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FORUM

On Depleted Uranium: Gulf War and Balkan Syndrome

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The complex clinical symptomatology of chronic illnesses, commonly described as Gulf War Syndrome, remains a poorly understood disease entity with diversified theories of its etiology and pathogenesis. Several causative factors have been postulated, with a particular emphasis on low level chemical warfare agents, oil fires, multiple vaccines, desert sand (Al-Eskan disease), botulism, *Aspergillus flavus, Mycoplasma,* aflatoxins, and others, contributing to the broad scope of clinical manifestations. Among several hundred thousand veterans deployed in the Operation Desert Storm, 15-20% have reported sick and about 25,000 died. Depleted uranium (DU), a low-level radioactive waste product of the enrichment of natural uranium with U-235 for the reactor fuel or nuclear weapons, has been considered a possible causative agent in the genesis of Gulf War Syndrome. It was used in the Gulf and Balkan wars as an armor-penetrating ammunition. In the operation Desert Storm, over 350 metric tons of DU was used, with an estimate of 3-6 million grams released in the atmosphere. Internal contamination with inhaled DU has been demonstrated by the elevated excretion of uranium isotopes in the urine of the exposed veterans 10 years after the Gulf war and causes concern because of its chemical and radiological toxicity and mutagenic and carcinogenic properties. Polarized views of different interest groups maintain an area of sustained controversy more in the environment of the public media than in the scientific community, partly for the reason of being less than sufficiently addressed by a meaningful objective interdisciplinary research.

Key words: *environmental exposure; leukemia, radiation induced; military personnel; Persian Gulf syndrome; radiation accidents; radiation genetics; radiometry; uranium; veterans; war.*

> *No time can be more unfavorable for philosophy than that in which it is misused on the one hand to further political objectives, on the other as means of livelihood. Some intend to live and indeed do live by philosophy (Primum vivere deinde philophari). Yet, nothing is to be had for gold but mediocrity, the truth will always be of few men and must equally and modestly wait for those few whose unusual mode of thought may find it enjoyable. Life is short but truth works far and lives long.*
>
> *Schopenhauer*

The ostrich syndrome preceded the two syndromes. Yet, denial does not eliminate the fact that veterans of Gulf War and Balkan conflict are sick and dying. While the etiological factors of the clinical entities, known as Gulf War syndrome, are far from being understood, well-described facts still remain. Sharp increase in cancer rate in the Gulf War veterans (1) point to exposure to oncogens and mutagens, among which depleted uranium (DU) has been identified by objective research as one of the agents present in the internal environment of the contaminated veterans. It has been identified as an oncogene-inducing factor by both *in vitro* and *in vivo* experimental research (2).

The use of uranium as a warfare agent of mass contamination is not that new. Towards the conclusion of World War II, when Japan launched over 6,000 explosive-laden air balloons to the continental United States, there was a serious concern of a possible use of uranium oxide against US megacities in the form of aerosol for mass contamination.

Depleted uranium as a product of the environment of natural uranium for the reactor fuel and nuclear weapons is partially altered by the extraction of U-235 to about one third of natural uranium content (2). This residue, also known as *tails,* is a radioactive waste with the current stockpiles of over 600,000 metric tons of depleted uranium hexafluoride (UF_6). UF_6 is an unstable toxic chemical, which forms uranyl fluoride (UO_2F_2) and hydrogen fluoride (HF) if released in atmosphere. It is identified as toxic substance (3) with serious health consequences if inhaled, by both chemical and radiological properties (1). The United States Nuclear Regulatory Commission (NRC) governs the use and transportation of depleted uranium for the use and transfer of maximum

of 15 pounds at a given time and 150 pounds in a calendar year. Also, the NRC requires detailed documentation of DU intended use, training of personnel, compliance with health, safety, and environmental standards (4). Depleted uranium is an internal health hazard. By its parenteral entry in the extracellular fluid, it gets incorporated in the target sites of its retention – predominantly skeletal tissue and kidneys, where it exerts nephrotoxicity by its effect on the proximal convoluted tubules. It has also been demonstrated that it induces transformation of human osteoblasts into the neoplastic phenotype in cell culture studies (5). *In vivo* studies reported mutagenic activity in the experimental animals implanted with DU pellets (5). Human data of spatiotemporal models of mapping cancer mortality reported an elevated lung cancer rate in the vicinity of DU processing facilities (6). Some recent reports indicate the increase in urinary excretion of DU in US Gulf War veterans wounded by the shrapnel during the operation Desert Storm (7). Similar findings were reported in the British, Canadian, and US veterans exposed to DU by inhalation during the Desert Storm Operation, where the presence of DU was verified by the methods of neutron activation analysis (8) and mass spectrometry (9). The isotopic ratio of DU and the presence of U-236 – an uranium isotope not found in nature, in Desert Storm Operation veterans opens yet another compartment of Pandora's box. It poses an inevitable question of the origin of DU used in the Gulf war, recently further augmented by the finding of traces of plutonium and other actinides (americium, neptunium) in DU shrapnel. The scientific inquiry into DU as a possible etiological factor in the causology of Gulf war and Balkan conflict illnesses has not been met with unbiased scientific criticism.

