Armed Forces Radiobiology Research Institute

Chronic Radiation Sickness Among Techa Riverside Residents

Urals Research Center for Radiation Medicine
Chelyabinsk, Russia

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PREFACE

Until recently there were relatively few studies in humans on the effects of chronic whole body radiation exposure on tissues where the radiation response is considered to be deterministic. Acute radiation syndrome and its component subsyndromes have been well studied, from human experience with the casualties in Japan and the firefighters at Chernobyl. A large database exists from clinical experience related to treatment of widespread neoplastic disease and supporting laboratory studies in cellular and animal models. Cataracts and other chronic or late changes related to damage of a specific organ system are also well known as a result of radiation therapy clinical experience. Stochastic effects, primarily neoplastic, dominate current attention to the late effects of chronic radiation exposure. When Dr. A.K. Guskova and Dr. G.D. Baysogolov first described chronic radiation sickness (CRS) in several hundred workers at the Mayak Production Association (the USSR's first plant for processing plutonium for weapons, located near Chelyabinsk, Russia), much of the scientific world was skeptical. No such syndrome had been, or has since been, described in the West, in large part because chronic exposures of one gray or more had not been experienced.

The most frequent complaints in villagers along the Techa river, where liquid radioactive wastes less than one millicurie per liter were initially dumped directly into the river, were headache, dizziness, easy fatigability, disturbances of mood, appetite, and sleep, decreased memory, and bone and joint pain. Physical findings included increased vascular permeability, weight loss, apical systolic murmurs, and abnormal peripheral reflexes and ataxia. Decreased blood pressure was often noted initially; with time there has been an increased prevalence of hypertension in persons who have had CRS. Pathognomonic symptoms or findings for this disease have not been described. Laboratory studies routinely demonstrated pancytopenia, gastric hyposecretion, asthenia, and micronecrotic changes in the myelin membranes at the higher ranges of exposure. In general the disease fell into two main subsyndromes: a hematologic type of illness (the most common) manifested by peripheral pancytopenia, confirmed on occasion by bone marrow biopsy, and a neurologic type with four main symptoms: asthenization, disturbances of vascular regulation, vertebrogenic disorders, and organic changes in the nervous system manifested by diffuse micronecrotic changes in the myelin accompanied by glial proliferation and circulatory disturbances. A third of the patients had both.

In 1994 the Armed Forces Radiobiology Research Institute published a contract report entitled "Analysis of Chronic Radiation Sickness Cases in the Population of the Southern Urals." The principal author of both reports was Dr. Mira M. Kossenko of the Urals Research Center for Radiation Medicine (URCRM, formerly Branch 4 of the Institute of Biophysics of the Ministry of Health of the USSR). The first report documented the extent of radiation exposure along the Techa river and gave an overview of the health effects of this exposure on the population. There were 940 individuals diagnosed with CRS; of this large group, 66 met the criteria of a dose of at least one gray received over three years, no concurrent disease with symptoms similar to CRS, and signs and symptoms as described by Guskova and Baysogolov.

In this report the dynamics of CRS, its clinical course, and the long-term outcomes for patients with this disease are described in much greater detail. Once the patient was removed from exposure, the course of CRS stabilized. Most patients eventually recovered, with the time to recovery being inversely related to the total dose received. Severity of symptoms was directly related to dose. A significantly increased percentage of patients died from leukemia or other blood dyscrasias and solid tissue neoplastic diseases compared to a control group. However, except for early

deaths resulting from malignancies, there was no life span shortening. Today there are no patients who have CRS; all have either recovered completely (the majority), at least stabilized, or have died.

The Techa river villagers, from whom the groups in this study were taken, represent the largest group of people ever exposed to relatively high doses of chronic radiation over a very long period. Their experience affords a unique opportunity to contribute to our understanding of injury/repair processes in humans related to tissue or organ damage and carcinogenic effects of high radiation doses protracted over one or more years. Comparisons with the early and late effects of acute exposures will be illuminating.

Grateful acknowledgment is given to Modeste Greenville for editorial advice, to Carolyn Wooden for publication layout, and to Mark Behme and Guy Bateman for graphics support.

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INTRODUCTION

Chronic radiation sickness (CRS) in the population exposed to radiation in the Urals was analyzed in 1993 at the Urals Research Center for Radiation Medicine (URCRM). The study was initiated by the Defense Nuclear Agency (DNA) and published by the Armed Forces Radiobiology Research Institute (AFRRI). The extensive report [1] contains information on population exposure sources, accumulation and assessment of doses, characterization of the exposed population, sources of basic information on the disease and its clinical course, status of organs and systems, and the different diagnoses of CRS.

The report contains a critical analysis of the validity of a CRS diagnosis based on then current concepts of the development of radiation pathology. The results of the analysis enabled the authors to conclude that the diagnosis of CRS in a number of cases had been wrong: the symptoms of general somatic diseases were erroneously taken for CRS manifestations.

The two principal causes of an incorrect CRS diagnosis were (1) lack of information on individual body burdens for exposed people and (2) underestimation of the general somatic conditions that developed in the Techa riverside residents and imitated conditions associated with radiation exposure but had developed before actual onset of exposure. At the same time, it was established by the authors that 66 of the 940 cases were considered adequately ascertained. Consequently, the conditions of radiation exposure that existed in the Techa riverside villages could lead and in some cases did lead to the development of CRS.

The latter assumption is not shared by all foreign readers of the report. A certain skepticism about CRS has been shown at international conferences in the course of discussions addressing deterministic effects. Actually, CRS as a clinical entity has never been described anywhere in the world except in the southern Urals of Russia in the vicinity of the Mayak Production Association, a military industrial complex that produced plutonium for weapons.

In our opinion, there are several reasons for such a prudent attitude. First, nowhere else did such a specific radiation condition exist: chronic irradiation of humans for decades at doses approaching 0.5–1.0 Gy/year. Such unique exposures were observed in Mayak nuclear workers [2] who began working at the plant in the first years of its operation (1949–1954) when γ-radiation doses amounted to 30–120 mSv per working day, and average annual doses were estimated to be 1 Sv. High dose rates to red bone marrow were also recorded in residents of the upper Techa into which radioactive wastes from the Mayak radiochemical facility were dumped from 1949 through 1956. People were exposed to such dose rates for long periods of time. Second, all data on radiation exposure and the resulting pathologic injury among Mayak's workers and the offsite population in the Southern Urals remained classified for decades (up to 1990). Specialists in the field of radiobiology and radiation medicine had no knowledge of this specific pathology.

Questions about the occurrence of CRS among people in the Southern Urals can now be raised and discussed openly. Is it true that doses of about 1 Sv/year to the whole body or red bone marrow accumulating over decades are reasonably safe for the human organism and do not cause any illness? Or does chronic radiation exposure give rise to an actual radiation pathology that has a clear-cut symptomatology and can be designated by the term chronic radiation sickness?

