# Atoms for War, Atoms for Peace

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**Abstract**

We review new information on Nuclear Warfare and Nuclear Energy before, during and immediately after the 7th International Congress on Energy, held in Manchester, England, 2017.

Our primary goal is to encourage all countries in this world to prohibit, Nuclear Warfare i.e. 'Atoms for War' as it might bring the human race and animals living on the planet Earth close to extinction. Our secondary goal is to highlight 'Atoms for Peace', to make it possible to provide renewable energy to the whole world, as this cannot be achieved on a global scale by all other renewable energies combined: wind, solar, and water.

As long-term staff members of the now defunct Radiobiological Institute of TNO in Rijswijk, the Netherlands, directed by the late Dick van Bekkum, we participated in Radiobiological studies of Total Body Irradiation (TBI), such as experienced by human being during Nuclear Warfare. We identify several new beneficial applications of Atoms for Peace in animal studies and human patients. (1)

Atoms for Peace studies in human patients should be allowed to proceed and not be stifled by the fear that all nuclear energy studies will eventually lead to more nuclear warfare.

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***Keywords***
Nuclear Warfare
Total Body Irradiation (TBI)
Graft versus Host Disease, (GvHD)
Blood transfusion,
Radiolabeled Immunoglobulin Therapy (RIT)

## Atoms for War

The detonation of two nuclear bombs, '*Little Boy'* and *'Fat Man'* on respectively August 6, 1945 above Hiroshima and on August 9, 1945 in Nagasaki causes more than 200.000 fatalities. (2-4) On August 15, 1945 the Emperor of Japan surrenders in a previously recorded radio speech.

On December 2, 1945, the surrender of Japan is codified by the signing of the surrender papers on the US battleship Missouri, in Tokyo Bay. US General Douglas Mac Arthur, becomes the new, temporary, leader of Japan. He closes the proceedings on the Missouri by:

'It is my earnest hope -indeed the hope of all mankind- that from this solemn occasion a better world shall emerge out of the blood and carnage of the past, a world founded upon faith and understanding, a world dedicated to the dignity of man and the fulfillment of his most cherished wish for freedom, tolerance and justice.'

General MacArthur orchestrates a fast recovery of Japan's recovery to serve as a 'buffer' state to resist expansion of the Soviet Union. In contrast, the Allied Forces during the Potsdam meeting and Nuremberg trial put many punitive economic restrictions on Nazi-Germany. Stalin ordered all 'European' countries in the influence sphere of Russia to refuse 'Marshall Aid'.

Mac Arthur's statement on the Missouri did not prevent him from granting immunity to Dr. Ishii, leader of unit 731 in Harbin, Manchuria with more than 3000 employees, who performed serious war crimes, including vivisection, chemicaland microbiological experiments on, large populations in China with plans to do the same in California, USA.

## Atoms for Peace

General/President Dwight D Eisenhower gives a speech for the United Nations Assembly in New York, entitled *'Atoms for Peace'*.

Eisenhower invites other nations capable of engaging in Nuclear Warfare to make some of their fissionable material available to other nations under the condition such nations will use the material only for peaceful purposes.

## Global distribution of Nuclear Warheads

Energy Agency (IAEA) is established in Vienna, Austria. Its mission is to decrease the risks for disastrous Nuclear Warfare and to increase the peaceful use of radiation. IAEA has 168 member countries. It reports to the United Nations General Assembly and Security Council. Eight countries harboring most of the nuclear warheads are listed in Table 1.

**Table 1**

| **Countries with nuclear warheads** | **Number of warheads** | **Comments** |
|---|---|---|
| United States | 7300 | First country to store nuclear warheads. First nuclear war test in 1945. Eisenhower's promise to the UN in 1953 to decrease the number of nuclear warheads is piecemeal implemented by his successors |
| Russia | 8.000 | Second country to store nuclear warheads First nuclear test in 1949. Reagan and Gorbachove commit to decrease the number of nuclear warheads. When Gorbachov resigns, ten 'nuclear' cities in Russia become rudderless. Highly skilled nuclear scientists have access to vast amounts of fissionable material; have no passports and no longer receive a salary. Nuclear engineers of the Hanford reactor site in the State of Washington, USA try to educate the Russian Nuclear engineers in 'Atoms for Peace' applications. April 1986, Chernobyl's reactor 4 explodes due to its flawed desigand serious mistakes by the reactor operator. Thirty operators and firemen, identified in Russian documents as 'liquidators', die from bone marrow aplasia, skin burns, notwithstanding ultimately futile bone marrow transplant attempts by Bob Gale, financed by the Ukraine/USA business man Armand Hammer. Dramatic increase note in treatable, non-lethal thuroid cancers in children |
| United Kingdom | 160 | First Nuclear bomb test in 1952. Submarines located in Plymouth Bay contain presently outdated nuclear warheads. October 10, 1957 graphite in one of the piles in Windscale, Umbria (in use for making fissionable material for an upcoming H-bomb test) catches fire and burns for three days. Radioactivity cloud is blown over Britain and Europe. Health effect survey in 2010 of workers involved in clean-up finds no adverse health related outcomes due to radiation. |
| France | 290 | First nuclear bomb test in 1960. Launching warheads from submarines. |
| India | 90-110 | First nuclear bomb test in 1974 |
| Pakistan | 120-130 | The only nuclear weapon State in the Islamic world. Adverse relationship with neighbor India about the Kashmir territory |
| Israel | 80? | Does not deny or confirm it harbors nuclear warheads. |

