

Follow-up of Survivors of Serious Radiation Accidents in the United States

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Introduction

The long-term follow-up of survivors of radiation accidents is warranted both on humanitarian and scientific grounds. By periodic, routine physical examination, individual survivors may benefit from early detection and treatment of adverse health effects that may be related to the accidental exposure. The health and mortality experience of survivors also contributes to the body of scientific knowledge of the acute and delayed effects of radiation on previously healthy humans, and the management and treatment of radiation-induced injuries. The Radiation Accident Registry, maintained by REAC/TS for the U.S. Department of Energy since 1974, documents the medical aspects of serious radiation accidents that occurred in the United States from 1944 to the present.⁽¹⁾ The current status of this registry, which provides a basis for the long-term follow-up of survivors of these accidents, is presented elsewhere in this volume.⁽²⁾

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The Medical Basis for Radiation Accident Preparedness
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The purpose of this paper is to summarize the mortality and notable morbidity experience of the survivors of a subset of the major radiation accidents that occurred in the United States through 1980. Specifically, it updates the causes of death among survivors of accidental acute whole-body irradiation alone, or in combination with significant radiation exposures locally or from internally deposited radionuclides, with particular reference to the survivors of the 1958 and 1971 accidents in Oak Ridge, Tennessee.

Background and Interim Medical Histories

The principal features of the radiation accidents characterized above are shown in Table 1. The technical details and the acute clinical effects of several of these accidents were reviewed at the REAC/TS International Conference in 1979, and information was presented on the follow-up of the survivors up to 1979.⁽³⁾ In contrast to the more recent major accidents discussed at the present conference, the majority of the earlier accidents in the United States that had serious medical consequences were contained within federal or other limited access facilities. They generally involved small numbers of people and had no immediate impact upon the public health. Four accidents each resulted in the death of one individual due to acute whole-body irradiation alone or in combination with severe local irradiation. Nonfatal radiation injuries primarily were the result of external or internal exposure to a radiation source separately rather than in combination, and they typically occurred in the absence of nonradiation trauma or life-threatening medical conditions.

Only in one instance, namely the 1954 Marshellese Islands accident, which is included here as an "U.S." accident, did survivors experience acute whole-body and local injuries due to irradiation from external sources and also from radionuclides deposited internally and on the skin. Increased morbidity due to benign and malignant thyroid disease has been a significant consequence of this accident. The regular "hands-on" medical follow-up of this population is the responsibility of Brookhaven National Laboratory's medical team which, under the leadership of Dr. William Adams, recently completed the 1985-87 survey of survivor health.^(4,5)

The Idaho Falls SL-1 reactor and the Hanford (ARCO) glove box accidents in 1961 and 1976, respectively, have provided limited experience in the U.S. with the medical response to acute radiation-induced injuries in combination with nonradiation trauma. Blast injuries were immediately fatal to the three individuals directly involved in the SL-1 accident. This accident thus contributed significantly more information about the postmortem management and disposition of heavily contaminated victims than about the treatment of combined injuries.⁽⁶⁾ In the Hanford accident, one individual incurred serious internal contamination by inhalation in combination with multiple contaminated

Table 1. Major Radiation Accidents, 1944-1980: U.S. Long Term Follow-Up of Survivors : TBI±Local Irradiation

Year	Site	Radiation Source	No. of Persons Involved	Significant Exposures*
1945	Los Alamos (I)	Criticality	2	
1946	Los Alamos (II)	Criticality	8	
1952	Argonne	Criticality	4	
1954	Marshall Is.	Fallout	239 M.I's	
1958	Oak Ridge (I)	Criticality	8	
1958	Los Alamos (III)	Criticality	3	
1960	Lockport	Accel.	9	
1961	Idaho SL-1	Criticality	21	
1964	Wood River Jct.	Criticality	7	
1967	Pittsburgh (Gulf)	Accel.	3	
1971	Oak Ridge (II)	⁶⁰ Co (Fixed)	1	
1974	Parsippany (I)	⁶⁰ Co (Fixed)	1	
1976	Hanford	²⁴⁷ Am	1	
1977	Parsippany (II)	⁶⁰ Co (Fixed)	1	

* = ≥ 250 mSv TBI; $\pm \geq 6000$ mSv locally

= Fatality = TBI = TBI + Local = Internal S = Surgery
 = Trauma Death = Deceased, "Natural Causes" F = Female
R = Responder

skin lesions as the result of ²⁴⁷Am being expelled, together with flying shards and splinters of glass and corrosive chemicals, by the explosion of a cation resin exchange column in a glove box. Follow-up to death from cardiovascular disease, of this individual by Dr. Bryce Breitenstein and his colleagues has contributed significantly to the literature on the management and care of patients who are heavily contaminated externally and internally, and specifically on the long-term use of the calcium and zinc salts of diethylenetriaminepentaacetic acid (DTPA) in the chelation of internally deposited actinides.⁽⁷⁾

Clinical evidence of injuries due to acute radiation exposure alone among other persons represented in Table 1 ranged from minor deviations from normal hematological profiles among asymptomatic individuals to potentially life-threatening acute radiation sickness and serious local radiation injuries requiring major medical and surgical intervention. However, the survivors of the acute effects of these accidents generally recovered without systemic detriment and eventually returned to work, many of them to full-time employment at the facility at which the accident occurred. Periodic cytogenetic analyses of metaphase chromosomes in samples of cultured lymphocytes obtained from

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selected groups of survivors contribute to the understanding of the long-term effects of radiation at the cellular level and the biological implications of such injuries.⁽⁸⁾

Where evaluated, there were temporary post-irradiation reductions in the sperm counts of individuals who received acute whole-body doses as low as 12 cGy.⁽⁹⁾ The severity and duration of the period of oligospermia or azospermia and associated infertility in these cases were directly related to dose. There was no evidence of permanent sterility among survivors of high sub-lethal radiation doses who later desired to have children, nor of adverse effects on secondary male characteristics. Also, there has been no evidence of unexpected or a greater frequency of malformations or other congenital defects among the children later conceived by the survivors than among unexposed persons.