The report of 1994, cited above, analyzes many aspects of this pathologic condition that were observed in 940 residents of the Techa riverside villages. However, the report does not address the questions of dynamics of the course of CRS, recovery

times, and most importantly, the outcomes of CRS. Our effort is aimed at compensating for this limitation, and it should be regarded as a logical continuation of the previous work. We will address the following issues: extent of injury and the stage of CRS at the time of diagnosis, dynamics of the disease course, clinical symptoms at different stages of CRS, outcomes of the disease (recovery, death), death rate and structure, and average age of the deceased.

CHAPTER 1

Scope of Pathologic Injury and Clinical Stages of CRS

Population exposure and the occurrence of CRS in residents of the Techa riverside are associated with discharges of high- and medium-level wastes into the Techa-Iset-Tobol river system from the Mayak Production Association (MPA), a military radiochemical plant for plutonium production [3–5].

According to the information provided by MPA, radioactive waste was discharged into the river system from September 1949 through 1956; however, 95% of the waste entered the river system from March 1950 through November 1951. In the first 2 years of the discharges, no measurements of either radionuclide concentration in the water and bottom sediment or gamma background levels were made on the banks of the river system nor in the villages. The residents of the riverside villages used the river water for drinking, cooking, and other domestic needs and were not warned about the radioactive wastes that were contaminating the river.

The first attempt to assess radiation wastes in the river Techa was made in the summer of 1951. Even the first measurements showed that in some areas on the shores of the Metlinsky Pond, within 7 km of the discharge site, gamma background levels were 5 R/h. This observation gave rise to a suspicion about the occurrence of deterministic effects in the residents of riverside villages who had been exposed to an open source of ionizing radiation, the river.

The most harmful nonstochastic effect of irradiation is radiation sickness. The radiation conditions on the Techa did not suggest any occurrence of acute radiation effects. However, by 1951, at the time of the first medical examinations of the riverside villagers, cases of CRS had already been diagnosed in the workers of the reactor and radiochemical plants of MPA [6–7]. Development of the disease was preceded by exposure for many months to radiation sources of considerable power. The clinical symptoms of the disease included primarily red bone marrow hypoplasia, cytopenia in the morphological composition of peripheral blood, and a number of neurological symptoms. Those cases formed the basis for the description of the clinical picture of CRS [8].

A. K. Guskova and G. D. Baysogolov gave the following definition of the clinical entity "chronic radiation sickness" in their monograph: "Chronic radiation sickness is a complex, clearly outlined syndrome that results from long-term exposure of an organism to radiation of which single or cumulative doses regularly exceed those regarded as admissible for occupational exposure." The authors classified CRS by the degree of severity and the stage of development.

- Stage I (mild): the period of development coinciding with the period in which the basic fraction of the total exposure dose was accumulating.

- Stage II (moderate): the period of recovery (usually 3–12 months after termination of exposure or a significant reduction in exposure rates); during this period the basic cycle of destructive changes was complete, and repair processes began to predominate.

- Stage III (severe): the period of possible CRS outcomes and sequelae—complete recovery, incomplete recovery, or progression to leukemia, other-site cancer, or hypoplastic anemia.

The first medical examinations of the residents of the Techa riverside villages were organized in the summer of 1951, and the first cases of CRS were diagnosed in 1952. The patients complained of headache, dizziness, easy fatigability, general weakness, excessive sweat, irritability, insomnia, decreased memory, decreased appetite, and pains in the epigastric area, bones, or joints. The basic objective symptoms included leukopenia, neutropenia, thrombocytopenia, increased permeability of the vessels, weight loss, decreased arterial pressure, systolic murmur over the heart apex, decreased secretory function of the stomach, asthenia, nonuniform tendon and periosteal reflexes, static ataxia, and nystagmus.

The highest incidence of the disease (540 of the 940 cases diagnosed in different years) was observed in 1955–1956. By that time, access to the river had been officially banned, and further contributions to the external radiation dose had stopped. The assessment of dose accumulation dynamics for the exposed residents shows that, by 1957, the total dose of external radiation had been accumulated, the deposition of radionuclides in human bodies had ceased, and the annual internal radiation rates had decreased significantly. Thus, at the time when most CRS diagnoses were established, the accumulation of the bulk of the total exposure dose had either been completed or was reaching its end.

It is evident that at that time (1953–1956) no cases of CRS at a stage of development could be diagnosed. The degree of severity (stage I or II) was usually indicated in the description of the diagnosis, but the stage of the disease course was not specified. Data on such cases were entered into the computer for analysis by a convention designated as a first-diagnosed condition at an unidentified stage.

Of the total 940 cases of CRS, 899 were identified at the time of diagnosis as cases of stage I severity characterized by the presence of functional disorders in the organism's physiological systems that could readily become reversible following termination of exposure. Stage II severity was diagnosed in 41 cases in which persistent organic disorders along with functional disturbances were diagnosed.

CHAPTER 2

Dynamics of Disease Course

In a number of cases it was impossible to trace the course of CRS due to the lack of data on the dynamic follow-up of patients.

An assessment of radiation conditions that existed in the summer of 1951, two years after the beginning of discharges of radioactive wastes into the Techa, showed both the likelihood of deterministic radiation-related injuries in the residents and the need to take steps to provide radiation protection. One such measure was to evacuate the residents of the riverside villages to "clean" territories. However, this measure was considerably delayed, and doses were again accumulated by the people before they were evacuated. The first resettlements involving a few families from the village of Metlino were carried out in 1953; the entire village population was finally moved in 1956. People residing in villages in the lower reaches of the river were resettled at even later times. Some of the villages of the middle reaches (Krasnoarmeysky District) were evacuated as late as 1961.

Although evacuation of select villages was intended to move the population to certain specified clean villages, a number of families moved by themselves to other villages or nearby towns where they had relatives. These individuals were as a rule lost to the medical follow-up conducted by the medical staff of the specialized clinic, the Institute of Biophysics, Branch 4 (FIB 4; currently URCRM) due primarily to the remoteness of their new residences from FIB 4. The residents of Metlino were evacuated for the first time to a small settlement in which Mayak's Experimental Research Laboratory was based. However, after the accident of 1957 and the formation of the East-Urals Radiation Trace (EURT) quite close to the settlement, Metlino residents had to resettle for the second time. Many of them moved to the town of Chelyabinsk-65 (currently Ozyorsk) and started working at the Mayak facility. They were then followed up by the physicians of Mayak's medical institutions.

The elimination of several riverside villages thus led to intense emigration, and patients with diagnosed CRS were lost to subsequent follow-up. There was no opportunity to elucidate the dynamics of the course of CRS in 44 patients who left the riverside villages in 1954–1960 and were then lost to follow-up (table 1). The medical records of these patients contain only information on one or two examinations; their vital statuses and current residences were unknown.

Table 1. Times of "lost to subsequent follow-up" of persons with diagnosed CRS at an unidentified stage.