| | | |
|---|---|---|
| North Korea | ? | Refuses to comply with IAEA inspections. Has been expelled from IAEA. Detonated a hydrogen bomb underground in 2017. Negotations between USA President Trump and North Korean President Kim inconclusive. |

**Nuclear warheads in other countries**

Five nations harbor US nuclear warheads as part of a NATO nuclear warheads sharing agreement: *Belgium, the Netherlands, Italy, Germany and Turkey*. War heads are to be delivered by local pilots and bombers. Warheads can only be activated by a USA code. Twenty three additional countries are part of other 'nuclear alliances'.

The highest risk for nuclear warfare occurred in October 1962 in the *'Cuban Missile Crisis'*. Nikita Khrushchev and John Kennedy negotiate for two weeks till they reach a mutually acceptable solution. Russia removes its nuclear warheads from Cuba. Secretively, the US removes its nuclear warheads from Italy and Turkey. The USA promises not to invade Cuba, in what would be a repeat of the failed Bay of Pigs invasion.

In October 1994, President Clinton signs an agreement with North Korea pledging more than 4 billion dollars to resolve the energy crisis in North Korea by helping to finance and build new nuclear reactors for energy and softening the trade embargo. At that time, there are 37.000 US troops in South Korea. North Korea pledges to allow IAEA officials to do full inspections of known or suspected nuclear energy sites. North Korea does not live up to their part of the agreement; IAEA inspectors are not allowed to visit. North Korea is expelled from the IAEA.

**Physical and Biological effects of Nuclear Warfare**

The physical effects of Nuclear Warfare become obvious for the first time in the early morning of June 16, 1945, when the first atomic bomb, named *'Trinity'* is detonated in the Jornado del Muerto Valley near Almagordo, NM, USA. A civilian pilot observes by radio:

"Sunrise in the South today?"'
No response
"Halloho?"
A nearby military airport radio answers:
"Don't go here!"

**Table 2**
Physical and biological effects of Nuclear Warfare in 1945

| *Physical effects* | *Biological Effects* |
|---|---|
| Extreme heat | Fires, Melting human beings |
| Strong winds | Collapsing buildings |
| Light flash/shockwave | Blindness, Bone fractures |
| Total Body Irradiation with gamma rays and neutrons | Lethal Brain-, Vascular-, Gastrointestinal-, Bone Marrow-syndromes, Increased incidence of various malignancies. Combined fatalities in Nagasaki and Hirosima: > 200.000 |

**Table 3**

Limited treatment options for victims of nuclear warfare

*Based on 'Medical Implications of Nuclear War', National Academy Press, Washington D.C. 1986, (5) and (6,7,8)

| | |
|---|---|
| *Fatalities* | In the hundreds of thousands |
| *Triage of survivors* | Estimate combined dose received by gamma rays and neutrons |
| *Palliation/ Comfort care* | Temporary survivors receiving ≥4.0Gy will die within a week or two. Bone Marrow Transplantation not an option, due to lack of the appropriate infra-structure and the severe gastro-intestinal damage generated by TBI from neutrons. (6) |
| *Long term survivors* | Survivors receiving ≤4Gy need careful follow-up for years due to increased incidence of various malignancies |
| *Pregnant Women surviving nuclear detonation* | Women need an abortion only when irradiated between pregnancy weeks 8-16 (7, 8) |
| *Fall-out shelters* | Of limited use; Only 1-2% of the US citizens build one during the 'Cold War'. US Generals gave US soldiers near a nuclear explosion the ludricous advice to quickly build a wall of sand 3 feet high and take shelter behind it. |

Hydrogen *(fission plus fusion)* bombs are orders of magnitude stronger than the bombs used in Japan in 1945. Hydrogen bombs have been detonated by USA, Russia, China, France, United Kingdom and recently North Korea.