Overall, the survivors of acute exposure to radiation in the accidents identified in Table 1 have had a generally normal health experience consistent with their age and other risk factors unrelated to irradiation, until the development of a terminal illness or to the present. Among the exceptions to this generalization were individuals among the survivors of the Oak Ridge Y-12 plant (see below), Lockport,⁽¹⁰⁾ and Wood River Junction⁽¹¹⁾ accidents. The individual (KS), who was exposed to X-radiation from an unshielded klystron tube in the Lockport accident, subsequently developed fibroatrophy, particularly affecting the right side of the face including the eye. He developed a cataract of the right lens which was treated surgically in 1963. Increasing discomfort and inconvenience due to photophobia and chronic dryness and irritation of the conjunctiva of the right eye necessitated surgical removal of the eye in 1970.⁽¹²⁾ An individual who was aged 25 years when he received an estimated 30 mSv to the whole body in the Wood River Junction accident in 1964, reportedly had a diagnosis of follicular carcinoma of the thyroid in 1978. The tumor was treated surgically.

Causes of Deaths Among Accident Survivors

The survivors of acute exposure to significant levels of radiation in U.S. accidents who have since died are identified in Table 1 by a black dot. Some of these deaths were reported at the 1979 conference,⁽³⁾ but are included here for completeness. Among the deaths that have occurred since 1979 or were not previously reported, was that of the individual identified as Case 10 in earlier reports of the 1945 and 1946 Los Alamos accidents.⁽¹³⁾ This individual received 7 cGy neutron and 2 cGy gamma-ray radiation in the 1946 Los Alamos accident. He was reported to be in good general health in 1979 but later developed amyotrophic lateral sclerosis from which he died in 1988 at age 65 years. This brings the total number of deaths among the survivors of the acute effects of these two accidents to six. Four additional deaths, all due to nonmalignant

diseases, have occurred since 1979 among the group of 64 Marshallese Islanders who received estimated average whole-body doses of 1.75 Gy from fallout following the BRAVO nuclear test in 1954. A total of 26 deaths has now occurred among this group, including 5 prior to 1980 that were due to malignant disease.⁽⁵⁾ Other deaths reported since 1979 include those of one survivor of each of the Los Alamos III (1958),⁽¹¹⁾ Lockport (1960), Pittsburgh (1967),⁽¹⁴⁾ and Rockaway (1977)⁽¹⁵⁾ accidents. The survivor of the Los Alamos III accident died in 1980 of obstructive lung disease at age 59 years, 22 years after receiving a whole-body dose equivalent of 1.34 Sv of mixed gamma-ray and neutron radiation.⁽¹⁶⁾ A cerebrovascular accident with underlying congestive heart failure caused the death, 8 years after the Lockport accident, of a survivor whose accidental whole-body exposure to X-radiation over a 2 hour period in 1961 reportedly totaled "200 to 350 R" (64.5 to 104.2 mC/kg). The survivor of an estimated 6.0 Sv whole-body irradiation and 27.0 to 39.0 Sv locally to the feet and hands, respectively, in the Pittsburgh accident, died of a myocardial infarction 17 years later at age 57 years. Multiple trauma received in a motorcycle accident resulted in the death in 1984 of the Rockaway accident survivor who, 7 years earlier at age 32, had received a whole-body dose equivalent of an estimated 2.5 Sv.⁽¹⁷⁾ Also, the test supervisor who received 250 mSv in responding to the Idaho SL-1 accident in 1961 died in 1984. The immediate cause of death in this case was pneumonia; hypereosinophilia diagnosed about 4 years earlier was cited as a contributing cause of death.⁽¹⁸⁾

Oak Ridge Accident Survivors

Since 1979 REAC/TS staff have continued the medical follow-up at approximately annual intervals of the six remaining survivors of the June 16, 1958, criticality accident at the Oak Ridge Y-12 plant.⁽¹⁹⁾ Interim medical and other pertinent histories have been obtained together with hematological, biochemical, and cytogenetic profiles. Ophthalmological and dermatological evaluations have been conducted by consultant specialists. The survivors have been referred to their personal physicians or consultant specialists for continued care of existing conditions or for further evaluation of abnormal findings of the periodic physical and laboratory examinations. An updated summary is presented in Table 2 of the technical, immediate, and long-term medical aspects of the Y-12 criticality accident.

