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EDITORIAL

Undiagnosed Illnesses and Radioactive Warfare

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The internal contamination with depleted uranium (DU) isotopes was detected in British, Canadian, and United States Gulf War veterans as late as nine years after inhalational exposure to radioactive dust in the Persian Gulf War I. DU isotopes were also identified in a Canadian veteran's autopsy samples of lung, liver, kidney, and bone. In soil samples from Kosovo, hundreds of particles, mostly less than 5 μm in size, were found in milligram quantities. Gulf War I in 1991 resulted in 350 metric tons of DU deposited in the environment and 3-6 million grams of DU aerosol released into the atmosphere. Its legacy, Gulf War disease, is a complex, progressive, incapacitating multiorgan system disorder. The symptoms include incapacitating fatigue, musculoskeletel and joint pains, headaches, neuropsychiatric disorders, affect changes, confusion, visual problems, changes of gait, loss of memory, lymphadenopathies, respiratory impairment, impotence, and urinary tract morphological and functional alterations. Current understanding of its etiology seems far from being adequate. After the Afghanistan Operation Anaconda (2002), our team studied the population of Jalalabad, Spin Gar, Tora Bora, and Kabul areas, and identified civilians with the symptoms similar to those of Gulf War syndrome. Twenty-four-hour urine samples from 8 symptomatic subjects were collected by the following criteria: 1) the onset of symptoms relative to the bombing raids; 2) physical presence in the area of the bombing; and 3) clinical manifestations. Control subjects were selected among the sympotom-free residents in non-targeted areas. All samples were analyzed for the concentration and ratio of four uranium isotopes, ^{234}U, ^{235}U, ^{236}U and ^{238}U, by using a multicollector, inductively coupled plasma ionization mass spectrometry. The first results from the Jalalabad province revealed urinary excretion of total uranium in all subjects significantly exeeding the values in the nonexposed population. The analysis of the isotopic ratios identified non-depleted uranium. Studies of specimens collected in 2002 revealed uranium concentrations up to 200 times higher in the districts of Tora Bora, Yaka Toot, Lal Mal, Makam Khan Farm, Arda Farm, Bibi Mahro, Poli Cherki, and the Kabul airport than in the control population. Uranium levels in the soil samples from the bombsites show values two to three times higher than worldwide concentration levels of 2 to 3 mg/kg and significantly higher concentrations in water than the World Health Organization maximum permissible levels. This growing body of evidence undoubtedly puts the problem of prevention and solution of the DU contamination high on the priority list.

Key words: *Afghanistan; Iraq; nuclear medicine; nuclear warfare; uranium*

"From this basic power of the universe, there is no protection."

Albert Einstein

The reality of thermonuclear strategic war is best summarized by Einstein's statement that its energy is sufficient to split the earth (1). The nuclear battlefield is no longer limited to a country or continent, but transcends far beyond political and geographic borders, turning every area into one huge war zone. If a strategic nuclear exchange involving a ten thousand megaton arsenal would occur, more than a billion people would die instantly from the immediate, combined injuries (blast, thermal, radiation), another billion would succumb to radiation illnesses (2), and the surviving population of the planet would be confined to an environment permeated by radioactive fallout causing somatic and genetic effects with possible irreversible consequences for the biosphere.

The Nuclear Race

The first nuclear weapon test, Trinity, was deployed in Alamogordo, near Los Alamos, New Mexico, USA, on July 16, 1945. Within one millionth of a second, the first nuclear bomb reached the heat of millions of degrees centigrade, releasing over 400 radioactive isotopes and a vast binding energy at a pressure of thousands of tons per square centimeter. For a fraction of a second, the bomb core was eleven times hotter than the surface of the sun. The fireball was hundreds of meters high as the bomb core mixed with oxygen and nitrogen atoms, revealing the bright inner core of the explosion. Within a second, the vaporized ground surged upward into a mushroom cloud 3,000 meters high. The fireball was seen by the train passengers of the Union Pacific Railway 150 miles away in Arizona. Witnesses offered different interpretations, describing the effect as a possible air force bomber crashing, atmosphere catching fire, or meteorite (3). Witnesses from the city of Gallup, 235 miles north of the explosion site, thought it was an explosion of an army ammunition storage site (3).

Twenty days after the Trinity Test, an uranium bomb was dropped on Hiroshima at 8:15 a.m, August 6, 1945. The bomb exploded about 633 meters above the city, darkening the sun, killing 130,000 people, incapacitating 80,000, and injuring an additional 90,000 by the delayed effects of the radioactive fallout. Within hours, a black rain fell and white ash covered the hypocenter, causing skin burns. Most of the initial victims died from the combined effects of heat, blast, and acute radiation injury. Hiroshima was practically erased from the map (4).

Two days later, on August 8, 1945, at 11:01 a.m., a plutonium bomb, named Fat Man, was dropped on Nagasaki. Similar to Hiroshima, the sun disappeared as the stalk of the mushroom cloud rose. The population of the obliterated city died of the same combined injuries encountered in Hiroshima. The result was the end of World War II and the Soviet Union achieving territorial gains. As Kurchatov's weapon research team started developing a Russian bomb in the fall of 1948, the nuclear test race began (Table 1). Simultaneously with the United States, testing was in progress in the Soviet Union. Following the death of Stalin in 1953, the Soviets exploded the first mobile hydrogen bomb on August 12. It was their second thermonuclear weapon. The United States realized that the Soviets were gaining in the nuclear race and began to accelerate their nuclear testing program.