Lewis Thomas, MD, president emeritus, Memorial Sloan Kettering Cancer Center sounds a loud and clear alarm bell in a foreword in the *'Medical Implications of Nuclear War'*:

'(…) Nuclear War is for sure, beyond question, dead certainly, figuratively, any way you don't want to think about: *unthinkable.*

(…) some crafty statesman or some other crafty unbalanced military personage, one side or the other, is going to do something wrong, drop something, misread some printout, and there will go 30,000 years of trying ever since Lascaux right up to Bach and beyond in this benighted century –all civilization gone without a trace. Not even a thin layer of fossils left of us, no trace, no memory

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**Human Radiation Experiments of the USA Department of Defense (DOD) between 1940-1974. Report of the President's Advisory Committee, Oxford University Press, 1996**. (9)

**DOD** wants to get information on the risks run by US soldiers ordered to decontaminate a nuclear bomb battlefield. A proposal to expose US soldiers to low level radiation without their consent is dropped as unethical. Instead, more than 2000 US patients with end-stage cancer receive Total Body Irradiation (TBI) in more than 40 medical institutions in the US with a dose between 0.15 and 2.15Gy. (Gy is the unit for absorbed energy in Joule per kg tissue.) Informed consent of the patients not done or inadequate with blatant ethical deficiencies. No patient obtains a measurable, significant tumor response. Temporary decreases in peripheral blood counts were noted in patients getting a TBI dose around 2.0 Gy.

Under persistent pressure of the USA press President Bill Clinton forms a Presidential Advisory Committee to analyze and evaluate the TBI studies. Clinton presents the book written by his Committee at a Press Conference in Washington D.C, April,1995.

(…) '*By making ourselves accountable for the sins of the past... we are laying the foundation for a new era.* (…) *'Under our watch, we will no longer hide the truth from our citizens.'*

President Clinton's speech receives little attention, because it is delivered on April 19, 1995: the day 168 people are killed in the Oklahoma City bombing

Earlier in 1993, Clinton stated in his State of the Union address he was going to stop all nuclear energy related research, because it was *'no longer necessary*'. Clinton did not explain why nuclear energy related research was no longer necessary.

**President Jimmy Carter's interview in 2010** (10)

'The most difficult issue I've ever had to face as a human being is what to do if a nuclear threat materialized (…) during the Cold War. I prayed constantly that I would not be faced with this decision. I don't see the rationality -it is difficult for me to talk about it. I couldn't sit acquiescently and let the Soviet Union destroy my country without a response when we had the capability to do so. (…)

I can't say in good conscience now that my decision to respond would have been the correct one. It would have cost millions of American lives if we were the subject to attack and it would have cost millions of Russian lives if we attacked. I cannot answer your question adequately. It is incompatible with my basic Christian beliefs to do that. What Jesus would have done, I don't know. (…) The fact that the Russians believed I would respond was the essence of mutual deterrence. If I made any sort of insinuation that the Russians could attack us with nuclear weapons without being the recipient of a response-that would have been unimaginable for me to do.'

**United Nations Website -** a document of 11 pages entered in July 2017-
**Treaty on the Prohibition of Nuclear Weapons**

One hundred twenty-two nations sign the document. Only the Netherlands votes no, and Singapore abstains. The document will be open for signature for all UN member States on September 20, 2017 during the Annual General UN Assembly in NY. Countries with Nuclear Arms capabilities did not participate in the conference convened for preparing the treaty. The United States, Britain and France release a joint statement: *'We do not intend to sign, ratify or ever become party to it.'*

This response does not surprise anybody. The treaty will be become binding to all countries who have signed the document as soon as 50 days after 50 countries have signed the treaty documents. The hope/expectation of the countries, who <u>did</u> sign the treaty, is that over time nations with nuclear warheads will come around and condemn the first use of nuclear weapons, just like the use of chemical or biological warfare has been prohibited.

## Radiobiological research of 'Atoms for War'.

### 1. Discovery of Graft-versus-Host Disease (GvHD)

A multidisciplinary team research team led by Dick van Bekkum, Director of the Radiobiological Institute of TNO in Rijswijk, the Netherlands, explored the therapeutic options after TBI in experimental animals. (11, 12, 13)

The team discovers the intravenous administration of autologous/isologous bone marrow cells after TBI can 'rescue' mice after TBI doses as high as 9.0Gy. Instead of dying from *'primary disease'* within two weeks after TBI from bone marrow aplasia, the animals survived.