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Table 2. Summary of Immediate and Follow-Up Medical Course of All Eight Patients

Patient Status at Time of Accident	Dose (cGy) Y, II	Hospital Course	Convalescent Course, 12/58	Subsequent History through 9/88
<p>A</p> <p>40 yrs., married, 2 children P.H.; non-contrib. smoker Chemical operator 6 ft from source</p>	<p>269 Y, 96 II; dose=365 cGy</p>	<p>0-48 hrs: nausea (persisting 5 days), vomiting 49 hrs: lymphs 9%: 873 Day 17: epilation began Day 25-28: mild thrombocytopenic signs Day 29: pyrexia, acute tonsillitis Day 44: discharged Wt change: -2 lbs, +8 lbs</p>	<p>Joint stiffness, fatigability, vague visual symptoms, disturbance of balance, decreasing gradually, mild depression</p>	<p>Generally good health with minor complaints. 1962: "about recovered" from weakness, joint and muscle symptoms. 1970: bronchial asthma. 1976: c/o asthma, arthralgia. Hypothyroid, Synthroid prescribed. 1979: Several non-malignant nevi excised in interim. Arthralgia minimal, asthma continues, otherwise in good health. Interim: Continued medical control of hypothyroidism. Rectal polypectomy, benign, transurethral resection for benign prostate hypertrophy (1982). Retired; no recurrence of allergic asthma subsequently (1983). No progression of previously reported minimal opacities of lenticular cortex; general health good, consistent with age; no evidence of radiation related disease (1988).</p>
<p>B</p> <p>32 yrs., married; 2 children P.H.; non-contrib. electrician 15 ft from source</p>	<p>199 Y, 71 II; dose=270 cGy</p>	<p>0-48 hrs: nausea (persisting 3 days), vomiting, headache 49 hrs: lymphs 9%: 882 Day 10: furuncle Day 13: pyrexia, mild pharyngitis, otitis media Day 27: rare RBCs in urine Day 44: discharged Wt change: -2 lbs, +13 lbs</p>	<p>Tendency to tire easily, some muscle soreness, several mild URI's</p>	<p>1965: mild or incipient diabetes, obesity, hyperuricemia. 1968: fasting blood sugar, serum uric acid normal. 1979: good general health continues, no medications. Faint lenticular opacities. Interim: Borderline diabetes controlled by diet and oral medication. Atypical lymphocytes identified (1984).</p>

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Table 2. Summary of Immediate and Follow-Up Medical Course of All Eight Patients (continued)

<p>1985); results of lymphocyte analysis within normal range (1986); no recurrence. Asymptomatic benign prostatic hypertrophy (1985). Basal cell carcinomas excised from mid back and pinna of right ear. Previously identified posterior capsular opacities described as early bilateral cataracts, possibly radiogenic. No major changes in general health (1988).</p>			<p>1960: spontaneous bruising. 1967: fatigue, weight loss; infiltrate in apex of right lung; tuberculosis. 1967-69: treatment with tuberculostatica. 1970: infiltrate I.U.L. lobectomy, invasive multinodular bronchogenic carcinoma; cobalt therapy. Hypercholesterolemia. 1972: metastatic spread. 1973: died 1/13/1973.</p>
<p>Some weakness in thighs. Headache in sunlight. Some fatigue.</p>	<p>0-48 hrs: generalized warmth, nausea, vomiting 30 mins day 2 only 49 hrs: lymphs 15%, 1276 Day 10: pyrexia, URI Day 17: epilation Day 25-30: petechiae over trunk, legs; mild fatigue Day 44: discharged Wt change: +8 lbs</p>	<p>250 Y, 89 μ; dose=339 cGy</p>	<p>C 39 yrs., married; 4 children P.H: coal miner 12 yrs., smoker Machinist 17 ft from source</p>
<p>Weakness, forgetfulness, headache, fatigability, abdominal discomfort, nervousness, insomnia, mild depression.</p>	<p>0-72 hrs: intermittent nausea, vomited twice 49 hrs: lymphs 21%, 1827 Day 17: epilation Day 24: discomfort RLQ Day 25: rare RBC in urine Day 44: discharged Wt change: -2 lbs, +3 lbs</p>	<p>241 Y, 86 μ; dose=327 cGy</p>	<p>D 50 yrs., married; 1 child P.H: non-contrib. Electrician 16 ft from source</p>
<p>Persistent symptoms, numerous minor complaints, arthralgia and weakness especially in the legs. 1961: hypertrophic degenerative arthritis by X-rays. Continued employment at Y-12 until 1972. 1974: IgA gammopathy, no B-J protein, bone marrow hypocellular, not diagnostic. Medically controlled hypertension. 1976: IgA level still elevated but decreased. B-J protein negative, bone marrow non-diagnostic. 1979: IgA level still elevated but less than in 1976. No B-J protein, bone scan negative.</p>			

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Table 2. Summary of Immediate and Follow-Up Medical Course of All Eight Patients (continued)

<p>E 35 yrs., married, 4 children P.H: non-contrib. Machinist 22 ft from source</p>	<p>174 Y. 62 u. dose=236 cGy</p>	<p>0-48 hrs: asymptomatic for 24 hrs Nausea, vomiting (X3) day 2 only, malaise, aches in legs 49 hours: lymphs 2196; 945 Day 3: furuncle Day 17: epilation Day 26, 27: St. gingival bleeding on brushing Day 44: discharged Wt change: +10 lbs</p>	<p>Fatigability, weakness in leg. Photophobia in sunlight. 8/23/58, nervousness.</p>	<p>Prostatic hypertrophy. Physically active. Interim: Gastric ulcer, treated medically, degenerative arthritis (1980). Central posterior subscapular opacities bilaterally, probably radiogenic (1983). Fluctuations in total serum/urinary proteins, IgG and IgA; B-J protein absent. Arterio-sclerotic heart disease, cardiac insufficiency treated medically (through 1986). Nephrotic syndrome, amyloidosis. Bone marrow biopsy positive for multiple myeloma, B-J protein absent (6/87); died 7/26/1987.</p>	<p>Persistent fatigability; minor complaints. 1959: hospitalized for left anterior pain. 1962: hypoglycemia 1965-present: erythroplasia of Queyrat. 1971: renal infection. 1979: prostatitis 1979: good general health; dermatological consultation. Interim: Recurrent squamous cell carcinoma of skin excised (1980, 1981, 1982). Bilateral lenticular opacities unchanged (1982). Recurrent hyperkeratotic skin lesions (1984). Arthritis. Maturing bilateral cataracts, possibly radio- genic; retired (1985). Recurrent hyperkeratotic plaque excised. Thrombo- phlebitis, left lower leg (1986). General health consistent with age, no major major changes (1988).</p>
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Table 2. Summary of Immediate and Follow-Up Medical Course of All Eight Patients (continued)