Year of emigration	Numbers of emigrants with unknown addresses
1954	2
1955	3
1956	14
1957	3
1958	5
1959	10
1960	7

Diagnostic Mistakes and Rejection of CRS Diagnosis

It has been stated above that lack of information on a patient's exposure dose and the general somatic diseases that developed before radiation exposure made it difficult to correctly diagnose CRS. It is clear from the description of the clinical picture of CRS [8] that it has no single symptom that can be regarded as an exclusive characteristic of CRS. Therefore, in cases when patients had symptoms suggestive of CRS for the first time, their medical records indicated that the examination findings suggested CRS, but the actual diagnosis was established only on the basis of dynamic follow-up data. However, in a number of cases such an approach could not guarantee a correct diagnosis either, because there was no certainty that the symptoms observed had been induced by radiation. Diagnoses of CRS have often been revised, indicating that a CRS diagnosis is not an easy one to make.

In 1964, a commission of medical experts was set up to verify the diagnosis of CRS. Patients with the diagnosis were invited to submit to expert clinical examinations; all relevant records, including dosimetric and anamnestic data, findings of laboratory investigations, and functional tests in dynamics were reviewed. From 1965 through 1967 the commission discarded 199 of the 940 diagnoses of CRS as inadequately substantiated low-dose exposures; some patients had somatic diseases that imitated radiation injury. The conclusions of the commission of experts include statements about both incorrect CRS diagnoses and diseases erroneously attributed to CRS; table 2 lists the most common of them.

The conditions cited occurred in the patients before radiation exposure or at the time of exposure and were commonly manifested by symptoms typical of radiation injury—leukopenia, anemia, asthenia, impaired blood vessel regulation, ostealgia, arthralgia, etc. All 199 cases of erroneous CRS diagnosis were excluded from the analysis of clinical course dynamics and outcomes of chronic radiation injury.

It should be noted that the diagnosis of CRS was revised more than once to ensure the most efficient verification of the diagnosis of a radiation-induced condition. The results of the latest of such revisions, based on the data of long-term follow-up dynamics and the most exact estimates of individual doses, were presented in the previous report [1]. The revision, based on more rigid criteria, validated 66 of the 940 CRS cases diagnosed earlier.

Mortality Shortly after CRS Diagnosis

It was also considered impossible to evaluate the dynamics of the course of CRS in cases when deaths occurred from different causes shortly after CRS was diagnosed. By the time of death, the diagnosis of CRS of indefinite stage had not been rejected, but in all likelihood the causes of death were unrelated to radiation exposure.

Table 2. General somatic diseases simulating radiation injury and mistaken for CRS.

Clinical diagnoses	Number of cases
Infectious diseases	
Tuberculosis	14
Brucellosis	66
Helminth infestation	5
Malignant growth	2
Thyroid gland pathology	7
Chronic alcoholism	2
Postcontusion syndrome	6
Focal infection (tonsillitis, otitis, pyodermia, salpingitis, oophoritis, etc.)	12
Rheumatism with involvement of the heart	7
Ischemic heart disease	5
Atherosclerosis	8
Chronic bronchitis, chronic pneumonia	8
Chronic hepatitis	20
Ulcer of the duodenum	5
Metrorrhagia	5
Pregnancy	4
Other	23

Data are listed in table 3 on 23 individuals whose deaths occurred within 5 years of CRS diagnosis. In one case, a woman's CRS (degree of severity I, unidentified stage) had been diagnosed 5 years before she died of an unknown cause at age 71. In 6 cases, death occurred due to violent causes: suicide,

Table 3. Causes of death for patients who died shortly after diagnosis of CRS.

Systemic number	Sex	Year of diagnosis	Internal and external dose to RBM, Gy	Difference between diagnosis and death, year	Year of death	Age	Class	Group	Subgroup	Cause of death
5007	F	1953	2.091198	1	1954	19	2	208	9	Acute leukemia
11175	F	1953	2.104477	5	1958	22	6	340		Menyngo-encephalitis, disseminated sclerosis
42902	F	1955	0.7886477	2	1957	60	17	959	9	Multiple traumas
43106	F	1955	0.7971345	5	1960	46	2	150	9	Cancer of the esophagus
62309	F	1955	0.5119344	2	1957	67	17	797		Senile asthenia
67530	M	1955	0.6031555	2	1957	54	2	151	9	Gastric cancer
68408	M	1955	0.6262668	5	1960	39	9	567	9	Acute abdomen
68416	F	1955	0.6031555	5	1960	71				Unknown cause
148220	F	1954	0.3748812	0	1954	40	9	571	4	Hepatitis, achylic gastritis
164125	M	1956	0.454779	5	1961	59	7	414	0	Cardiosclerosis, pneumofibrosis
193531	M	1955	0.2560158	2	1957	69	2	188	9	Cancer of the bladder
206007	M	1955	0.3852318	2	1957	23	17	850	0	Concussion of the brain
207185	M	1956	0.282203	1	1957	56	2	151	9	Gastric cancer
212088	F	1955	0.377623	3	1958	17	17	959	9	Multiple traumas
216087	F	1955	0.2560158	5	1960	70	1	38	9	Sepsis
226885	M	1955	0.2451282	1	1956	63	8	492		Pulmonary emphysema
232158	M	1955	0.3451516	3	1958	32	17	959	9	Multiple traumas
308513	M	1957	0.4771494	2	1959	21	17	994	7	Suicide
339486	M	1955	0.1543645	5	1960	71	16	785	4	Gangrene
362497	M	1955	0.06277061	4	1959	30	17	980	9	Alcoholic intoxication
389813	M	1955	0.1949964	5	1960	58	7	394	2	Mitral defect
512698	F	1956	0.2343817	1	1957	24	7	394	2	Mitral defect
524620	F	1956	0.2316606	5	1961	78	7	440	9	Atherosclerosis

alcoholic intoxication, and car/railway accidents. Only one of the subjects was over 60 (67 years old); in the remainder of cases, death occurred at ages under 33.

Five of the 23 patients (22%) discussed in this section of the report died of malignant neoplasms. One of the patients (G.N., systemic number 5007) was described in detail in the first report on CRS [1]. CRS was diagnosed in this 18-year-old patient, a resident of Metlino, in 1953. By that time the dose had accumulated in red bone marrow due to external and internal radiation that amounted to over 2 Gy. A year later, the patient developed acute nondifferentiated leukemia and died. Four other patients with CRS died at ages 46–69 of cancer of the stomach, esophagus, and bladder.

In three cases the causes of death were acute inflammatory processes that were not clearly enough defined in the death certificates (gangrene, acute abdomen, sepsis, meningoencephalitis). It may be suggested that chronic exposure manifested by inhibition of bone marrow hematopoiesis aggravated the inflammatory processes.

Duration of CRS

We were thus only able to analyze the dynamics of the CRS course and recovery times for 674 patients—for those whose diagnoses were verified at the FIB 4 clinic and who were followed up for long periods of time.

The dynamic follow-up enabled us to diagnose CRS at the stage of stabilization in a number of patients whose condition and laboratory findings showed improvement. CRS at the stage of repair or recovery was diagnosed when the patient's condition was considered to be normalized, and the symptoms of radiation injury were absent. In the majority of cases, the stabilization stage was bypassed, and the stage of recovery was reached. Figure 1 demonstrates the time of diagnosis and recovery from CRS.