No Turn Left Unstoned

Some of the arguments relate to the short range of alpha particles (10), the other to the radiation being too low to induce mutagenic and oncogenic effects. Most of the polemics are in the arenas of extremely polarized interest groups on both sides of the fence, each side conspicuously lacking presence of the actual experts on actinides. The opinions are commonly exchanged in the mass media by the non-experts, and often by non-professionals, inevitably ignoring the complexity of DU interactions with the internal environment of stem and dividing transit cell population (11), basic laws of radiation biology and cellular radiosensitivity to alpha interactions (12,13), and effects of organotropic radionuclides in the human body (14), unskillfully navigating through uncharted seas of low level radiation. As usual, truth is often found between the extremes of Confucian pendulum, easier found in the science textbooks than on the Internet screen, which often lacks the basics of chemical synchronization, mitotic selection, fundamentals of the mitotic cell collection, and uniformity of cell cycle, cell culture, survival curves, and cellular response to radiation. The biological effects of DU do not differ from other alpha and beta internally deposited emitters and have to be considered in the light of cellular radiosensitivity as related to the mitotic cycle, with clear concepts of radiosensitivity and radioresistance in different phases of the mitotic cycle. The intermitotic and dividing cell population in the vicinity of final retention sites of depleted uranium includes pluripotent stem cells, hematopoietic system, intestinal villi crypt cells, intermitotic pool in the bone marrow, and basal cells of the skin. The mechanisms of DU interactions are far from being adequately understood even by the experts. Thus, it is perhaps premature to classify DU as a non hazardous substance, even if the proponents manage to master the basics of the host of factors that determine the biological consequences of internal particulate emitters, including dose-rate effects, linear energy transfer, oxygen effects, relative biological effectiveness, repair mechanisms, and damage recovery. Furthermore, the established concepts of cell survival curves are currently being re-examined in the realm of low-dose radiation (15). Radiation-induced cancer incidence at low dose exposure with BEIR (Biological Effects of Ionizing Radiation) and UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) adopted linear non-threshold curves postulate no safe dose for any exposure to ionizing radiation. But, no threshold hypothesis was more conceptualized on mathematical than biological considerations. Reassessment introduces biphasic curve, addressing the mechanisms of damage of radiosensitive cells. It postulated, by the experimental evidence, that a part of the radiation-damaged cell population would become more susceptible to mutagenic alterations as the dose increases from point zero. It also includes the transformation to neoplastic entities. With further increase of the dose, radiosensitive cells would sustain lethal damage with a consequent fall in mutations. At that point, less sensitive cells would start a new rise in oncogenic events, which, after the second peak, would result in a death of the organism (16). Second event theory, although new, has attracted considerable attention. It postulates that two hits can interact with the same cell. The first one creates high sensitivity phase, and the second further damages the cell in its sensitive phase, with both events occurring during cell replication. This is of importance to contamination with uranium isotopes, where the size of a particle determines the delivered dose. DU particle of 0.2 microns in diameter would deliver an alpha dose equal to annual exposure of 2 mSv, rapidly increasing delivery dose by the increased particle size (16). Current reevaluations of the human and animal data recognize a large error of the conventional models of the risk assessment in the low-level exposure health risk evaluation.

Chernobyl Revisited

Recent application of the re-examination of low dose effects applied to Chernobyl accident has identified new relationships between the actual number of cases with malignant alterations and the numbers predicted by the conventional model of radiation risk (17). There is a significant increase in the number of the children with leukemia while being exposed *in utero* to radionuclides from Chernobyl fallout. The infant leukemia cohort has been reported in Scotland (18), Greece (19), United States (20) and Germany (21). It is being applied to current research on Gulf war legacy, which, unlike multiradionuclide Chernobyl fallout exposure, is a result of a mass contamination with the isotopes of a single radionuclide. Naming of the non-existent syndrome rages in the semantic controversy, which – for the sake of

sanity, we may temporarily call Gulf war illness or Gulf war syndrome.

No single thing abides, but all things flow
fragment to fragment clinges; the things thus grow
until we know and name them. By degrees
they melt and are no more the things we know.
Lucretius

Whatever the name of the illness, the fact remains that 15% to 18% of several hundred thousand of Desert Storm veterans are sick and over 25,000 are dead, regardless of the official statements of various Departments of Defense and Ministries of Defence that no unique illness can be associated with the Operation Desert Storm (22).

Several criteria of classification of the Gulf war syndrome have been considered, ranging from the terminology such as Haley's factor analysis classification in six syndromes (23), to a broad category of Mucocutaneous-intestinal-rheumatic Desert Syndrome, with three major and 17 minor categories (24), or a neuroimmune syndrome (25) – all distinctly different from postraumatic stress syndrome (PTSD), which was for some time meant to phagocytize the Gulf war syndrome (26).