<p>F 41 yrs., married; 4 children P.H.: emphysema nephrolithiasis since 1950, smoker, asbestos exposure W/der 20 ft from source</p>	<p>50.5 Y, 18 μ; dose=68.5 cGy</p>	<p>0-48 hrs: weakness 49 hrs: lymphs 25%: 2548 Day 3: nausea 2 hrs. Day 9: discharged Wt change: +5 lbs</p>	<p>Aches, fatigue of thighs, severe "snapping sounds" in many joints. Intermittent fatigability. 1972: right nephrolithotomy.</p>	<p>1961: right nephrolithiasis, mild hydronephrosis; bleeding peptic ulcer. 1967: mild hypertension, albuminuria. 1973: gastrojejunostomy for acute peptic ulcer. 1974: left nephrolithiasis. 1976: COPD 11/76: hospitalized with pneumonia, medical disability retirement from Y-12. 1979: COPD, little change; physical activity limited; report past asbestos exposure. Interim: Facial seborrheic and actinic keratoses; moderate eosinophilia; malaise (1980). Immunoglobulins normal (1983). Malaise, dyspnoea. Multiple hospitalizations for respiratory disease; weight lost (1984). Bronchogenic carcinoma diagnosed, radiation therapy. dermatitis secondary to fungal infection of hands and feet (1985). Died 3/21/1987, acute myocardial infarction, related to COPD and pulmonary carcinoma.</p>
<p>G 56 yrs., married; 5 of 8 children living F.P.: 1957: M.I. Maintenance mechanic 20 ft from source</p>	<p>50.5 Y, 18 μ; dose=68.5 cGy</p>	<p>0-48 hrs: asymptomatic 49 hrs: lymphs 15%: 1989 Mild emphysema Day 9: discharged Wt change: +1/2 lb</p>	<p>Considerable nervousness about late effects of irradiation. Few brief weak spells in mid-July 1958. Some depression. Weakness in legs not prominent.</p>	<p>Few minor complaints. Nervousness about accident persisted. General health good. 1962: early retirement. 1972: mild hypertension, RHHB and occasional PVCs. 1976: CVA, fatal in 45 minutes.</p>

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Table 2. Summary of Immediate and Follow-Up Medical Course of All Eight Patients (continued)

<p>25 yrs., single P.H: emotional problems F.H: hemoglobinopathy, possible psychoneurosis 50 ft from source</p>	<p>16.8 Y, 6 μ; dose=22.8 cGy</p>	<p>0-48 hrs: asymptomatic 49 hrs: lymphs 33%; 1914 Day 6: URI responded to symptomatic treatment Day 9: discharged Wt change: -1 lb, + 4 lbs</p>	<p>Nervousness, fatigability. Married 2 mos. after accident. Special study of hemoglobin led to incidental discovery of pre-existing familial hemoglobinopathy of no clinical significance.</p>	<p>Continued psychoneurotic difficulties. Normal, healthy daughters born in 1959 and 1965. Marital problems; separated 1973. 1975: continued good health through 8/75. Adenocarcinoma colon in 9/75. No evidence of recurrence or metastases through 3/79. 1976: ventricular bigeminy. 1977: auto crash; w/ splash injury. 1979: Healthy and more stable. Interim: Rectal polypectomy, benign (1980). Benign subcutaneous tumor excised (1985). Rectal polypectomy, benign; continues fulltime employment; good general health (1988). CEA negative through 1988.</p>
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Studies in November 1961 showed sperm count in six patients who had aspermia or oligospermia 4 months after the accident were consistent with good potential fertility. aspermia persisted in patient C.

In the interim, survivors of the 1958 accident in Oak Ridge who were identified in previous reports⁽¹⁹⁾ as Patients A, B, E, and H, have experienced no major changes in their general health status beyond those typical of the aging process. Patient A was 40 years old in 1958 when he received an estimated whole-body dose of 3.65 Gy. Hypothyroidism, related to potassium iodide therapy for bronchial asthma, developed in 1976 and remains under medical control with daily administration of Synthroid. This individual has continued to develop multiple benign skin tumors, particularly over the thoracic region. Several of these tumors have been excised by a dermatologist in the interim because of irritation and bleeding; the majority have been seborrheic keratoses. In 1982 he took full retirement from the Y-12 plant where he had continued to be employed since the accident. Symptoms of allergic asthma present since the late 1960's have been absent since retirement, and so, may more possibly have been occupationally related. In 1982 a benign rectal polyp was excised; subsequent hemocult tests have been negative. Urinary tract symptoms associated with benign prostatic hypertrophy were relieved following a transurethral resection in 1982. He complains of arthritis in the right knee but remains physically active. Results of the hemogram, and biochemical and thyroid function tests performed in September 1988 were within the normal range except for a depressed LDH value (117 IU/ml; range 118-242), and an elevated triglyceride level (254 mg/dl; range 30-200) for which dietary modification was recommended. Previously identified opacities in the cortical lens bilaterally and a choroidal nevus in the right eye were unchanged in 1988 from previous examinations.