Repeat experiments with the intravenous administration of allogeneic BM cells after TBI are successful in recovering a functional, donor type, hemopoietic system. However, 2 to 4 weeks later mice start to die from *'secondary disease'*, later renamed Graft versus Host Disease (GvHD). Cause of death: generalized skin-, gastro-intestinal-, liver-damage and infectious complications.

### Pathogenesis of GvHD after a Bone Marrow Transplant (BMT-GvHD) or a Blood Transfusion associated (Ta-GvHD)

The effector cells for both forms of GvHD are T-lymphocytes, in which the T stands for Thymus, where lymphocytes are educated to differentiate between self and non-self. Non-self-cells will be destructed by T-lymphocytes. Further studies at the Radiobiology Institute in Rijswijk, the Netherlands in the '60s, '70s and '80s, identified the five variables controlling the incidence and severity of GvHD and the reverse Host versus Graft disease (HvGD )for BMT as well as Blood transfusions. (1,12-14)

**Table 4**. Variables controlling GvHD and HvGD

| | |
|---|---|
| 1 | Number of donor lymphocytes administered per kg bodyweight of the recipient |
| 2 | Number of recipient lymphocytes available to oppose incoming donor lymphocytes |
| 3 | Administration of immunosuppressive therapy to recipients of a BMT or one or more blood transfusions |
| 4 | Mayor Histocompatibility Complex (MHC) identity between donor and recipient |
| 5 | Gastrointestinal microflora of the recipient |

Variables 1 and 2 identify the two armies of T-lymphocytes, which are fighting each other. Decreasing the number of donor lymphocytes administered (variable 1) increases the probability of graft rejection, HvG, by host T-lymphocytes. Vice versa, decreasing the number of viable T-lymphocytes in the recipient (variable 2) before the transplant by radiation or chemotherapy increases the chance for the host/recipient to develop serious GvHD.

Variables 3 and 4 are powerful - *peace/armistice*- generating variables because they simultaneously decrease both reactions GvH and HvG. If the proper balance can be found between the two armies and by as of yet unidentified factors, an armistice is called: BMT will be successful; recipient will not experience life threatening GvHD. Recipient of blood transfusions will not develop Transfusion-associated GvHD. (TaGvHD)

Variable 5, Total or selective decontamination of the GI tract of the recipient, before and after TBI can decrease the severity of GvHD after BMT. It requires patient management in laminar airflow for 40 days or more. Total decontamination of the GI tract is more effective than selective removal of Gram negative micro-organisms- in the GI tract of the recipient. Selective decontamination is easier to maintain than total decontamination. (1,19)

Most human BMTs are performed between a sibling donor-recipient pair which are identical for the human MHC HLA. The human MHC contains many different loci: all very polymorphic. Searching for HLA compatible donors for a given patient without a HLA compatible family donor can only be successful when a very large HLA-typed donor bank is available. The target organs for GvHD are listed in Table 5. (12)

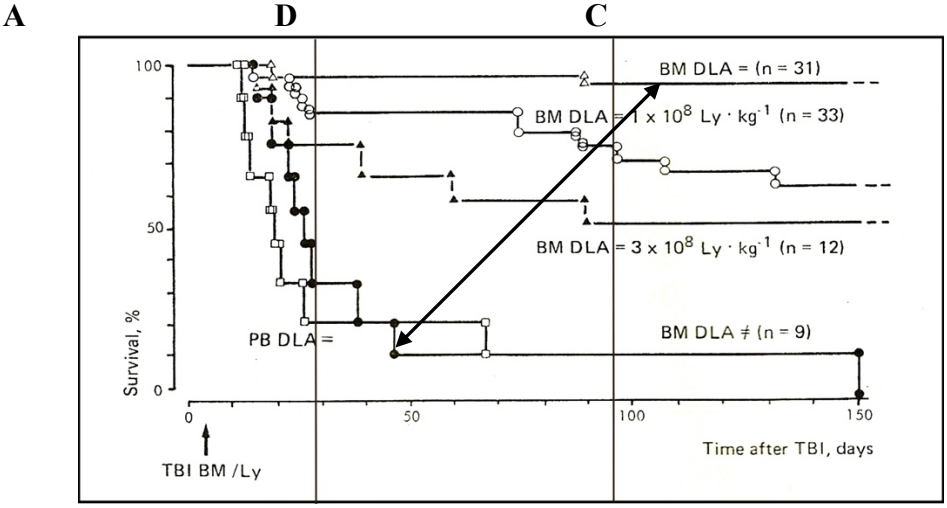
Table 5. Targets of GvHD causing lymphocytes