In 1955, it became apparent that nuclear testing did irreparable damage to the biosphere (5). Over 400 radioactive isotopes released in each test have been identified as the cause of environmental pollution. Forty of these isotopes present a risk to human health. For each kiloton yielded, several grams of radioisotopes are formed with organotoxic properties. Strontium-90 poses the main risk due to its long half-life, beta decay, and bone-specific properties. Parallel to the nuclear testing, there were accidents involving nuclear weapons. In 1958, a B-57 Air Force plane dropped the first nuclear bomb near Florence, South Carolina. The unarmed weapon did not explode, but spread radioactive material over the countryside. The same year, a B-52G dropped a two megaton nuclear weapons near Goldsboro, North Carolina. Other USAF accidents followed, including Tula, Greenland, and Palomares, Spain. In Palomares, two plutonium bombs contaminated a large area of land and the Atlantic coast.

In 1958, after a catastrophic accident at Chelyabinsk-40, the Soviet Union suspended nuclear weapons testing. However, it soon resumed testing of megaton weapons in the Arctic territory of Novaya Zemlya, with a 50 megaton blast on September 9, 1961. Meanwhile, in the United States, evidence was accumulating regarding the environmental contamination and the increased incidence of cancer, leukemia, and other health problems among atomic veterans. This evidence, along with radiation safety concerns, ultimately resulted in abolishment of the large inept bureaucracy of the Atomic Energy Commission. It was replaced by the Energy and Research Administration and Nuclear Regulatory Agency (NRC) in 1974.

Table 1. Chronology of the nuclear test race in the USA. **A.** Atmospheric test series. **B.** Underground tests at the Nevada Test Site (NTS) – subsurface cratering shots. **C.** Underground Tests at the Nevada Test Site – underground testing.*

A.

Operation	Year	Location	Number of explosions
Trinity	1945	Alamogordo New Mexico	1
Crossroads	1946	Bikini Atoll	2
Sandstone	1948	Enewetak Atoll	3
Ranger	1951	Nevada Test Site	5
Greenhouse	1951	Enewetak Atoll	4
Buster-Jangle	1951	Nevada Test Site	7
Tumbler-Snapper	1951	Nevada Test Site	7
Ivy	1952	Enewetak Atoll	2
Upshot-Knothole	1953	Nevada Test Site	11
Castle	1954	Bikini Atoll, Enewetak Atoll	6
Teapot	1955	Nevada Test Site	14
Wigwam	1955	Pacific Ocean	1
Project 56	1955	Nevada Test Site	4
Redwing	1956	Bikini Atoll, Enewetak Atoll	17
Plumbbob	1957	Nevada Test Site	30
Project 58	1957	Nevada Test Site	2
Project 58 A	1958	Nevada Test Site	2
Hardtack I	1958	Bikini Atoll, Enewetak Atoll, Johnston Island	35
Argus	1958	South Atlantic	3
Hardtack II	1958	Nevada Test Site	37
Nougat	1961-1962	Nevada Test Site	32
Dominic (with Fishbowl)	1962	Christmas Island, Johnston Island, Central Pacific	36
Storax (Coaster)	1962-1963	Nevada Test Site, Nellis Air Force Range	56

B.

Test series	Test name	Date	Location
Nougat	Danny Boy	1962	NTS Area18a
Whetstone	Sulky	1964	NTS Area 18d
Whetstone	Palanquin	1965	NTS Area 20k
Crosstie	Cabriolet	1968	NTS Area 20l
Crosstie	Buggy	1968	NTS Area 30
Bowline	Schooner	1968	NTS Area 20u

C.

Test series	Test name	Date	Location
Nougat	Danny Boy	1962	NTS Area 18a
Whetstone	Sulky	1964	NTS Area 18d
Whetstone	Palanquin	1965	NTS Area 20k
Crosstie	Cabriolet	1968	NTS Area 20l
Crosstie	Buggy	1968	NTS Area 30
Bowline	Schooner	1968	NTS Area 20u

*Adapted from: *http://nuketesting.enviroweb.org/hew/Usa/Tests*

In 1955, Bertrand Russell, Albert Einstein, and nine more eminent world scholars established the Pugwash movement, with the purpose of addressing nuclear proliferation and nuclear war. In annual meetings since 1957, Pugwash began its work that led to an international treaty to ban further testing of nuclear weapons and production of new arsenals and delivery systems (6). In 1969, Pugwash contributed to the initiation of the Strategic Arms Limitation Talks (SALT). This initiative was supported by Linus Pauling's campaign against nuclear weapons and environmental pollution. After the Cuban Missile Crisis, a real threat of nuclear confrontation between the United States and the Soviet Union led Kennedy and Khruschev sign a nuclear test ban treaty in 1963. Nevertheless, underground testing continued, leading eventually to the failure of the Comprehensive Test Ban Treaty (CTBT). The assassination of Kennedy, fall of Khrushchev, and Vietnam War led to the end of nuclear détente.

The realistic possibility of the Soviet Union outracing the United States in the testing and development of nuclear weapons finally prompted the SALT I Treaty in 1972, with a partial prohibition of antiballistic missile deployment. The Soviet Union already had a protective missile perimeter system around Moscow and the US had a similar system in North Dakota. Eight years later, Reagan's Administration started SALT II negotiations, which led to arms reduction (START) but not arms limitation. This was described by the chairman of the Pugwash Conference executive committee, Bernard Field, as "the repetitious stupidity of this futile charade" (7). Paul Warnke, the chief negotiator of the SALT II Treaty, said that *"The sorry history of arms control may become the final chapter in the history of humanity"* (8).