Patient B, who received 2.70 Gy at age 32 continues full-time employment at the Y-12 plant 30 years after the accident. He has continued to be treated medically for mild to moderate hypertension and adult onset diabetes. Evaluation of an apparent excess of atypical lymphocytes found by hematological examination in 1984 failed to identify any lymphocyte abnormalities. Asymptomatic benign prostatic hypertrophy was detected on rectal examination in 1985. Early multicentric basal cell carcinomata were removed from the dorsal aspect of the right shoulder and mid back in 1987 and 1988, respectively. Also in 1988, a basal cell carcinoma was excised from the pinna of the right ear. Multiple epidermal cysts were noted on the trunk and face together with a seborrheic keratosis on the nose. Previously observed bilateral early posterior capsular lenticular opacities have progressed little and do not interfere with vision; in 1988 they were recognized as possibly being radiation induced. At the 1988 examination, the hematological and urinary parameters were within the normal range. The hemocult test was negative. The standard battery of biochemical tests also showed values which were generally within the normal ranges; exceptions included elevated serum levels of glucose (250 mg/dl; range 70-105), cholesterol 284 mg/dl; range 100-220), and triglycerides (274 mg/dl; range 30-200). The patient was referred to his personal physician for management of these problems.

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Patient E was 35 years old when he received a whole-body irradiation dose of 2.36 Gy in 1958. His general health has remained good since the accident. He has continued to experience multiple skin tumors. Recurrent squamous cell carcinoma of the skin was excised from the penis in 1980, 1981, and 1982. Recurrent hyperkeratotic actinic lesions have been excised periodically from exposed skin; topical application of a sun screen was recommended for outdoor activities. He has remained physically active, playing golf several times a week following retirement from full-time employment at the Y-12 plant in 1985. Maturing bilateral lenticular cataracts observed in 1985 are possibly attributable to radiation exposure, and may be responsible for glare symptoms experienced in night driving. He was treated medically for thrombophlebitis in the left lower leg in 1986. When examined in 1987 the hematological and urinary profiles were normal. The hemocult test showed a slight trace of blood. A follow-up examination by the patient's personal physician ruled out a tumor of the lower bowel. Serum chemistries were normal except for slight elevations of the cholesterol (223 mg/dl; range 100-200) and triglycerides (209 mg/dl; range 30-200).

Patient H, at age 25 years, was the youngest of the eight persons involved in the Y-12 accident, in which he received a whole-body dose of 22.8 cGy. He has remained in good general health since 1979 and continues in full-time employment. There has been no evidence of a recurrence of adenocarcinoma of the colon that was diagnosed and treated surgically in 1975; subsequent periodic carcinoembryonic antigen (CEA) tests consistently have been negative. Benign rectal polyps were excised in 1980 and 1988. At examination in 1988 all hematological, urinary, and biochemical results were within the normal ranges with the exception of total serum protein (6.2 g/dl; range 6.5-8.0).

Patient D, who received 3.27 Gy whole-body dose at age 50 years, and Patient F, who received 68.0 cGy at age 41 years, were followed annually from 1979 until their deaths in 1987. Patient D had a history of asymptomatic IgA gammopathy with no evidence of Bence-Jones protein beginning in 1974. He was treated medically for a bleeding gastric ulcer diagnosed in 1980. In 1983, asymptomatic posterior subscapular opacities noted originally in 1961, were attributed to acute exposure to radiation in 1958. Beginning in 1985 he was treated medically for arteriosclerotic heart disease, hypertension, cardiac insufficiency, and prostatitis associated with existing benign prostatic hypertrophy. His general health declined significantly thereafter, with exacerbation of symptoms of degenerative arthritis, cerebrovascular insufficiency, and impaired hearing. In 1985 painful mammary gland hyperplasia developed in the subareolar tissue of the right breast; this condition was determined to be a benign side effect of medication prescribed for prostatitis. The parameters of the hematological profile obtained in 1986 were generally within the normal ranges; the differential white cell count showed an elevated eosinophil count (12%, normal 0-3%); a low normal platelet count was obtained ($166,000 \text{ mm}^3$; range

140,000-440,000). Biochemical tests showed elevated levels of serum creatinine (2.0 mg/dl; range 0.5-1.4) and triglycerides (172 mg/dl; normal 10-150), and decreased levels of HDL cholesterol (25 mg/dl; range 30-70) and total proteins (5.9 g/dl; range 6.0-8.3). The latter result was consistent with the results of serum electrophoresis in 1986 which showed a decline in total serum protein to 5.8 gm% from 6.2 gm% in 1985, and an increase in 24-hour urinary protein from 7.40 gm in 1985 to 10.09 gm. Previously observed fluctuations in serum immunoglobulins⁽¹⁷⁾ continued in the absence of Bence-Jones proteinuria. He was hospitalized three times between November 1986 and his death at home in July 1987 for treatment of symptoms of coronary insufficiency, arteriosclerotic heart disease and associated proteinuria and anemia. In May 1987 generalized ascites and subcutaneous edema were identified by CT scan. A bone scan showed no osteoblastic activity; no degenerative lesions were detected by a bone survey. A diagnosis of multiple myeloma with amyloidosis was made based on the finding of moderate plasmacytosis (10-15%) in a bone marrow aspirate and positive tests for amyloid. Autopsy permission was refused.