Most CRS cases (80%) were diagnosed before 1958. The first cases in the stabilization stage were registered about the same time, 1955–1957, as the first cases in the recovery stage. By that time, 6 to 8 years had elapsed since the beginning of exposure, and residents had stopped using the river as a source of water. Annual dose rates had decreased considerably by that time, and long-lived radionuclides of strontium and cesium, which had accumulated in the bodies of exposed residents, remained the only contributors to the dose. However, in most CRS patients, the recovery process began much later. About half the CRS patients who recovered had done so by 1960, and 90% had recovered by 1970.

A conclusion may be made that all patients diagnosed with CRS in the 1950s did reach the stage of recovery, but the times at which that stage was reached differed. A very crude calculation of the mean duration of the course of the disease yields the value of 9–11 years (90% of all CRS cases were diagnosed by 1959, and recovery stages were registered for 90% of patients by 1970). However, a more accurate calculation made with the actual time of CRS diagnosis and recovery for each patient shows that the average disease course was 7.35 years.

Compared to stage 1 CRS, recovery occurred in patients with stage 2 CRS by 1976, about 4–5 years later.

Analysis of Recovery Time's Dependence on Dose. The calculation of the dose to a patient's red bone marrow (RBM) has identified several "dose" groups and assessed the duration of the disease with

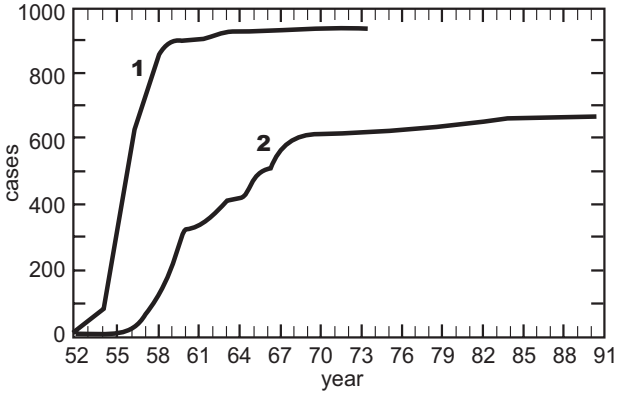

Fig. 1. Time of CRS diagnosis (1) and recovery (2), 1952–1988.

Table 4. Dependence of CRS duration on absorbed dose in RBM.

Dose to RBM, Gy	Mean dose to RBM, Gy	Patients with CRS	Mean dose by 1950	Duration of CRS: years (confidence intervals)
0.03–0.1	0.05	53	22.7	4.57 (3.42–5.99)
0.1–0.2	0.16	103	27.2	4.22 (3.44–5.13)
0.2–0.3	0.25	116	31.1	5.33 (4.38–6.29)
0.3–0.4	0.34	79	23.8	6.89 (5.46–8.58)
0.4–0.5	0.45	69	24.7	7.68 (5.97–9.59)
0.5–0.7	0.59	63	22.1	7.97 (6.34–10.20)
0.7–1.0	0.83	63	24.1	9.24 (7.11–11.80)
1.0–1.2	1.07	39	28.3	11.08 (7.88–15.14)
1.2–1.4	1.3	38	29.5	9.37 (6.63–12.86)
1.4–2.0	1.62	35	19.1	14.66 (10.2–20.38)
>2.0	2.34	16	12.3	12.5 (7.15–20.25)

relation to the dose. The results of the analysis are listed in table 4 and figure 2.

The dependence of recovery time on dose accumulated in the RBM can be traced by the duration of CRS increases with dose. This dependence can be described by the linear equation $I = a + bD$, where D represents the dose value in Gy, and the coefficient b is estimated to be 4.17 years per Gy.

It may well be that the processes of radiation injury repair depend not only on the level of radiation exposure but also on the age at which a patient developed CRS. Patients' calculated mean ages by 1950, the beginning of radiation exposure for different dose groups, are presented in table 4. Mean ages in groups with doses from 0.03 to 1.4 Gy do not differ significantly, ranging from 22.1 to 31.1 years. Much lower mean ages, 19 and 12 years, are observed in high-dose groups (more than 1.4 Gy to the RBM). A specific feature of radiation conditions in the Techa riverside area is the close dependence of exposure dose on age. As cited in chapter 3 of AFRRI Contract Report, CR94-1 [1], the highest doses were received by residents who were adolescents when exposure began. This analysis of the dependence of the length of the course of CRS on age was thus undertaken.

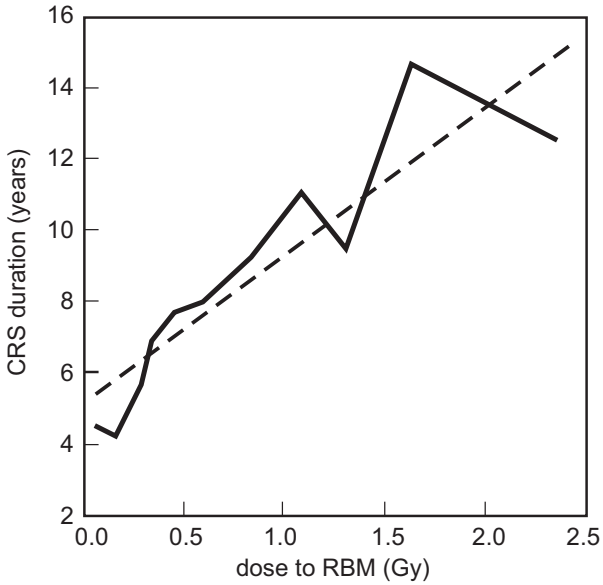

Fig. 2. Dependence of duration of CRS on accumulated dose: years of duration (—); approximate fit (---).

Table 5. Age dependence of CRS duration.

Age by 1950 (years)	Mean age by 1950 (years)	Patients with CRS	Mean dose to RBM, Gy	Duration of CRS, years and confidence intervals
<1		7	0.15	5.25 (2.10–10.81)
1–14	8.7	209	0.7	8.63 (7.49–9.79)
15–19	17.0	39	0.88	9.2 (6.54–12.58)
20–29	24.1	133	0.44	7.06 (5.92–8.4)
30–39	34.7	151	0.52	7.2 (6.08–8.45)
40–49	44.1	100	0.46	5.69 (4.63–6.92)
50–59	52.9	28	0.53	4.93 (3.28–7.15)
60–69	64.3	6	0.44	2.5 (0.92–5.45)
70+	70	1	0.3	<1

Analysis of Recovery Time's Dependence on Age. Dependence of CRS duration on the age of exposed individuals was analyzed on the basis of table 5 and figure 3.

Recovery processes developed most slowly (for 8–9 years) in children and teenagers who received the highest doses. Age dependence of the duration of CRS, when determined by a linear model, has a negative coefficient (equal to -0.09).