Since the partial test-ban treaty of 1963 there have been about 50 nuclear tests a year: 55% performed by the United States, 30% by Russia, and the remaining 15% by France, England, China, India, and Pakistan. The proliferation of nuclear weapons implicates over 90% of the surface of the earth as a potential target, with satellite delivery technology developing at a rapid pace. The security of nations is no longer guaranteed by the number of nuclear weapons. Even after the end of the Soviet Union, nuclear weapons remain a major security issue, regardless of Washington-Moscow cooperative initiatives. The new dangers of nuclear confrontation are contained in current international political scenarios. These include the recent United States withdrawal from the antiballistic missile treaty, the new "first use" doctrine, and the recent emergence of new nuclear nations (9). The nuclear threat continues as a consequence of nuclear proliferation, including a widening list of scenarios from military use, terrorist activities, nuclear and environmental catastrophes, and Mutually Assured Distraction (MAD).

Nuclear and Radiological Terrorism

An increased awareness of the possibility of nuclear and radiological terrorist attacks developed after September 11, 2001. Before the New York disaster, such possibilities were taken rather lightly. Training and disaster drills for nuclear and radiation casualties were either nonexistent or conducted very sporadically, even in government institutions mandated to maintain response capabilities. Enhancing national readiness in confronting the issue of acute and chronic radiation effects, environmental contamination, psychological and social impact, and the fiscal consequences of nuclear terrorist attacks are re-emerging as a priority of industrial nations (10). The Clausewitz's doctrine has been advocated, mandating armed forces to prevent and repel attacks by outside enemies and attack other countries if it is determined to be in the international interest (11). Chronic radiation injury is beeing reevaluated in light of potential implications of the mass casualties of nuclear terrorism.

Nuclear and radiation accident and attack preparedness must also address the psychological effects in view of the well-studied fact that for every casualty in the nuclear terrorism scenario there would be 500 people with psychological and psychosomatic alterations that may be difficult to distinguish from the actual contaminated victims (12).

Although pharmacological interventions are being studied as a radiation prevention measure, health care protagonists should be aware of the dismal past failures in the field of radio-protective agents. New evidence of vascular and parenchymal cells recovering rather than dying from the radiation injury is being studied in an attempt to develop mechanisms to modify the response of the organism in conjunction with other therapeutic strategies, such as corticosteroids, angiotension-converting enzyme (ACE) inhibitors, pentoxyfilline, and superoxide dismutase (13). The focus of management of nuclear and radiation injury has shifted from the unmanageable consequences of strategic nuclear confrontation to ways of dealing with large numbers of casualties. This response must be conducted by multidisciplinary efforts. Much work is needed immediately to develop the concepts of clinical management of radiation victims (14). Simultaneously, research has to continue in the understanding and management of radio nuclide contamination, radiation toxic effects, disruption of chemical bonds, free radicals, cellular DNA and enzyme damage (15). A multidisciplinary efforts must include planning, triage, decontamination, decorporation, chelation therapy, and conventional symptomatic management of the affected patients.

A potential terrorist attack poses serious challenges due to the almost total lack of training, expertise, and fiscal constraints (16). The radiation casualty preparedness lessons from Gulf War I and the Balkan Conflict have not yet been adequately addressed (17). The sudden event of a potential terrorist attack requires an effective public health response, which is almost nonexistent in the logistical capacity of most nations likely to become a terrorist target, particularly in large urban areas, where the allocation of resources requires restructuring of priorities to match the consequences to society. It is particularly important in the nuclear terrorism scenario to be aware of terrorists' potential use of actinides, with particular emphasis on plutonium as a possible mass contamination agent. Plutonium is considered the most dangerous substance known to man (18). If dispersed as radioactive dust or released into the water supply, it takes only a few grams to contaminate a large city. Plutonium has been illegally sold in clandestine markets, mainly the former Soviet Union, finding its way to various parts of the world through illegal trade. Plutonium dispersal has been viewed as the most devastating of the possible terrorist attack scenarios (19). The emphasis of the medical profession should be prevention rather than therapeutic management of the mass casualties of nuclear terrorism after the fact. Physicians of the world have recently joined a coalition of over 1,000 organizations to collaborate and support the elimination of nuclear weapons and reduce the possibility of devastating effects of nuclear and radiological terrorism (20).

Radiological Warfare

Radioactive weapons were used for the first time in 1991 in the Persian Gulf, introducing a new scenario of chemical-biological-radiological-nuclear (CBRN) warfare. The use of weapons of indiscriminate effects is not new. At the conclusion of World War II, the United States was seriously concerned about the Japanese threat of launching several thousand uranium-laden balloons into the continental United States, with the purpose of contaminating its mega cities (21). During Gulf War I (GW I), depleted uranium (DU) munitions dispersed millions of grams of radioactive dust into the atmosphere (22). The environmental and health implications of uranium isotopes used in GW I remain controversial, reaching well beyond the concerns of the scientific community. Nevertheless, numerous recent reports have confirmed two centuries of well-established scientific evidence of uranium-induced somatic and genetic toxicity (21,23-25).

The cost of cleanup procedures in the aftermath of military or terrorist use of uranium weapons remains a serious concern. Radiological decontamination in a recent joint-team experiment under a Swedish/Canadian accord, conducted in Umea, Sweden, demonstrated that two common methods of decontamination were ineffective in adequate cleanup. High-pressure water spray and forced water pulse water jet were unsuccessful at decontaminating military light armor vehicle from Na-24 external contamination (26). This clearly points to a need for better planning and preparation of a public health infrastructure in radiological warfare or terrorist attack (27). The current lack of a comprehensive strategy for facing a terrorist threat from Radiation Dispersion Devices (RDD) emphasizes the need for better coordination of chemical, biological, radiological and nuclear (CBRN) preparedness in the current crossroads between conventional and the new, never before encountered weapons (28).