Patient F was seen at REAC/TS on five occasions after 1979. Radiography of the chest in 1980 showed evidence of chronic pulmonary disease that was unchanged from findings reported in February 1979. Moderate eosinophilia, considered to be an allergic response was found at examinations in February, June, and July 1980. Evaluation of the bone marrow was refused. Increasing respiratory symptoms resulting in decreased physical capabilities were reported by the patient in 1983. Eosinophilia persisted; electrophoretic evaluation of serum immunoglobulins showed no abnormalities. Chest radiography in May 1984 showed few changes from previous films. In 1984 the hematological profile, including the eosinophil count, was within normal limits. The results of biochemical tests also were normal except for an elevated alkaline phosphatase level (103 mU/ml; range 20-95). The patient was hospitalized on three occasions between August and October 1984 for treatment of acute respiratory symptoms. Bronchogenic carcinoma of the lung was diagnosed by biopsy in February 1985 for which the patient underwent a series of radiation treatments. He was rehospitalized in July 1985 for treatment of acute respiratory failure associated with carcinoma of the lung and "pulmonary asbestosis" (biopsy of lung tissue in 1985 found no evidence of asbestosis). His physical condition deteriorated until his death in March 1987 which was attributed to acute myocardial infarction associated with chronic obstructive pulmonary disease and bronchogenic carcinoma. There was no autopsy in this case either.

The individual who was accidentally exposed in 1971 at age 32 years to radiation from a 7700 Ci (24.49 teraBq) cobalt-60 source being used for seed irradiation experiments at the University of Tennessee Comparative Animal Laboratory, showed no long-term adverse effects 8.5 years post-exposure.⁽²⁰⁾ Follow-up examinations at REAC/TS through May 1984 showed no major changes in health status. He continued to complain of periods of fatigue and

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dizziness that occurred at irregular intervals, and of non-specific pain in the right hand when used forcefully. No physical, hematological, or biochemical abnormalities were identified during this time, and the individual continued full-time employment. In Fall 1985, he was seen by his personal physician and complained of feeling "washed out." A diagnosis was made of acute lymphoblastic leukemia. Chemotherapy was begun and resulted in a period of remission. His death in April 1987 was attributed to acute lymphoblastic leukemia.

Cytogenetic Studies

The frequencies of radiation-induced chromosome aberrations in cultured lymphocytes of the Y-12 accident survivors were first quantified by Bender and Gooch, two and one-half and three and one-half years after the accident^(21,22) and subsequently by Goh at seven, eight, and ten years post-exposure.^(23,24) On several occasions since 1974, the cytogenetics staff at REAC/TS has evaluated the incidence of persistent chromosome aberrations in lymphocytes of six of the survivors. A summary of the cytogenetic findings for the six survivors 25 years post-exposure is presented in Table 3.

Blood samples for lymphocyte cultures were obtained during their regularly scheduled physical evaluations. For all cytogenetic evaluations, lymphocytes were cultured in either TC-199 or RPMI 1640 culture medium, and harvested at 48 hours. Since 1979, we have employed bromodeoxyuridine culture methodology, and chromosome aberrations have been quantified in preparations having greater than 90% first division metaphases. Detailed microscopic evaluations of metaphases having 45 or 46 centromeres were undertaken to ascertain the incidence of all types of asymmetrical ("unstable") and symmetrical ("stable") chromosome type aberrations (for details see 23,24). Those metaphases having asymmetrical aberrations (i.e., di- or multicentric chromosomes, centric rings, or acentric fragments) and those having symmetrical aberrations (i.e., abnormal monocentric chromosomes, including translocations, inversions, or chromosomes with deleted segments) were photographed and karyotyped for confirmation of the suspected aberration. Depending on workload of staff, and availability of scorers, 100-500 metaphases were evaluated from the various cultures.

Detailed results of the cytogenetic findings in cultures initiated 16-17 years after the accident were presented previously.⁽²⁵⁾ A summary of cytogenetics data from lymphocyte cultures initiated 25 years after their radiation exposure is shown in Table 3. In lymphocyte cultures from all six men, the most frequent types of chromosome aberrations were those of the stable type, of which balanced translocations predominated. In this particular series of cultures, the

percentage of lymphocyte metaphases with one or more symmetrical aberrations varied from 1.5 to 16.3%, with the highest frequencies of aberrant metaphases observed in cultures from the three men with the highest doses. In cultures initiated since 1975 (i.e., >17 year post-exposure), unstable chromosome-type aberrations have been observed only occasionally and their frequencies do not correlate with radiation dose.

As previously noted, Patients D and F died in 1987. At the time of his death at age 79, Patient D suffered from multiple myeloma. In 1974, his serum immunoglobulins (which had not been measured earlier) were found to be abnormal, and 6% plasma cells with some young forms were found in his marrow.⁽¹⁸⁾ Because of these aberrant clinical findings, follow-up cytogenetic evaluations of his cultured lymphocytes were conducted at regular intervals. Data from his preparations are compared with findings observed in the other survivors in Table 4. From 17 to 28 years after his exposure the average frequency of metaphases with stable chromosome type abnormalities in this lymphocyte cultures was 11.2% ranging from 8.5 ± 2 in cultures initiated eleven months before his death, to 16.3 ± 2 in cultures initiated in 1983. The observed variability in aberration frequencies among his various cultures can readily be attributed to minor differences in ascertainment of stable aberrations by different scorers and to random sampling error. Throughout the entire time period, the frequency of persistent aberrations in his lymphocytes was among the highest observed in these six men, a finding which is consistent with the fact that he received the second highest radiation dose.

In September 1975 Patient H had a right colectomy for carcinoma of the colon. He currently shows no symptoms of the disease. At five years after surgery no cytogenetic abnormalities were observed in the 100 metaphases scored for aberrations, and in 1983, 1.5% of his cells were observed to have stable aberrations. As in Patient D, cytogenetic findings in this individual have been completely unremarkable, with his aberration frequency being in line with that expected based on the relatively low radiation dose that he received.