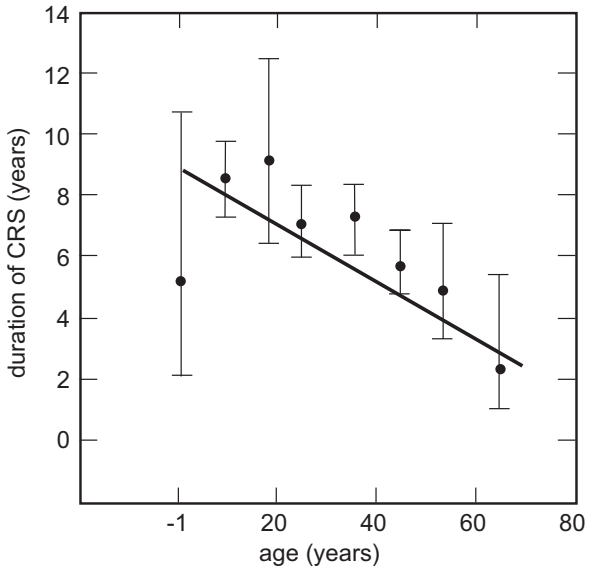

Fig. 3. Dependence of CRS duration on age at time of exposure.

CHAPTER 3

Clinical Symptoms at Different Stages of the Disease

According to the definition by Guskova and Baysogolov [8], there are two variants of CRS—the developed clinical syndrome resulting from effects of external radiation or intakes of isotopes that are uniformly distributed in the body and the clinical syndrome manifested by the predominance of injury to individual organs and systems as a result of internal or external exposure. To analyze the prevailing type of injury in cases of CRS in residents of the Techa riverside area, the incidence of injuries to individual organ systems or a combination of systems was studied. The results are shown in table 6. However, the table does not specify other symptoms regarded as consequences of radiation exposure—for example, reduced immune resistance, hypoacidic state of gastric secretion, or manifestations of hepatitis of nonviral etiology. These symptoms were not regarded as key pathological signs, and their presence alone could not serve as the basis for making the diagnosis of CRS. Immune incompetence revealed in laboratory investigations was often associated with leukopenia, neutropenia, and monocytopenia.

The diagnosis of CRS in 49.5% of the cases was established only on the basis of reduced counts of cellular elements (leukocytes and thrombocytes) in the peripheral blood. Perhaps it would have been possible to reveal some signs of bone marrow hypoplasia if such examinations had been performed for most of the patients who were followed up. Since the methods of bone marrow puncture or trephine biopsy are rather sophisticated and

Table 6. Body systems most frequently injured by CRS.

System	Number of patients with this symptom	Percent of total subjects with diagnosed CRS
Bone marrow hypoplasia	10	1.1
Changes in peripheral blood		
Leukopenia	53	5.6
Neutropenia	118	12.5
Thrombocytopenia	13	1.4
Leukopenia and neutropenia	221	23.5
Leukopenia and thrombocytopenia	18	1.9
Neutropenia and thrombocytopenia	8	0.8
Leukopenia, neutropenia, and thrombocytopenia	36	3.8
Bone marrow hypoplasia and changes in the peripheral blood	28	3.0
Changes in the nervous system	105	11.2
Changes in peripheral blood and neurological symptomatology	253	26.9
Bone marrow hypoplasia and neurological symptomatology	70	7.4
Cataracts (radiation-related)	3	0.3
Endocrine disturbances	4	0.4

traumatizing, they were only applied in a few patients for diagnostic purposes. It was shown in the first report on CRS [1] that bone marrow examinations were performed for 278 CRS patients. Among the 82 cases examined in 1951–1955 there were 38 cases with changes in bone marrow composition manifested by slight reductions in myelokaryocyte counts, increased rates of neutrophil maturation, and increased plasma cell counts.

Thus, the hematologic syndrome in 53.6% of patients was of primary significance in the diagnosis of CRS. This correlates with data cited in the publication by the International Commission on Radiological Protection [9] that the hematopoietic system is a highly radiosensitive one, and that the threshold of occupational exposure that inhibits hematopoiesis is 0.4 Sv.

The neurologic syndrome is next in the order of diagnostic significance. It can be described as a complex of four leading symptoms: asthenization, vegetovascular dysfunction (most commonly manifested by disturbances of vascular regulation), vertebrogenic disorders, and manifestations of organic affections of the nervous system (diffuse micronecrotic changes in the myelinic membrane of the nerve conductors accompanied by disseminated glial proliferation and circulatory disturbances). The presence of the neurological syndrome alone in 105 patients (11.2%) was regarded as sufficient basis for the diagnosis.

In a considerable number of patients (232, 34.3%) the impairment of hematopoiesis was combined with a neurological symptom, and this combination represented the most typical symptomatology of CRS.

Radiation-related cataracts were only registered in three residents who received significant doses of external exposure in a comparatively short time. Endocrine disorders were found in patients who had been exposed in childhood; these disorders were manifested by sex organ hypoplasia.

Dynamics of CRS Symptoms

The symptoms listed above were most often observed at the time of establishing the diagnosis of CRS, i.e., during the periods of exposure to external radiation, radionuclide incorporation, and substantial annual dose rates. After access to the river, the open radiation source, was restricted, external irradiation ceased, and dose rates diminished significantly. After 1956, dose rates were only calculated for long-lived radionuclides incorporated in the organism.

By that time the clinical picture was characterized by a regression of pathological symptoms and gradual development of repair processes. Only in a small number of patients exposed perinatally or in early childhood was it possible to observe maximum manifestations of certain pathological signs later, particularly in the pubertal period.

Since the hematological syndrome was the key manifestation of CRS, it is logical at this point to discuss the results of dynamic peripheral blood studies with a more detailed presentation of the periods with the highest dose rates. The previous report focused on blood count findings only in patients without somatic conditions (table 7.2 in reference [1]). This report presents data on all blood counts made for patients with diagnosed CRS (3,146 counts made from 1952 through 1956) regardless of the purpose of laboratory blood tests, whether aiming at the study of radiation effects on the patient's health or because of some somatic disease suffered by the patient. This approach is based on the point of view that radiation exposure may lead to increased incidence and a more severe course of general somatic diseases, e.g., infectious diseases without adequate reactions of the peripheral blood.

This analysis of blood count dynamics is based on actual results of each peripheral blood test made for each patient not on averaged values. Figure 4 shows data on leukocyte count dynamics between 1952

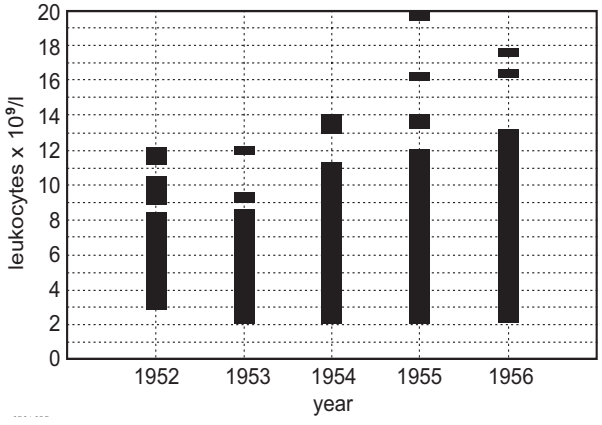

Fig. 4. Dynamics of leukocyte counts, 1952–1956.

and 1956. The lowest values (1.9 x 10^9/L) were registered in 1953. In 1954–1956, leukocyte counts in some patients were as low as 2.1 x 10^9/L. The lowest variability of blood count values was noted for the early years of exposure (1952–1953), which resulted particularly in the lower average leukocyte counts registered in that period. No substantial normalization of leukocyte counts occurred in the period 1952–1956.