In the clearly distinct scenario of a radiological attack, the scope of the management of the radiological warfare and terrorism extends, not only beyond public health, but also beyond the capacity of the armed forces reserve (29,30). Medical defense against radiological warfare remains one of the least emphasized aspects of current medical education (31). Radiological and nuclear terrorism is the ultimate threat to modern society. Nuclear proliferation has resulted in the opportunity for subversive organizations to easily obtain radioactive materials (32).

In 2000 only, USA spent 10 billion dollars for Weapons of Mass Destruction (WMD) counter-terrorism, with exceedingly higher fiscal commitments after September 11, 2001. Current studies reveal the vulnerability of western society to nuclear terrorism, emphasizing that WMD-armed terrorist organizations can induce more destruction with nuclear and radiological devices than with any other kind of weapon. The US capability to deal with a radiological or nuclear attack is considered to depend on four areas of action: improvement of intelligence on terrorist organizations, improvement of security of nuclear facilities in the former Soviet Union, counteracting nuclear and radiological effects, and improvement of response capabilities against clandestine organizations already in possession of nuclear and radiological weapons (33).

The risk of nuclear and radiological attack against the US is enhanced by the easy access to technology, availability of nuclear and radiological materials, economic instability of Russia, and a general discontent with US foreign policy in many countries. Inadequate security measures in the former Soviet Union, combined with increased determination and lethality of terrorist attacks, greatly increase the probability of the use of RDD's in near future (34). The question of ecological and health implications has to address the issue of cleanup and allocation of operational budgets to save lives, reduce health risks, and preserve culture, biodiversity, and ecological integrity at contaminated sites (35). Such efforts were unsatisfactory in the past, e.g., failed to provide fair and objective compensation to the victims of radioactive fallout in Utah and Nevada, USA. Inadequate screening and compensation for radiation-induced cancer and the persistent controversy in the government's interpretation of low-level radiation have been a point of discontent among the contaminated population during nuclear testing (36).

A recent British report was similarly questionable regarding the analysis of mortality and incidence of cancer among the participants in the UK atmospheric testing of nuclear weapons and experimental programs. The report contains a challenging conclusion that the overall mortality among British nuclear testing survivors was lower than in the general population (37).

Gallilean Dimension of Present-day Uranium Research

The freedom of independent science is hardly any different in the current times than in history. The trial of Gallileo by the Inquisition of 1610 resembles some of the events encountered by today's scientists. The controversy surrounding the findings of Dr. Ernest Sternglass' studies of infant and child death rates in New York State as a result of nuclear testing and radioactive fallout destroyed his academic and scientific career. When his classic paper on the death of children as a consequence of radiation was published in the Bulletin of Atomic Scientists in 1969 (38), the journal editor confided to him that he had been under pressure from Washington not to publish his article. The eminent physicist, Freeman Dyson, commented on it in the same journal in his letter to the editor, "If Sternglass' numbers are right, as I believe they may well be, he has a good argument against missile defense". Sternglass considered the children's deaths a consequence of Strontium-90 from radioactive fallout. When his estimate of close to 400,000 deaths were brought to the attention of Dr. John Gofman, Medical Director of Lawrence Livermore National Laboratory, he reevaluated Sternglass' report. While correcting some of numbers, he concluded that even by assuming a stochastic concept, the guidelines of the risk per radiation unit were set 20 times too high to be safe. He also concluded that the risks were greater at low radiation doses than at high radiation doses. Gofman concluded that cancer deaths related to nuclear testing and radioactive fallout would exceed 30,000 per year. The report was presented to the Committee on Underground Nuclear Testing chaired by Senator E. Muskie, who referred it to the chairman of the Joint Committee on Atomic Energy, Senator C. Holifield. Senator Holifield summoned Gofman to Washington and openly threatened him, "We got them and we will get you." In 1973, as a casualty of his integrity, Dr. Gofman lost his position in his laboratory. The Atomic Energy Commission (AEC) was abolished in 1974 (39).

Uranium Toxicity Revisited

The inevitable risk of uranium isotopes for the environment and human health has been clearly defined throughout two centuries of research (4). However, health care professionals are inadequately trained in the basic radio-toxicology and chemical toxicology of uranium isotopes (40). The current scientific re-analysis of the potential health effects of Radiation Dispersing Devices (RDD) is based mostly on data about Japanese bomb survivors, nuclear testing, and laboratory research. The research literature, particularly in the past five years, abounds with interdisciplinary work and reports regarding the consequences of actinides and uranium isotopes. The confirmation of the incidents of thyroid cancer (41), hepatocellular carcinoma (42), leukemia (43), and risks of acute and chronic exposure to uranium (44), has emphasized the importance of awareness of somatic and genetic consequences of contamination with uranium isotopes. Its correlation with atmospheric testing of nuclear weapons has been reconfirmed in recent reports of the levels of actinides, clearly associated with years of nuclear testing and radioactive fallout in the sea mammals of the northern Pacific (45). The revisited Hiroshima and Nagasaki studies indicate that not only the physical but also psychological impact of the chronic consequences of the use of nuclear weapons have been associated with a prevalence of psychiatric disorders, anxiety, and somatization of symptoms among the victims who were present in the Japanese cities at the time of explosion (46). This re-evaluation clearly indicates long-term psychological consequences, which have to be taken into consideration in the preparedness for future incidents.