In fact, for each of the six men we have observed, similar frequencies of metaphases with stable aberrations in their two-day lymphocyte cultures initiated over a time interval of 17-28 years since the accident. Our observation that the proportion of metaphases with symmetrical aberrations remains relatively constant over time post-exposure is in agreement with the findings of Buckton in the 30-year follow-up study of the ankylosing spondylitis patients who received localized and fractionated radiotherapy to the spinal column and sacrum.⁽²⁷⁾

Since 1974 we have also quantified the incidence of asymmetrical and symmetrical types of aberrations in cultured lymphocytes of the UT-AEC Accident survivor. Cytogenetic evaluations were conducted initially by Brewen et al.⁽²⁸⁾ on blood samples obtained approximately 4 and 24 hours after his exposure. At that time, the incidence of dicentrics plus centric rings in his

Table 3. Summary of Cytogenetic Findings in Cultured Lymphocytes of Six Y-12 Accident Survivors 25 Years Post-Exposure

Patient	Dose	# Cells Scored	Total # Aberrations						% Metaphases with aberrations	
			"Stable"		"Unstable"				"stable"	"unstable"
			Tran	Inv	Del	Dic	R	AC		
A	365	298	36	5	10	0	0	0	13.8	0.0
D	327	295	51	10	3	1	0	2	16.3	1.0
B	270	200	11	2	3	1	1	1	7.0	1.5
E	236	294	12	2	4	5 ^a	2	1	5.1	1.7
F	68.5	300	6	4	1	2 ^b	1	1	3.0	1.0
H	22.5	200	2	1	0	0	0	0	1.5	0

^a One tricentric and two dicentric chromosomes observed in one metaphase

^b Two dicentric chromosomes observed in one metaphase

Table 4. Percentage of Metaphases With One or More Stable Aberrations in Lymphocyte Cultures From Y-12

Patient (Dose)	17 yr	18 yr	22 yr	24 yr	25 yr	27 yr	28 yr	Total ^c	Mean + S.E.
A (365)	10.0 ± 2.5 ^a	---	---	9.0 ± 2.9	13.8 ± 2.0	9.0 ± 2.0	---	648/75	11.5 ± 1.3
D (327)	11.0 ± 2.5	9.0 ± 1.5	9.0 ± 2.9	10.0 ± 3.2	16.3 ± 2.0	12.0 ± 3.2	8.5 ± 2.1	1,253/140	11.2 ± 0.89
B (270)	6.0 ± 2.4	---	---	5.0 ± 2.2	7.0 ± 1.8	---	---	400/25	6.25 ± 1.2
E (236)	4.0 ± 2.0 ^b	---	4.7 ± 1.9	1.0 ± 0.99	5.1 ± 1.3	---	---	620/25	3.9 ± 0.77
F (68.5)	3.0 ± 1.7 ^b	---	1.0 ± 0.99	---	3.0 ± 0.98	---	---	500/13	2.6 ± 0.71
H (22.8)	3.0 ± 1.7	---	0	---	1.5 ± 0.85	---	---	400/6	1.5 ± 0.61

^a Standard error assumes binomial distribution

^b Culture initiated in 1974

^c Total metaphases scored in all cultures/number of metaphases with stable aberrations

Table 5. Summary of Cytogenetic Findings in Cultured Lymphocytes of UT-AEC Accident Survivors (4.7 - 13.3 Years Post-Exposure)

Year ^a	Culture ^b	# Cells Scored	Total # Aberrations						% Metaphases with aberrations	
			"Stable"		"Unstable"				"stable"	"unstable"
			Tran	Inv	Del	Dic	R	AC		
4.7 yr	48 hr	150	1	2	0	19	1	2	2.0 ± 1.0	11.3 ± 2.5
8.5 yr	48 hr ^c	200	3	0	1	4	1	6	2.0 ± 1.0	4.5 ± 1.4
12.3 yr	48 hr ^c	250	5	2	0	1	1	0	3.2 ± 1.1	0.8 ± 0.6
12.8 yr	48 hr ^c	500	18	3	0	7	3	2	4.0 ± 0.9	2.0 ± 1.0
13.3 yr	48 hr ^c	200	8	0	1	4	1	1	4.0 ± 1.4	2.5 ± 1.1

^a Number of years after accident

^b PHA-stimulated lymphocytes cultured at 37°C in TC 199 or RPMI 1640 culture medium

^c Data from cultures supplemented with BrdU; in preparations having >10% second-division metaphases, scoring of aberrations was restricted to first-division metaphases from differentiated slides

circulating T-lymphocytes was observed to be about 25% and remained at that level during the first five weeks post-exposure. When compared with data derived from an in vitro calibration curve for ⁶⁰Co gamma radiation, the chromosome aberration yield observed in his cultured lymphocytes produced an equivalent whole-body dose estimate of 144 rad.

Subsequently, the frequency of asymmetrical aberrations in his lymphocytes was quantified by Preston et al.⁽²⁹⁾ in cultures initiated during a period ranging from 5.5 to 156 weeks after the accident. During that interval the proportion of centric rings plus dicentrics was observed to decrease to slightly less than half that observed during the first 4.5 weeks after exposure.