| Target organ | Pathology | Symptoms |
|---|---|---|
| Skin | Acanthosis, Hyperkeratosis<br>Lymphocytic infiltration, Epidermal and Basal cell vacuolar degeneration, Skin ulcerations | Erythema, skin breakdown and ulcerations |
| Liver | Bile duct atypia, cholestasis | Serum increase of liver enzymes, low serumalbumen |
| Intestines | Villous flattening, Single cell necrosis, Crypt drop-out, mucosal ulcerations | Nausea,Voluminous diarrhea |
| Lymphocytes | Lymphopenia in Blood, Spleen, Lymph nodes | Opportunistic infections |
| Hemopoietic cells of recipient | Bone marrow aplasia (TaGvHD) or regeneration by donor hemopoietic cells (BMT GvHD) | Low blood counts or GvHD |

BMT GvHD occurs in 3 forms, before post-transplant day 30, 100 or later, labeled: **A**cute, **D**elayed and **C**hronic as depicted in Figure 1.

Figure 1*

*Survival of dogs after 7.5 Gy TBI and intravenous administration of allogeneic BM cells and lymphocytes allogeneic bone marrow transplantation*




*DLA is MHC of dog, PB is Peripheral Leucocytes, Ly are lymphocytes, DLA= indicates DLA dentity; DLA = plus slash indicates DLA mismatch.

**A** = Acute GvHD, death before post-transplant day 30, **D** = Delayed GvHD, death between post-transplant day 30 - 100, **C** = Chronic GvHD, not always lethal, but accompanied by immuno-deficiencies and auto-immune disease.

The double arrow line indicates the survival advantage of dogs receiving DLA identical BM cells can be neutralized by adding lots of peripheral blood lymphocytes. In that case the survival of DLA identical *matched* combinations starts to equal the very low survival of dogs receiving DLA *mis*matched BM cells.

The separation of GvHD in types A, D, and C in Figure 1 is also found in human patients treated with HLA identical BM cells, which in contrast to dog BM routinely contains many donor T-lymphocytes. (9,10) The selective removal of lymphocytes from a human BM cell suspension increases the risks for HvG and transplant failure, unless the host receives extra radiation, chemotherapy or immunotherapy. (1)

**Reciprocal interference or snake eats snake.**

The outcome of the battle between two armies of allogeneic T-lymphocytes is called 'Reciprocal Interference' (14). The host and donor T lymphocytes attack each other. This battle has three possible outcomes:

1. life threatening GvHD,
2. life threatening bone marrow aplasia by HvGD
3. An Armistice between HvG and GvH by mechanisms that remain to be identified. produce a 'mixed' chimera, with 2 different genotypes in their hemopoietic system.'

**Immunodeficiency and Blood Transfusions**

Patients with inborn Severe Combined Immunodeficiency Disease (SCID) cannot mount a HvG reaction. Therefore, SCID patients do not need to be 'conditioned' before BMT with chemo- or radiotherapy. SCID patients and babies in-utero with serious Rhesus antagonism will not survive unirradiated blood transfusions. Blood donor lymphocytes will cause lethal Acute, or Delayed GvHD. (15, 16, 17)

**Regeneration of the immune system and autoimmune disease**

It takes time and 'education' to generate a functional immune system after an allogeneic bone marrow transplant.

Immunological reconstitution will be difficult to achieve in patients older than 6 years of age. The 'educational' organs for T and B cells, the Thymus and the Bursa of Fabritius equivalen trespectively,disappear/'atrophy' spontaneously before the age of 6 and are not likely to reappear out of nowhere after an allogeneic BMT in adult patients. If this is indeed the case, 'dictionary' T and B cells, -determining which structures are recognized as 'self' or non-self-, remain absent. T and -B lymphocyte deficiencies will be chronic if not permanent and explain the autoimmune diseases and immuno-compromise in patients suffering from Chronic GvHD. A Bone Marrow Transplant in a young SCID patient can still generate a more complete immune system, if Thymus and/or Bursa are still present or can be regrown from residual cells.

**Prevention of TaGvHD**

All forms of TaGvHD, acute, delayed and chronic, as defined above in Figure 1 can and have been prevented by radiating donor blood with 25Gy prior to administration. (20) The same dose of radiation will decrease, probably eliminate, the transmission of donor DNA and RNA viruses to the recipient. Red cells, platelets, granulocytes, monocytes, macrophages are radio-resistant and survive with their normal half-life after transfusion, with or without radiation. Lymphocytes and HSC are the only radiosensitive cells in the hemopoietic system.

Phase2Therapy plans to study how many blood donor virus particles can be neutralized by 25Gy.