Another recent report on the Nagasaki survivors indicates that the consequences of nuclear and radiation effects on survivors have to be an essential aspect of health care management in future conflicts (47). Current data on nuclear testing indicate infant mortality, preterm births, and fetal deaths associated with radiation exposure in the US (48). Medical and ecological adverse effects of the radioactive contamination have been reevaluated in numerous test site areas throughout the world. They report adverse effects of the radioactive contamination at the sites of Krasnoyarsk in Siberia (49), Kazakhstan (50), Altai Mountains (51), Semipalatinsk test site, Kazakhstan (52), Techa River, Ural (53), Mayak nuclear workers (54), Sakha Republic, Yakutia (55), Amchitka Island, Alaska (56), Finland and Norway (57), as well as numerous other reports of the reassessment of the health consequences of radiation exposure at nuclear test sites. This current information provides the data for the proper assessment of the risk in preparation for a possible nuclear and radiological tactical exchange or terrorist attack as the ultimate health crisis (58). The current awareness of the worldwide dispersion and deposition of the released radio nuclides (59) in the biosphere extends well beyond the scope of experimental research and clinical management of radiation casualties, having global implications for the future (60).

Current Research on Health Consequences of Uranium Weapons

The largest single radionuclide contamination occurred in the Persian Gulf during Gulf War I, 1991. Depleted uranium, used as an armour-penetrating ordnance, contaminated the countryside of Iraq, chronically exposed the civilian population and military personnel to DU dust, vapours, and aerosols. A small number of the Allied forces veterans were wounded by DU shrapnel fragments.

Depleted uranium weapons alloy is 99.8% ^{238}U, emitting 60% of the alpha, beta, and gamma radiation of natural uranium. DU is a heavy metal, 160% denser than lead. It is organotropic and ultimately gets incorporated into target organs, such as the skeletal tissue, where it has a long-term retention. Slowly soluble, uranium isotopes are gradually decorporated from the retention sites and have been detected in the urine of Persian Gulf War I veterans 10 years after inhalational exposure or shrapnel wounds (23). Tissue distribution studies reported DU accumulation in the bone, kidney, reproductive system, brain, and lung, with verified genotoxic, mutagenic and carcinogenic properties, as well as reproductive and teratogenic alterations (61).

The internal contamination with DU isotopes was detected in the British, Canadian, and United States Gulf War veterans as late as nine years after inhalational exposure to radioactive dust in Persian Gulf War I. DU isotopes were also identified in a Canadian veteran's autopsy samples of lung, liver, kidney, and bone. They contained high concentrations of uranium, with the isotopic ratios indicating the presence of DU. Early studies performed in 1991, the same year as Gulf War I, by whole body counting, suggested evidence of the presence of uranium in the body and urine of the contaminated veterans (62). Logistical constraints and the controversy on DU delayed active and concentrated studies until 1998, at which time Gulf War veterans underwent testing by neutron-activation analysis. Although a sub-optimal method for detecting small quantities of uranium, the early use of this instrumentation methodology showed significant contamination with DU. The studies were reported at the International Congress of the Radiation Research Society in Dublin, Ireland, in 1998.

Experimental research was continued by the use of state-of-the-art methodology, mass spectrometry, at the Memorial University of Newfoundland, St. John's, Newfoundland, Canada, and later with the British Geological Survey, Nottingham, England. Both series of studies confirmed increased concentrations and the isotopic ratios of DU in 67% of the samples. The first presentation, using mass spectrometry data, was given at the European Congress of Nuclear Medicine in 2000, Paris, France. Continued research has progressed from the detection and measurement of DU in veterans' bodies to the current evaluation of the clinical effects of contamination with uranium in Gulf War I veterans, the civilian population of Iraq, military personnel and civilians in the Balkans, and civilians in Afghanistan and more recently, Gaza and West Bank, Palestine.

Depleted uranium, a low-level radioactive waste of the isotopic enrichment of natural uranium, has been identified as a definitive contaminant in the mentioned areas of military conflict. Its etiological role in the genesis of Gulf War disease has been the subject of sustained controversy since Gulf War I. The well-documented evidence of both chemical and radiological toxic properties of uranium isotopes has recently been an area of numerous research studies and scientific reports on its organotoxic, mutagenic, teratogenic, and carcinogenic effects (63). Recent biodistribution studies in experimental animals embedded with DU pellets confirm the findings of previous biodistribution studies that the kidneys and bones are target organs for uranium isotopes, with other identified sites in the lymphatic, respiratory, and reproductive and central nervous systems (64).

The toxic effects of uranium have been known for almost two centuries as renal chemical toxicity and have been confirmed in the recent studies on renal cells *in vitro* (24). The studies of depleted uranium in the central nervous system confirmed its retention in the sections of hippocampus, with additional evidence of nervous system electrophysiological changes in rats embedded with DU fragments (65). The potential mutagenic effects of internal contamination with DU have been recently suggested by the time dependent correlation of implanted uranium and tissue oncogen expression (66), with genomic instability (67). Neoplastic transformation of human osteoblasts in a DU containing cell culture confirms the risk of DU mediated cancer induction (68). This is in agreement with reports of carcinogenic risks of DU in endobronchial cells exposed to DU, as well as with the reports of recent quantitative evaluation of carcinogenic risk in the lungs of GW I veterans by the determination of time zero pulmonary burden of inhaled DU aerosols (69). The risk was evaluated by applying the Batelle model of simulated interstitial lung fluid and analysis of the 24 hour urine sample of a Gulf War veteran, containing 0.150 mg of DU nine years after inhalational exposure (70). It was found that lung burden corresponded to 1.54 mg of DU at time zero of exposure, with an alpha radiation dose of 4.4 millisievert (mSv) during the first year and 22.2 mSv within ten years of exposure. These values exceed the maximum permissible inhalational dose of DU and warrant further research into the possibility of DU induced malignant changes in the lungs.