Probable causology includes chemical, biological, and radiological etiology. All discussion in the literature in a considerable length often lacks objective analytical support, sometime in Swiftian resemblance of a Gulliver's encounter with scientists from an academy proudly explaining their success in the research of extracting sunbeams from the cucumbers. Be as it is, the DU research has been lacking for whatever reason, none being the lack of awareness of its toxic properties and health hazards.

Yesterday, upon the stair
I met a man who was not there.
He was not there, again, today.
I wish that man would go away.
Unknown

The present stockpile of DU in excess of 600,000 metric tons as a product of enrichment process is stored as radioactive waste in the form of DUF6 in approximately 50,000 carbon steel cylinders at three main sites in the United States: in the plants at Oak Ridge (TN), Paducah (KY), and Portsmouth (OH). Additional large quantities of DU are being continuously produced. The United States Enrichment Corporation (USEC) estimates production of 85,000 metric tons of DU through 2005, the disposal of which has not yet been determined (27). Over 350 metric tons of DU was used in Gulf war. If only 1 to 2% was released in the atmosphere in the form of submicron or micron size aerosol particles after pyrophoric impact of DU projectiles, a conservative estimate would amount to 3-6 millions grams of airborne aerosols. This presents an inhalation hazard by both alpha and beta emission due to U-238 daughter products thorium-234 (beta 0.26 NV) and protactinium-234 (beta 0.23 MEV), with respective half-lives of 24 days and 6.7 hours. Thorium and protactinium add to internal hazards of DU by beta interactions with orbital electrons, *bremsstrahlung* radiation of the free electrons, and their interactions with radiosensitive sites.

Que sais-je
(Montaigne)

Pragmatic question remains how to integrate all of the objectively verified properties of DU into a maze of Gulf war illnesses. Available data agree in at least one fact: depleted uranium is elevated in the urine of veterans contaminated by either a shrapnel or inhalational pathway. Several methods have been utilized in DU urinary analysis. Inductively coupled mass spectrometry (ICP-MS) demonstrated 0.2-0.33% of U-235 in the urinary concentration of 150 ng/L, whereas the non-exposed veterans contained 0.7-1.0% of U-235, with the urinary concentration of 14 ng/L (28). A rapid detection procedure for DU in metal shrapnel fragments provides a practical method of distinguishing between DU and non-DU shrapnels using pyridylazo dye. It might provide useful guidelines for early therapeutic decisions (29). The ICP-MS protocols have been critically evaluated in comparison with DU alpha spectrometric data (30). The results were in favor of IMP-MS with higher detection sensitivity (30). Kinetic phosphorimetric studies of DU isotopes in pellet-implanted rats have reported quantitative tissue distribution during 18 months after implantation (31). The highest retention was observed in the kidney and tibia, and measurable quantities of DU were found in the heart, brain, striated muscles, lungs, testicles, and lymph nodes (31). The utility of spot collection of urine for bioassay has been reported as a useful kinetic phosphorescence analysis method. It uses creatinine-corrected 24-h samples, suggesting a higher merit in DU bioassay than uncorrected spot sampling (32). The method was correlated with data of urinary excretion of DU in shrapnel wounded veterans (33). Surface ionization mass spectrometry seems the most accurate method, capable to measure DU isotopic composition in low nanogram quantities. The most precise results have been obtained by the mass spectrometers using two and three phase techniques (34). They were originally designed by the Knoll Atomic Power Laboratories and first used in the analysis of DU abundances of U-234, U-235, U-236, and U-238 in accidentally discovered DU contamination in environmental air filters collected at the US Navy training sites in New York States. Specific design of the system provided the detection capacity of one part per trillion, with 1-3% of accuracy. Commercial multi-collector Finnigan MAT-262 is a thermal ionization spectrometer that uses secondary electron multiplier (SEM) with an ion counting system. The results of urine analysis by this method demonstrated DU ratios in the urine of Gulf war veterans contaminated *via* the inhalation pathway with small but definitive presence of U-236. The data are being carefully re-evaluated and the initial findings repeatedly confirmed, taking into consideration the analysis of background contribution of the electron multiplier systems, filament, vacuum system, separation chemistry, and hydrocarbon background effects. The studies are continuing on the larger groups of British, Canadian, and US veterans.

Although DU shrapnel wounded veterans continue to excrete elevated quantities of uranium isotopes (33), not many casualties are the consequences of shrapnel wounds. Shrapnels are of a lesser importance in understanding DU role in Gulf war illnesses than mass contamination by the inhalation of DU containing dust, initially described as Al-Eskan disease (35). The effects of uranium-embedded particles have been known for almost two centuries (36). The causological correlation between depleted uranium and

Gulf war illnesses (37) remains the most important but unanswered question. The studies of DU role in Gulf war illnesses have been not only as diversified as the symptomatology of the illness, bur also inadequately studied (38), not for the want of expertise, technology, patient population, or resources, but rather due to incapability to subscribe to Francis Bacon's Utopian dream of New Atlantis and replace the politician with the scientist.

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