## TBI for patients with Leukemia

The radiobiology research by Van Bekkum and co-workers identified the therapeutic , albeit limited potential of BMT for survivors of a Nuclear warfare. (1, 11,12)

Thomas and co-workers in Cooperstown, NY, USA in dog studies and later in Seattle, WA, USA in human leukemia patients (21, 22) demonstrated that a significant proportion of previously incurable leukemia patients could be cured by TBI plus chemotherapy followed by a BMT from an HLA-identical sibling. The Procedure Related Mortality (PRM) remains high, especially in older patients, 20% or more. One of the reasons for the high PRM, is that the highest possible single fraction TBI dose was given in Seattle and an inaccurate calibration factor was applied, resulting in a high lung dose and frequently lethal interstitial pneumonitis. (1)

Later, the first author argued for deliberately non-homogeneous, fractionated TBI over 4 days leading to a lower lung dose and higher dose to the immune system of the recipient. (14)

## Less Atoms for War; Improved radiation safety and security of Nuclear Energy by exchanging Highly (HEU) and Low (LEU) Enriched Uranium (23)

In 2017 two improbable partners, USA and China, replace weapon grade HEU of the Ghana research reactor by LEU. LEU cannot be used for a nuclear bomb without further enrichment. The HEU reactor in Ghana came on line in 1995. The first collaborations between US and Chinese nuclear weapons scientists started in 1995 in four US locations: Los Alamos and Sandia in New Mexico, Livermore in California and Oak Ridge in Tennessee. Workshops were held in both countries.

In 1999 *the 'Cox report'*, Cox being a Republican member of the House of Representatives, alleges that China stole classified information in the USA. In December 1999 a federal grand jury indicts Wen Ho Lee, a Taiwanese-American physicist at Los Alamos, working on nuclear blast simulations, on 59 counts for stealing nuclear secrets on China's behalf. Lee spends the next 9 months in solitary confinement. He pleads guilty to one count of 'illegal retention' of defense information. The Government drops the other 58 counts and Lee successfully sues for damages.

The collaborations between China and the USA are resumed after the 9/11 terror bombings of the Twin Towers in NY due to renewed interest in keeping weapons-grade fissile materials out of the hands of terrorists. in .

In July 2017 Chinese, US and Ghana experts load the GHARR-1 reactor with LEU fuel; the HEU old core is transported to China.

A reactor in politically unstable Nigeria is next on the list for core replacement in 2018. The US could and should help to speed up further collaboration between Chinese and US nuclear scientists by offering an apology for the Cox report.

## Nuclear Waste Storage (24)

Two sites of deep, million-years old, sedimentary rock have been selected for storage of highly radioactive nuclear waste in the United States, Yucca Mountains, Nevada and in France, Bure in the Champagne-Ardenne region.

England is still looking for a Geological Depository Storage (GDS) site for its own highly radioactive waste as well as the radioactive waste from Germany, Italy and Sweden, which it received through Euratom. After Brexit, England will requestsa legal determination of who owns the highly radioactive waste from Germany, Italy and Sweden and who is going to pay for long term storage of same.

GDS remains the best answer for long-term storage of highly reactive waste. The selected and partially build sites in the US and France face strong opposition from local citizens inspired by biologists/agitators pontificating horror stories about nuclear energy, nuclear accidents, arguing all nuclear energy reactors need to be closed and mothballed. Most, better informed and more balanced, scientists acknowledge renewable forms of energy, such as

wind, water movement, solar energy cannot provide energy to every corner of the planet. Nuclear energy delivered in a safer manner from updated, less accident prone, nuclear reactors will be required to serve everybody, everywhere.

The serious environmental and health aspects caused by fossil fuel, oil and gas energy produced by large corporations are well documented; causing scores of fatalities on a yearly basis. Nuclear energy does not cause global warning and no annual fatalities, but is subjected to very detailed escalating safety restrictions, which are very expensive to implement.

## 'Atoms for Peace', Health Care applications:
## 1. Radiolabeled Immunoglobulin Therapy (RIT)

When Uranium 235 absorbs a neutron, it will fission in 2 lower molecular weight fission products, with atomic numbers, A, gathered around two peaks: A=95, strontium and cesium among others and A=140, Barium, Cesium and Iodine and others. The resulting graph of frequency versus atomic weight of fission products is called the 'Camel Curve' due to its two peaks, around Atomic numbers 95 and 140.