These human data reports are of particular importance when viewed in the light of recent evidence of the mutagenic effects of alpha particles on stem cells and alpha-radiation induced chromosomal instabilities in human bone marrow cells (71,72). The chromosomal instability as a consequence of DU alpha particles clearly demonstrates mutagenic effects in DU positive British Gulf War veterans, as recently reported from the study of the peripheral lymphocytes from the University of Bremen, Germany (73). This report is in agreement with previous studies of chromosomal instabilities induced by the a dose of alpha particles, as compared with identically transferred effects of photon irradiation (74). The studies of alpha particle after-effects and recent improvements in microbeam irradiation of mammalian cells allow a precise assessment of the traversal of a single particle through a nucleus of a cell with a capacity of measuring the carcinogenic effect of one single particle (75).

Although the mechanism of mutagenicity and oncogenic effects of inhaled alpha particles still remains unclear, it has been reported that low dose alpha particles can cause sister chromatid changes in normal human cells (76). The practical implications of these studies is important in view of the fact that over 10% of all cancer deaths in the United States are a result of pulmonary deposition of alpha emitters (77). It is also of importance in view of well-demonstrated alpha particle induced genome instability in normal human bronchial cells (78). Human lung cells have been demonstrated as more sensitive to the adverse effects of alpha particles than lung cells of most experimental animals (77). The quantitative evaluation of radiological risk following inhalation of uranium aerosols has to consider both the mechanisms of particle deposition and clearance by translocation to the pulmonary and tracheobronchial lymph nodes, crossing the alveolar-capillary barrier or by expectoration and translocation to the nasopharynx and gastrointestinal tract. The particle clearance model (ICRP-66) addresses the most recent assessment of uranium particle deposition and clearance pertinent to the evaluation of inhaled uranium aerosols and internal dosimetry. The study reported the peak uncertainty at particle size of 0.5-0.6 μm (79).

The lung remains the principal portal of entry of uranium isotopes into the internal environment of the body; the skeletal tissue being the final target organ. Most recent reports of chronic exposure to natural uranium ore are conclusive for both nonmalignant and malignant tumour risk in the lung (80). Current studies also indicate that DU can generate oxidative DNA damage by catalyzing hydrogen peroxide and ascorbate reactions (81). Radiation-induced cell death, chromosomal alterations, cellular transformation, mutations, and carcinogenesis are mainly the consequences of radiation deposited in the nucleus of the cell. Low-level radiation could induce genomic instability with no obvious dose rate effects, rendering high-dose extrapolation impossible and emphasizing the importance of the bystander effects in low-level alpha particle irradiation (82,83). Alpha-induced sister chromatic exchanges at variable doses may elicit changes in the nucleus expressed as a gene mutation, while interacting with cellular cytoplasm (74). These harmful effects challenge the criticism that low dosage of DU are incapable of producing genetic alterations (76).

Gulf War Disease and Balkan Syndrome

Gulf War I in 1991 resulted in 350 metric tons of DU deposited in the environment and 3 to 6 million grams of DU aerosol released into the atmosphere, by most conservative estimates. Its legacy, Gulf War disease, is a complex incapacitating multiorgan system disorder. It was originally described as a consequence of inhalation of desert sand (Al-Eskan disease) (21). It has since acquired different descriptions and names, the numbers of which appear inversely proportional to the actual knowledge and understanding of the disease itself.

The symptoms of this progressive disease have been as numerous as their names, including incapacitating fatigue, musculoskeletel and joint pains, headaches, neuropsychiatric disorders, affect changes, confusion, visual problems, changes of gait, loss of memory, lymphadenopathies, respiratory impairment, impotence, urinary tract morphological and functional alterations. The disease was underestimated and subsequently evolved in its clinical description through recognition of progressive symptomatology. Sometimes dismissed as "malingering", it passed through stages of being called a variant of chronic fatigue immune disorder, post-traumatic stress disorder, to its current acceptance by some countries and still not being recognized as a separate disease entity in others.

The objective research in etiology and pathogenesis of Gulf War illness has been discouraged, with clinical studies delayed, misdirected, and sometimes openly antagonized, with many adverse career consequences, for not being in accordance with the agenda of industrial and political interests. Our current understanding of its etiology appears far from being adequate. Some authors postulate that the causative agents include oil-spills and fires, some favor prophylactic medications, while others suggest biological and chemical agents, as well as multifactorial, nonspecific changes of the immune system and exposure to DU aerosols (84). The lack of a coordinated effort and interdisciplinary research carries this complex syndrome well into its second decade of confusion, with a working solution of temporarily retained names of "Persian Gulf Disease" and "Balkan Syndrome".