The dynamics of segmented neutrophil counts were approximately the same (figure 5). The lowest values, such as (0.2–0.3) x 10^9/L, were noted among CRS patients in 1956. However, during all preceding years the lowest neutrophil counts did not exceed 1.0 x 10^9/L. The variability of both neutrophil and overall leukocyte counts was increasing from 1952 to 1956.

Figure 6 presents data on peripheral blood thrombocyte counts for individual patients with diagnosed CRS. The characteristic features in 1952, the year of the highest dose rates for all analyzed years, were (a) very low variability of values, (b) highest thrombocyte counts not beyond the value $X + 1.5\sigma$, where X was the mean thrombocyte count for normal subjects and equaled 247 x 10^9/L, and $X + 1.5\sigma$ equaled 315 x 10^9/L, and (c) the lowest values of thrombocyte counts were 90 x 10^9/L. Thus the thrombocyte variability curve for CRS patients shifted significantly to the left in 1952 in comparison to the distribution of normal values, and the average values were lower than the normal values. The values selected from 11 of the most correct and substantiated studies listed in ICRP Publication 41 [9] were assumed to represent normal values of hematological parameters. These values based on probability theory and variational statistics are used for comparison purposes in solving the tasks of radiation medicine.

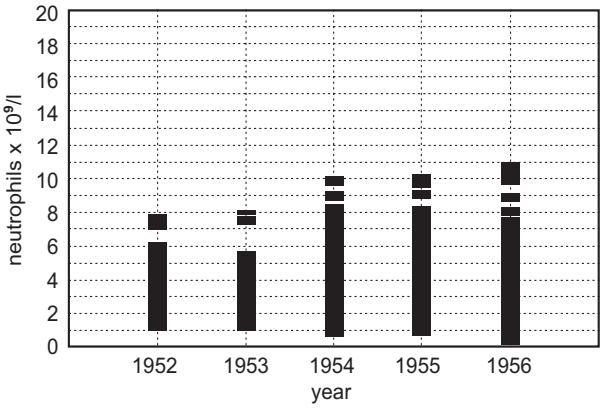

Fig. 5. Dynamics of neutrophil counts, 1952–1956.

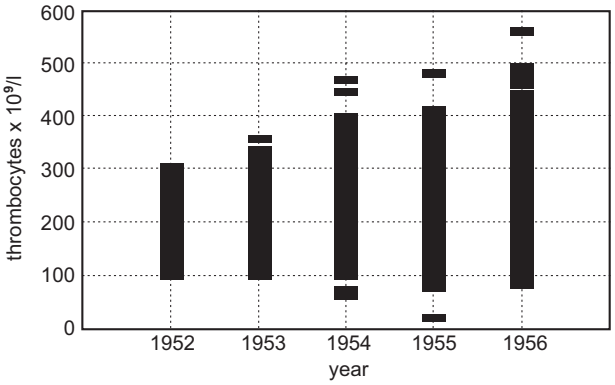

Fig. 6. Dynamics of thrombocyte counts, 1952–1956.

In the period 1953–1956, thrombocyte count variability increased. However, the lowest values were even lower than in 1952: 54 x 10^9/L in 1954, and 30 x 10^9/L in 1955 (in one patient). In a considerable number of cases, thrombocyte counts of patients with CRS were below the reference value of $X - 2\sigma$, i.e., lower than 157 x 10^9/L.

During the period of highest annual dose rates and lowest values of peripheral blood parameters (1952–1955), the dependence of leukocyte, segmented neutrophil, and thrombocyte counts on the dose accumulated in the RBM was assessed (figures 7–9). Decreased leukocyte counts were noted in patients with substantial doses to the RBM in comparison to patients with lower doses (figure 7). Approximation of this dependence by linear regression ($I = a \pm bD$) yields the value of the constant term "a" to 5.58. The dose slope is negative and equal to (-0.47).

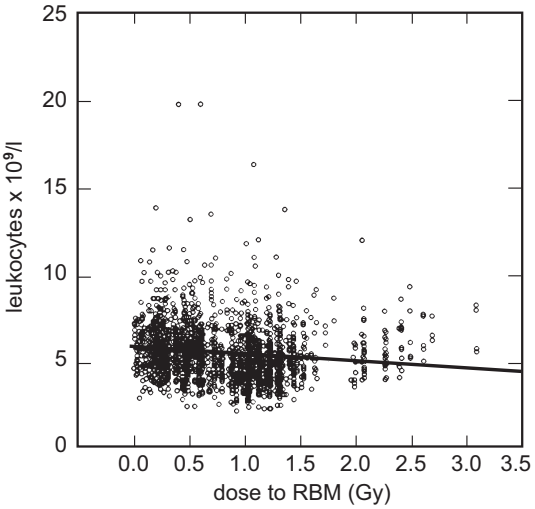

Fig. 7. Dose dependence of leukocyte counts, 1952–1955.

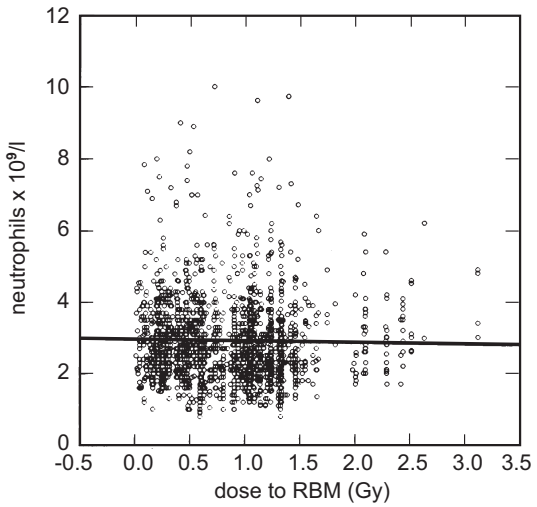

Fig. 8. Dose dependence of neutrophil counts, 1952–1955.

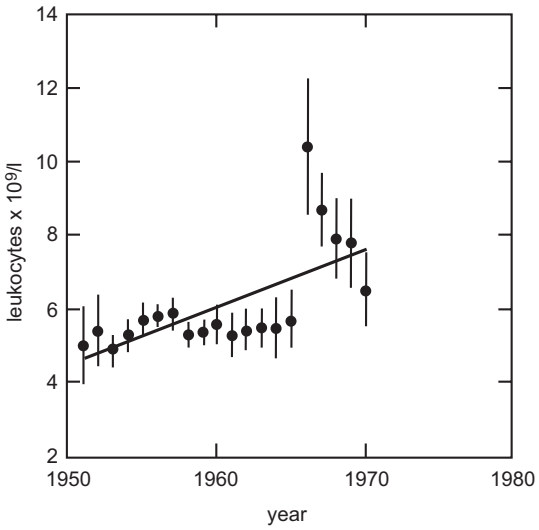

Fig. 10. Dynamics of leukocyte counts, 1950–1970.