Scientists at the Hanford, WA reactor site in the USA have successfully separated short lived Yttrium-90, a 'daughter' from its long-lived 'mother' Strontium-90. Y-90 is a radio-metal with a half-life of 64 hours, emitting electrons with a maximum energy of 2.27MeV and a maximum path-length in tissue of 11mm; delivering a negligible dose 6mm from its origin. The decay product is stable Zirconium. Hanford provided the first author with clinical grade Y-90 on a weekly basis for experimental studies in patients with end-stage Hodgkin's disease. (25, 26)

Another radio-metal and Yttrium's 'partner' is Indium-111. Clinical grade In-111 is commercially available. In-111 with a half-life of 2.4 days, emitting two gamma peaks at 0.17 and 0.25 MeV, which can be adequately focused by a medium energy collimator of a gamma camera.

Both radioisotopes, In-111 and Y-90 can be linked to immunoglobulins reactive with cancer cells with the help of the same bi-functional backbone substituted chelate, 2B, 3M DTPA, Di-ethylene, Triamine, Penta Acetic acid. (27) This chelate has 8 co-ordination points. The backbone is a chain of 4 carbon atoms forming the two ethylene bridges. One arm of the chelate is a benzyl group starting at C-2, which connects by a thio-urea bond with an amino group of a lysine amino acid on a random location within the immunoglobulin. The methyl group at C-3 increases the rigidity of the chelate. Radiolabeled Immunoglobulins carry on average 4 DTPA chelates per molecule and always remain reactive with its antigen in vitro and in vivo.

Other DTPA derivatives used for chelation have used one of the carboxyl groups for connecting to the Ig. This reduces the number of co-ordination point from 8 to 7, which makes the radio-immuno-conjugate unstable for Y-90 but not for In-111. Free Y-90 is a bone seeker and causes bone marrow aplasia. Preclinical studies in experimental animals with IgM and IgG chelated with 2B, 3M DTPA showed similar bio- distributions for the Ig's, i.e. they were not influenced by the radiolabel Y-90 or In-111. (28, 29, 30)

## 2. Pharmaco-vigilance for radiolabeled immunoglobulin therapy for cancer patients

Step 1. Two mg of In-111 labeled Ig is administered intravenously. Five sequential gamma camera scans are made at 3, 24, 48, 72 and 120 hours after administration. The 3D reconstruction of gamma camera image verifies the location of the Ig, 'does it arrive in all the known tumor masses?' and/or 'does it collect in radiation sensitive normal tissues?'

Step 2. Evaluation of images collected at step 1 will enable an informed decision on whether to proceed to step 2, the administration of the same Radio-Immuno-Conjugate (RIC), now labeled with Yttrium-90.

If all tumor masses are covered and normal tissues surrounding the tumor are not receiving unacceptable high levels of radiation, Yes! Proceed with step 2, the Y-90 labeled RIC administration. No! Patient will go off protocol, if the tumor masses are not targeted and/or

normal tissues will incur unacceptable radiation toxicity.

The RIC has 3 different half-lives:

1, the physical half-live of the isotope is known,

2.the effective half-life of the radioimmunoconjugate (RIC) is recorded with the help of the gamma camera studies.

3. The biological half-life can be calculated and eventually can be used when the proper software is developed to calculated radiation doses delivered to the tumor and tumor surrounding normal tissues.

Patients with long biological half-lives of the anti-ferritin often obtain a complete response. (25, 26)

### 3. RIT studies in Patients with end-stage Hodgkin's Disease. (HD)

Ninety heavily pretreated HD patients received intravenously 2mg of a polyclonal rabbit In-l11 labeled IgG reactive with human ferritin. The 95% of the known tumor masses of the patient identified by diagnostic X-ray, MRI and CT scans were confirmed by the RIC scans. An analysis of the 5% discrepancy rate between In-111 scans and traditional staging shows the +/- differences occur in both directions. Discrepant lesions were not biopsied.

The complete response rate in all ninety patients treated was 26%; overall response rate was over 60%. Patients were retreated 2-6 times. Responses last between 6-18 months. Side effects were limited to chronic hemopoietic insufficiency: low platelets, low white cells, low red cells. All patients eventually die from their disease.