The criteria of its classification remain unresolved (85). The best example of the diversity in classifying the Gulf War illness is contained in its multiple names and descriptions. Haley's factor analysis offers six dominant categories, including three major and no less than 17 minor syndromes (86). Other attempts of classification include descriptions such as neuroimmune syndrome, mucocutaneous-intestinal-rheumatic desert syndrome, post-traumatic stress syndrome, and numerous other nomenclature entities (87). Although some of the postulated causes, including oil spills and fires, and desert dust may well apply to Gulf War I, they could hardly be considered the etiological factors in the Balkan conflict. However, DU armour-piercing weapons were used in both conflicts. Mounting evidence in the recent literature of internal contamination of Gulf War veterans containing DU in both scenarios challenges the sustained attempts to downplay its existence (21,23,39,61,63, 70,73,85). The excretion of DU isotopes in contaminated and sick military personnel continues beyond ten years after their exposure in GW I and seven years after the Balkan conflict (21). Most other proposed factors should be re-examined in the context of an evaluation of DU's biological half-time and potential progressive health impacts on the organism (88). These factors would include low-level chemical agents, oil fires, immunization, botulism, aflatoxins, micoplasma, and other etiological factors (84). The long physical and biological half-life, alpha particle decay, and well-established evidence of somatic and genetic radiation toxicity suggest a viable potential role of DU in the genesis of Gulf War and Balkan Syndromes.

There is a conspicuous absence of a meaningful, comprehensive research effort that would correlate these syndromes with uranium contamination. Most recent reports, suggesting the lack of somatic effects of depleted uranium in the areas of Balkan conflict in Bosnia and Herzegovina (89), do not report the actual levels of uranium isotopes in either environmental or human samples. Thus, the conclusions cannot be evaluated in an objective manner without quantitative determination of the concentration and ratio of the isotopes of uranium. Similarly, there is no meaningful and credible explanation for the sharp increase in cancer rates among Gulf War veterans (90). And there are no objectives and independent programs addressing these questions other than the Uranium Medical Research Center (UMRC). UMRC is the only institution that has performed sustained research with continuous scientific and professional communications on internal contamination with DU, using state-of-the-art methodology of thermal ionization and plasma mass spectrometry. These methods, identifying 0.2-0.33% of ^{235}U in Gulf War I veterans, demonstrate uranium concentration of 150 ng/L at the original time of exposure, as compared to the nonexposed population in the Gulf who contained 0.7 to 1.0% of ^{235}U, indicating a urinary uranium concentration of only 14 ng/L (70).

Figure 1. The areas of the Uranium Medical Research Center's (UMRC) field trips in eastern Afghanistan, 2002 (outlined).

Afghanistan Uranium Studies

Although UMRC's studies of DU in the urine of Gulf War I veterans were conducted several years after the actual exposure, the most recent protocol of collecting biological and environmental specimens in Afghanistan coincided with the Operation Enduring Freedom (OEF, Afghanistan, since 2001). Afghanistan provided an opportunity to conduct studies close to the time of conflict. Operation Anaconda ended just as the first UMRC team entered eastern Afghanistan (Fig. 1). The team had access to stationary and fixed assets, since the mobile military equipment had either been removed or secured. UMRC's studies of the population of Jalalabad, Spin Gar, Tora Bora, and Kabul areas have identified civilians suffering from the same multiorgan, nonspecific symptomatology encountered in the Gulf War I and the Balkan conflicts. The symptoms included physical weakness, headache, muscular and skeletal pains, respiratory changes, fever, persistent dry cough, chest pain, gastrointestinal symptoms, neurological symptoms, memory loss, anxiety, and depression. Twenty-four-hour urine samples from the symptomatic subjects, as well as from a control population were collected by the following criteria: 1) the onset of symptoms relative to the bombing raids; 2) physical presence in the area of the bombing; and 3) clinical manifestations. Control subjects were selected among the symptom-free residents of nontargeted areas. An assessment of environmental contamination has been performed by the analysis of the soil, dust (91), debris, as well as drinking water (92), according to established criteria of the estimation of dispersal and hazards of actinides and post impact collection of environmental samples (Figs. 2 and 3). All subjects, including the controls, were briefed about the protocol and the sample collection in local Dari and Pashtu languages. Each subject signed a consent form. All samples were analyzed for the concentration and ratio of four uranium isotopes, ^{234}U, ^{235}U, ^{236}U, ^{238}U, by a multicollector and inductively coupled plasma ionization mass spectrometry in the laboratories of the British Geological Survey, Nottingham, England.

The first results from the Nangarhar Province revealed significantly increased urinary excretion of total uranium in 100% of the subjects, exceeding an average of 20 times higher values than in the nonexposed population. The analysis of the isotopic ratios identified non-depleted uranium (93). Subsequently, studies of specimens collected in a second fieldtrip in 2002 revealed uranium concentrations up to 200 times higher than in the control population. These high levels of total uranium excretion have been identified in the districts of Tora Bora, Yaka Toot, Lal Mal, Makam Khan Farm, Arda Farm, Bibi Mahro, Poli Cherki, and the Kabul airport districts. Both fieldtrips revealed identical signatures of non-depleted uranium (NDU) in all areas of study in eastern Afghanistan (Tables 2 and 3; Fig. 4).

Uranium levels in the soil samples from the areas of OEF bombsites were two to three times higher than worldwide concentration levels of 2-3 mg/kg. The

Figure 2. Soil and debris samples being collected from the bombing site by the Uranium Medical Research Center's (UMRC) field team during the second field trip outside Bibi Mahro district, Afghanistan, 2002.