With increasing doses to the RBM, the number of segmented neutrophils also decreases; however, the dependence of neutrophil counts on doses accumulated by patients is less manifest. The slope in figure 8 is smaller than the slope in figure 7, and using linear approximation, the dose coefficient was estimated to be (-0.05).

Dose dependence of thrombocyte counts in peripheral blood is shown in figure 9. A fairly clear-cut decrease in the number of thrombocytes with absorbed dose to the RBM can be seen. Calculation of the regression equation describing dose dependence showed that the intersection of the regression curve with the Y-axis (at X = 0) is 222.4 x 10^9/L. The angle of the regression curve tilt is determined by the value of coefficient "b", which is equal to (-14.23) calculated per dose unit.

To identify the times of recovery from radiation injury it was important to assess the hematological data not only for the first 7 years after the start of exposure but also for the entire follow-up period. The respective average values characterizing leukocyte, neutrophil, and thrombocyte counts in CRS patients are shown in figures 10–12. An increase was noted in these values in dynamics with a particularly manifest increase at significantly decreased dose rates. Moreover, in order to assess the rate of normalization of hematological parameters a suitable method was chosen to estimate the average values in patients with CRS (with the exception of

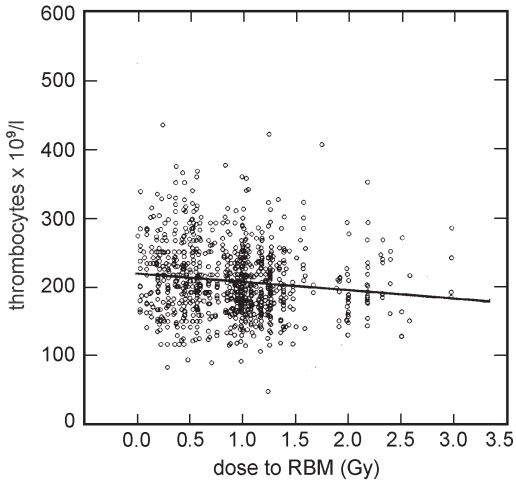

Fig. 9. Dose dependence of thrombocyte counts, 1952–1955.

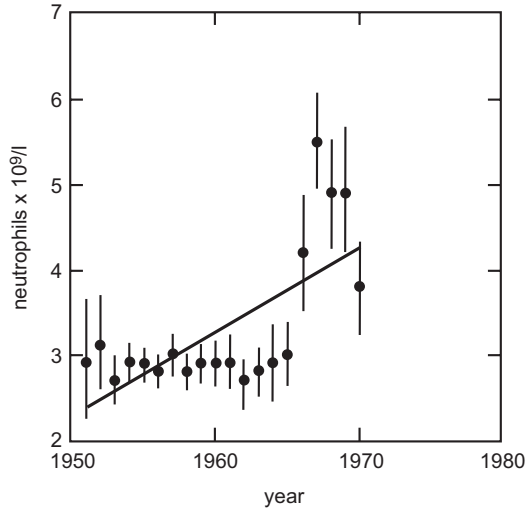

Fig. 11. Dynamics of neutrophil counts, 1950–1970.

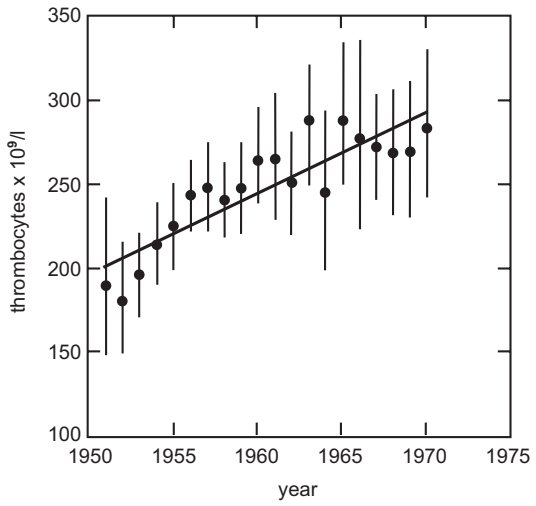

Fig. 12. Dynamics of thrombocyte counts, 1950–1970.

pathological conditions affecting blood parameters) in dynamics for periods 1951–1955, 1956–1959, 1960–1969, and after 1969. The values obtained were compared with reference values. Data are provided in figures 13–16.

The average leukocyte counts for CRS patients persisted at lower than 90% confidence intervals of the reference value for three decades after the beginning of exposure. Only after 1970 did the differences in leukocyte counts between followed-up patients and reference values disappear (figure 13).

The dynamics of segmented neutrophils correlated with leukocyte dynamics (figure 14A), indirectly corroborating the decrease in leukocyte counts in

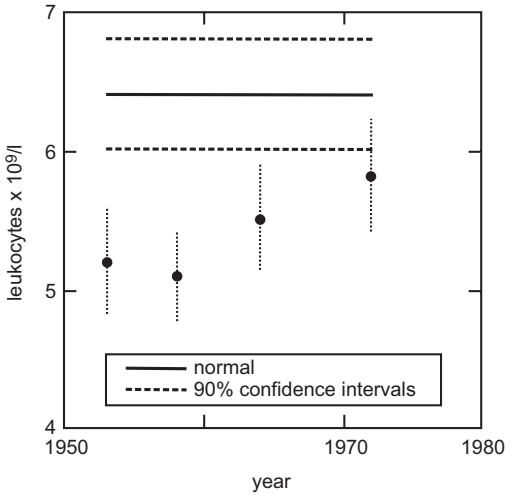

Fig. 13. Mean leukocyte counts at different times after beginning of exposure.

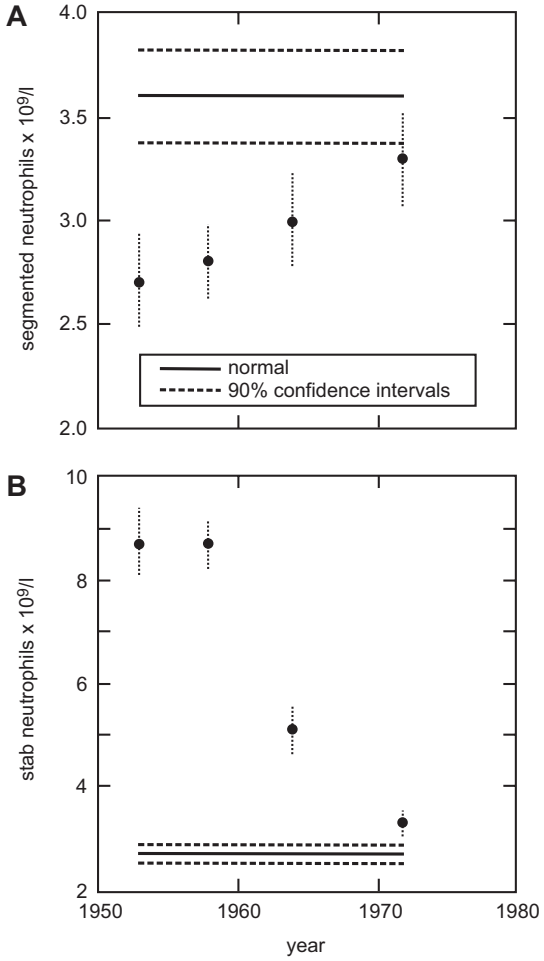

Fig. 14. Mean neutrophil counts at different times after beginning of exposure.