Monoclonal mouse anti-human ferritin IgG labeled with Y-90 is 5 x more effective in nude mice with human Hep G2 xenografts than *polyclonal* rabbit anti human ferritin, the same monoclonal labeled with In-111 fails to target HD. (23, 27) The great majority of the monoclonal IgG ends up in the *normal liver* of the patient, possibly due to the high affinity of the monoclonal anti-ferritin-ferritin complex for the 'Brambell' receptor in human liver cells. (31, 32)

### 4. RIT studies for patients with poor prognosis solid tumors

A new RIT approach for patients with a poor prognosis solid tumor such as a recurrent Glio-Blastoma-Multiforme or an inoperable, but localized adenocarcinoma of the exocrine pancreas has been identified and will be initiated by Phase2Therapy in The Netherlands soon. Tenascin-C has been selected as the target tumor antigen. (33) Monoclonal humanized IgM reactive with Tenascin-C will be administered directly into the tumor. The two-step pharmaco-vigilance described above will be used. (33)

### 5. Body Surface Area (BSA) vs Kilogram Bodyweight (BW) as prescription unit for cancer chemotherapy.

In 1966 Freireich and coworkers provided a simple, but dangerous simplification for finding a 'safe' initial dose for a Phase 1 studies of a new cancer drug in human patients. (34) Most cancer drugs are developed to stop rapidly growing cancer masses. Many normal self-renewal systems in the human body, such as e.g. the hemopoietic system are dividing rapidly as well. Most new cancer drugs cause bone marrow damage and low blood cell counts in cancer patients. Freireich et al. discovered that in 6 different experimental animal models the same highest acceptable dose of a new cancer drug can be applied to all species, if the dose is expressed per $m^2$ BSA. (34)

A priori, it is impossible to express a drug dose in a 2D unit. For a real dose one needs a volume, a 3D unit. Vriesendorp, Vriesendorp and Vriesendorp (35) and Vriesendorp and van Bekkum (10) argue that smaller species have lower body weights and relatively larger surface areas.

They determined the relative hemopoietic stem cell (HSC) concentration in experimental animals, mice, rats, dogs, and rhesus monkeys by titrating the number of intravenously administered autologous/isologous BM cells needed to achieve rescue/survival after a lethal dose of Total Body Irradiation. The human HSC concentration in BM was estimated from

radiation accident victims. Mice BM cells appear to have a ten-fold higher concentration of HSC than human beings. Mice can tolerate a 10 times higher chemotherapeutic drug dose prescribed per kg bodyweight than a human patient. A significant negative correlation between HSC and BW in man, monkey, dog, rat, mouse exists. (10)

**Table 1**
Comparison of BSA and KgBW prescription

| Species (BSA, kg; BSA/kg) | Body surface area | | Body weight | |
|---|---|---|---|---|
| | Equal toxicity dose[a] of cancer drugs (mg/m$^2$ BSA) | Relative HSC[b] concentration per m$^2$ BSA | Equal toxicity dose[a] of cancer drugs (mg/kg body weight) | Relative HSC[b] concentration per kg body weight |
| Mouse (0.007, 0.025; 0.28) | 1x | 125 | 12y | 10 |
| Rat (0.03, 0.2; 0.15) | 1x | 44 | 7y | 6.7 |
| Rhesus monkey (0.23, 2.6; 0.09) | 1x | 9.5 | 3y | 2.7 |
| Dog (0.55, 0.12; 0.05) | 1x | 2.3 | 2y | 1.1 |
| Man (1.85, 70.0; 0.03) | 1x | 1 | 1y | 1 |

The chemotherapeutic agents dosed as per Freireich et al. proposal per meter$^2$ BSA produces serious life-threatening toxicity in children. Arbitrarily, Pediatric oncologists elect to treat young cancer patients by cutting the BSA calculated dose in half. Small women have a relatively larger BSA than large women. As predicted small women with melanoma, breast cancer or chronic lymphatic leukmia (CLL) have higher response rates and response durations compared to large women and men when chemotherapy is prescribed per m$^2$ BSA.

## Summary

The threat of Atoms for War remains alive, notwithstanding prolonged, pacifying efforts of World Leaders with the notable exceptions of the current Presidents of North-Korea and the USA. The therapeutic options for citizens exposed to Nuclear Warfare are close to zero. Even palliative care is hard to implement due to the destruction of infra-structure by powerful Hydrogen Bombs. Eventually, hopefully, countries with Nuclear War capabilities will sign the UN agreement and commit to not being the first to use nuclear bombs in a conflict and will refrain from retaliating with nuclear bombs, but use conventional warfare to punish an aggressor.

In a recent article in the New Yorker Osnos argues: '*Iraq taught us the cost of going to war against an adversary that we do not fully understand. Before we take a radical step into Asia, we should be sure that we are not making that mistake again.*'

On a brighter note, 'Atoms for Peace' are making significant contributions to making nuclear energy safer and less operator dependent. Nuclear energy is needed to bring electricity to all. Wind, Solar, Oil, Gas will not be able to do so. 'Atoms for Peace' provide promising leads for improved, safer, more effective, more affordable health care. We hope the positive elements in Atoms for Peace, including safer nuclear energy reactors, will not be ignored due to the existential fears induced by the threats of Nuclear Warfare

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