Figure 3. Water samples being taken from wells downwind from the explosion site in Bibi Mahro district, Afghanistan, in 2002 during the Uranium Medical Research Center's (UMRC) second field trip.

concentrations in water were significantly higher than the World Health Organization (WHO) maximum permissible levels (our unpublished data). UMRC's research is expanding to central, western, and northern Afghanistan. In addition to the continuation of urine excretion studies to measure uranium isotopes, an interdisciplinary collaboration of extensive clinical assessments of renal and pulmonary function, cytogenetic studies of chromosomal aberrations in the peripheral blood of contaminated subjects, electron microscopic and nanopathology studies of selected tissue samples of biopsy and autopsy specimens have been initiated. Follow-up studies of Gulf War I veterans and the eastern Afghanistan population will continue along with evaluations of unexplained illnesses in veterans returning from the Gulf War II conflict areas. Clinical studies arranged in international university medical centers and research institutions will evaluate the effects of both DU and NDU in the renal and respiratory systems by using modern methodology of functional morphology and computerized imaging systems. The research will address several areas of interest including neoplastic transformation (94), cellular apoptosis (25), mutagenesis (95), and carcinogenic risks (96). Environmental contamination and biodistribution studies will address acute and chronic effects of uranium isotope compounds with the evaluation of cumulative radiation dose and its biological effects since the introduction of radioactive warfare. Field studies are now being extended to the civilian populations of Iraq, Gaza Strip, West Bank, the Bal-

Table 2. Total uranium concentration in the urine samples of 8 symptomatic civilians; eastern Afghanistan, 2002

Subject	Uranium (ng/L)
1	281.21
2	247.06
3	128.97
4	453.26
5	477.88
6	298.64
7	88.52
8	224.81
Average	275.04
SD*	137.80
Control†	32.06±25.64

*Standard deviation.
†Average value (±SD) from 3 asymptomatic civilians.

Table 3. Percentage of uranium isotopes in the urine samples of 8 symptomatic civilians; eastern Afghanistan, 2002

Subject	^{238}U	^{235}U	^{234}U	^{236}U
1	99.2732	0.7212	5.49×10^{-3}	3.67×10^{-6}
2	99.2757	0.7189	5.39×10^{-3}	6.63×10^{-6}
3	99.2727	0.7217	5.51×10^{-3}	9.53×10^{-6}
4	99.2750	0.7196	5.41×10^{-3}	8.84×10^{-7}
5	99.2756	0.7190	5.41×10^{-3}	2.16×10^{-7}
6	99.2751	0.7195	5.40×10^{-3}	2.63×10^{-6}
7	99.2741	0.7203	5.58×10^{-3}	7.73×10^{-6}
8	99.2743	0.7201	5.58×10^{-3}	7.30×10^{-6}
Average	99.2745	0.7201	5.47×10^{-3}	4.82×10^{-6}
SD*	1.07×10^{-3}	1.01×10^{-3}	8.14×10^{-5}	3.44×10^{-6}
Control†	99.2702	0.7220	7.66×10^{-3}	8.42×10^{-5}

*Standard deviation.
†Asymptomatic civilians.

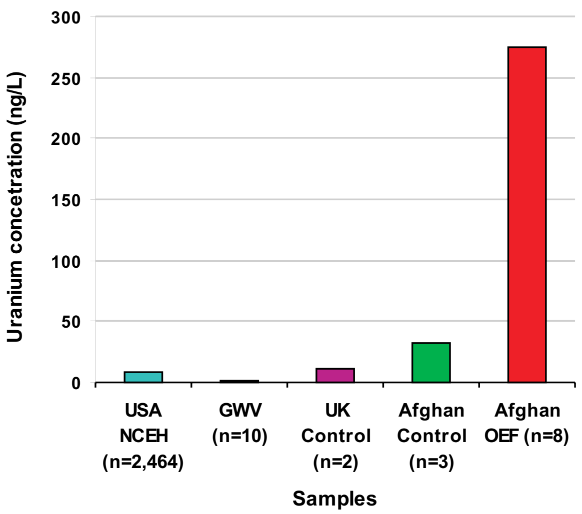

Figure 4. Concentration of uranium isotopes in the 24-hour-urine samples of symptomatic civilians and controls after the bombing raids in the Operation Enduring Freedom (OEF), Afghanistan, 2002. NCEH – National Committee of Environmental Health; GWV – Gulf War veterans.

kans, and new areas of Afghanistan. Our studies confirm the findings in Kosovo of ^{236}U in the soil samples from the targets areas in the Southern Balkans and the presence of small DU particles (95). The Kosovo samples contained hundreds of particles in milligram quantities of contaminated soil, with 50% of particle diameter less than 1.5 μm and most particles of less than 5 μm (98). We attempt to evaluate these findings in our field research trips to the post-conflict areas.

Conclusion

The current reality of the combined chemical, biological, radiological, and nuclear (CBRN) battlefield in the tactical warfare or a potential clandestine use of recently introduced radiological dispersing devices in the terrorist scenario presents a new dimension of the management of mass casualties. The role of medicine in nuclear and radiological warfare is limited due to the universal lack of preparedness in management of the complex consequences of acute radiation syndrome, combined injuries, or the contamination of the biosphere and human population. Recently encountered illnesses of unexplained etiology, pathogenesis, and clinical manifestations provide medical therapeutic interventions with still unresolved problems of the treatment modalities. The adverse effects of internally deposited radionuclides, in particular the isotopes of uranium as a consequence of the military conflicts in the past decade have been well documented in the current literature. The need of a well-planned and coordinated interdisciplinary research in addressing the current environmental and medical consequences of CBRN warfare, with objective and unbiased approach to clarification of the post-conflict unexplained illnesses, will provide a further insight in this challenging chapter of medical science by the inevitable progress of the objective research.

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