.41 -18-18-2	49 +3 In 114.82 -18-18-3	50 +2 +4 Sn 118.69 -18-18-4	51 +3 +5 −3 Sb 121.75 -18-18-5	52 +4 +6 −2 Te 127.60 -18-18-6	53 +1 +5 +7 −1 I 126.9045 -18-18-7	54 0 Xe 131.30 -18-18-8	-M-N-O
56 +2 Ba 137.33 -18-8-2	57* +3 La 138.9055 -18-9-2	72 +4 Hf 178.49 -32-10-2	73 +5 Ta 180.947₉ -32-11-2	74 +6 W 183.85 -32-12-2	75 +4 +6 +7 Re 186.207 -32-13-2	76 +3 +4 Os 190.2 -32-14-2	77 +3 +4 Ir 192.22 -32-15-2	78 +2 +4 Pt 195.09 -32-16-2	79 +1 +3 Au 196.9665 -32-18-1	80 +1 +2 Hg 200.59 -32-18-2	81 +1 +3 Tl 204.37 -32-18-3	82 +2 +4 Pb 207.2 -32-18-4	83 +3 +5 Bi 208.9804 -32-18-5	84 +2 +4 Po (209) -32-18-6	85 At (210) -32-18-7	86 0 Rn (222) -32-18-8	-N-O-P
88 +2 Ra 226.0254 -18-8-2	89** +3 Ac (227) -18-9-2	104 +4 — (260) -32-10-2	105 — (260) 32 11 2	106 (263) 32 12 2												O P Q

anides	58 +3 +4 Ce 140.12 -20-8-2	59 +3 Pr 140.9077 -21-8-2	60 +3 Nd 144.24 -22-8-2	61 +3 Pm (145) -23-8-2	62 +2 +3 Sm 150.4 -24-8-2	63 +2 +3 Eu 151.96 -25-8-2	64 +3 Gd 157.25 -25-9-2	65 +3 Tb 158.9254 -27-8-2	66 +3 Dy 162.50 -28-8-2	67 +3 Ho 164.9304 -29-8-2	68 +3 Er 167.26 -30-8-2	69 +3 Tm 168.9342 -31-8-2	70 +2 +3 Yb 173.04 -32-8-2	71 +3 Lu 174.967 ± 0.003 -32-9-2	N O
nides	90 +4 Th 232.0381 -18-10-2	91 +5 +4 Pa 231.0359 -20-9-2	92 +3 +4 +5 +6 U 238.029 -21-9-2	93 +3 +4 +5 +6 Np 237.0482 -22-9-2	94 +3 +4 +5 +6 Pu (244) -24-8-2	95 +3 +4 +5 +6 Am (243) -25-8-2	96 +3 Cm (247) -25-9-2	97 +3 +4 Bk (247) -27-8-2	98 +3 Cf (251) -28-8-2	99 +3 Es (254) -29-8-2	100 +3 Fm (257) -30-8-2	101 +2 +3 Md (258) -31-8-2	102 +2 +3 No (259) -32-8-2	103 +3 Lr (260) -32-9-2	O P Q

Numbers in parentheses are mass numbers of most stable isotope of that element.

Why Iodine?

ICRP Committee 2 Table 7 shows that Iodine is concentrated in two systems

(1) Thyroid
(2) Blood

These two are the first and main systems to succumb to radiation exposure: anemia, leukemia and thyroid cancer

I suggest that the Thyroid gland is a built in radiation detector and that the thyroid hormones up-regulate radiation repair system genes

Finally

- It has recently been discovered that the celebrated child leukemia cluster in Fallon Nevada occurs in an area where there are high levels of tungsten particles (W = 74) in the atmosphere
- There are certainly high levels of uranium particles in the atmosphere of Iraq and also near Sellafield and the Irish Sea where other child leukemia clusters are found.
- The idea opens up the possibility that many unexplained biological or catalytic properties of high atomic number elements (Pt, Pb) may have an origin in these photoelectron enhancements
- The effect is easy to examine, since we just have to further examine the biological effects of combinations of gamma or X-rays with uranium or gold.
- I need hardly add that these ideas have significant policy implications: my paper on these effects is with the reviewers of the *Proceedings of the Royal Society B.*
- We must assume that Uranium is seriously underestimated health hazard and that other high Z elements may also be.