In 1974 we initiated 48-hour lymphocyte cultures for the purpose of ascertaining the frequencies of symmetrical and asymmetrical aberrations at 4.7 years after the exposure (Table 5). In our group analysis of 150 metaphases, we observed three abnormal monocentric chromosomes and 20 dicentrics plus centric rings. Thus, the incidence of metaphases with asymmetrical aberrations was approximately the same as that observed in cultures initiated one and one-half years earlier. By 8.5 years post-exposure, the frequency of metaphases bearing unstable types of aberrations had decreased to about 4.5%, whereas the

proportion of metaphases with stable types of aberrations remained at approximately 2%. In lymphocyte cultures initiated during his routinely scheduled physical exams at 12.3, 12.8, and 13.3 years after the accident, the proportion of metaphases bearing asymmetrical types of aberrations had decreased to approximately 2%, and appeared to have reached a plateau. Over the entire sampling period, the proportion of metaphases with stable aberrations remained relatively constant between 2 and 4%.

It is well known that specific structural chromosomal aberrations including balanced and non-balanced translocations, inversions, and chromosomes with deletions of segments are associated with many types of malignancies, including diseases affecting hematopoietic tissues. As recently reviewed by Heim and Mitelman,⁽³⁰⁾ 15 different, consistently occurring chromosomal rearrangements have now been identified in malignant cell populations of various patients with acute lymphocytic leukemia. Clones of cytogenetically aberrant malignant cells have also been identified in nearly 100 patients with multiple myeloma. The most consistent abnormality associated with this lymphoid neoplasia is a 14 q+ marker which has been observed in about one-third of the cytogenetically abnormal patients. In both of these diseases, the most frequent structural abnormalities observed are reciprocal translocations. Reciprocal translocations are of special interest in studies of cancer genesis, since data accumulated during recent years have demonstrated that proto-oncogenes are located at the chromosomal break points of several symmetrical rearrangements that are known to be specific for a number of malignancies. As discussed by Rowley,⁽³⁰⁾ one consequence of the transposition of DNA segments from one chromosomal region to another is that proto-oncogenes may be removed from their normal locations to new regions where their gene functions are under different mechanisms of genetic control. In such cases, altered expression of gene products may be observed.

Because ionizing radiation is a carcinogen and is efficient in inducing chromosomal aberrations, it has been speculated by many authors that radiation-induced chromosome aberrations in exposed cells may be related to subsequent cancer risk. At the time of radiation exposure, symmetrical and asymmetrical aberrations are induced with equal frequencies^(27,32) and at random⁽³²⁾ among various chromosomes of the complement. Thus, it might be anticipated that the great majority of the induced symmetrical exchanges would be genetically neutral. However, it is possible that, as a rare event, transposition of specific DNA sequences from one location to another during the formation of an induced translocation might result in a meaningful genomic alteration (or mutation) that potentiates that proliferative capability of the cell bearing the specific rearrangement. In such instances clones of lymphocytes derived from such stem cells having a selective proliferative advantage might be observed in lymphocyte populations many years after exposure.⁽²⁷⁾ Indeed, clones have been observed in

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Table 6. Possible 'Clones' Identified in 48-Hour Lymphocyte Cultures of Y-12 and UT-AEC Accident Survivors ^a

Patient	Dose	Karyotypic Rearrangement	# of Affected Metaphases
A	365	46, XY, t(1-;Dq+)	2
		46, XY, t(2p-;Cp+)	2
D	327	46, XY, t(?-;Dp+)	2
		46, XY, inv (F)	2
		46, XY, inv (B)	2
		46, XY, inv (2)	2
		46, XY, t(Bp-; Cp+)	2
E	236	46, XY, t(Bq-; Dq+)	5
		46, XY, t(1-; Gq+)	2
		46, XY, del (F)	2
UT-AEC	144	46, XY, t(Bq-; Bq+)	2
		46, XY, t(1+; Bq-)	2

^a Two or more metaphases having morphologically identical structural aberrations in Giemsa-stained preparations

cultured lymphocytes of ankylosing spondylitis patients,⁽²⁷⁾ Bikini Island fisherman,⁽³⁴⁾ and in both marrow⁽³⁵⁾ and lymphocytes⁽³⁸⁾ of A-bomb survivors. To date these clones have not been associated with clinical manifestations of specific diseases in these persons.

To determine whether any clones of lymphocytes bearing apparently identical chromosomal rearrangements could be identified in preparations from the Y-12 or UT-AEC accident survivors, karyotypes of all cells having symmetrical aberrations in the 25-year (Y-12) preparations and all available karyotypes from the 4.7-13.7-year cultures of the UT-AEC survivor were reviewed by a single observer (Table 6). In preparations from three Y-12 survivors (i.e., A, D, and H) and the UT-AEC survivor, two or more metaphases having apparently identical structural aberrations were observed. Since these preparations were not banded, precise identification of the specific chromosome and the site of the breakpoint could not be made, and it is possible that some portion of these suspected clones do not have identical chromosomal

abnormalities. In any case clones did not comprise more than 1.7% of the responsive lymphocytes in any of the men, and in no instance did we detect specific translocations known to be associated with lymphoid malignancies.

Conclusion

Our findings in the medical follow-up of these persons, heavily irradiated in radiation accidents, have largely been those that are to be expected in unirradiated persons. The expected high incidence of shortened lifespan, malignancies after short latent periods, and rapidly progressing leucemias and opacities has not been found. The several malignancies, cataracts, and degenerative diseases that have been observed could not be attributed with a degree of certainty to their accidental irradiation were it not for the cytogenetic findings of persistent chromosome abnormalities that correlate well with radiation-exposure estimates. But in this regard also, the history of the accident irradiation is a stronger indicator of untoward effects to come than the cytogenetic events themselves. The rationale for this experience is found in the small population of survivors under study and the comparatively short period of time that has passed up until now.

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