CRS patients as associated mainly with the decreased number of granulocytes. At the same time, a substantial increase in the number of stab neutrophils was noted, particularly during the first two decades after the beginning of exposure (figure 14B). An increased percentage of stab neutrophils, in comparison with normal values, was typical of CRS patients over all periods of follow-up.

The normalization of thrombocyte counts occurred much earlier (figure 15A). Average values of thrombocytes below 200 x 10^9/L were only registered during the first 5 years after exposure. By 1958, the average thrombocyte values were restored to their normal values and did not change throughout further follow-up periods.

The values characterizing the erythrocyte series were also analyzed on the basis of the data on peripheral blood counts. During the first 5 years under

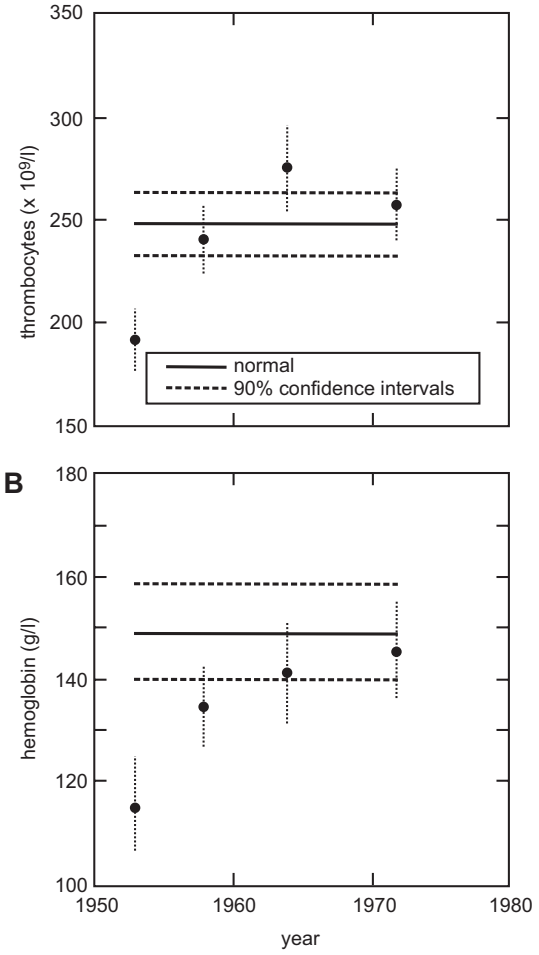

Fig. 15. Mean values of (A) thrombocyte counts and (B) hemoglobin in men at different times after beginning of exposure.

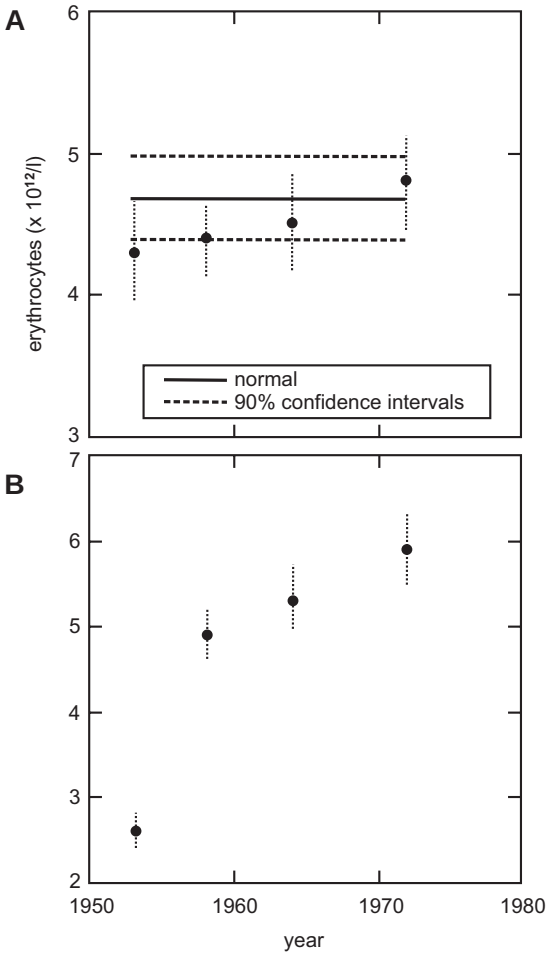

Fig. 16. Mean values of (A) erythrocyte counts in men and (B) reticulocytes in both men and women at 5 and 10 years after beginning of exposure.

the conditions of ongoing external exposure and radionuclide incorporation, the hemoglobin level in men (figure 15B) had decreased in comparison to normal values (figure 16B). However, there were no substantial decreases in erythrocyte counts in men (figure 16A). The reticulocyte counts in both men and women had decreased in comparison to normal values (figure 16B). There were no decreases in erythrocyte counts and the level of hemoglobin in women. There was a relatively quick restoration of average values of hemoglobin in men by 1957.

The pathogenetic mechanisms of hematologic effects in chronic radiation exposure have not yet been conclusively established. There is no evidence to suggest that the loss of nondividing granulocytes is the underlying factor [11], which is why the pathological processes initiated by exposure evidently begin in the bone marrow. At the stage of development of CRS, hematopoiesis suppression is caused by kinetic disorders rather than by damage to stem cells.

It is believed that, in the case of acute radiation injury, cell maturation either proceeds with normal speed or decreases at the times of maturation and differentiation in response to the reduced proliferative ability of stem cells [11]. As for chronic exposure, it was concluded on the basis of studying the relationship between different granulocytic pool compartments in the bone marrow that a delay in maturation of the myeloid elements occurs [11,12]. As a rule, mitotic cell activity was preserved.

According to our data for individuals with CRS (82 bone marrow preparations in 1951–1955), there was an increase in the fractions of myelocytes and metamyelocytes in the bone marrow corresponding to the occurrence of leukopenia and

granulocytopenia in peripheral blood. Such findings can be interpreted as delayed maturation and differentiation of granulocytes at the final stage of cell development.

As for the effects of long-term exposure on the megakaryocytic-thrombocytic system, it is considered that "mature megakaryocytes are insensitive to radiation, their processes of maturation and thrombocyte production go on unaffected" [11]. Therefore, the cause of peripheral blood thrombocytopenia may lie in radiation injury to precursor cells. Unfortunately, data are unavailable on the number of megakaryocytes in the bone marrow of patients with CRS during the period of its development.

Recovery of the hematopoietic system after radiation injury proceeded slowly in patients with CRS. Even after cessation of external exposure and radionuclide body intakes, leukopenia and neutropenia persisted for a long time and may have been due to incorporation of long-lived strontium that contributed to irradiation and maintained a certain dose rate.

The dynamics of hematological and other symptoms of CRS are presented in figure 17. Neurological symptoms such as organic changes in the central nervous system associated with an injury to the myelinic membrane of nerve conductors, ostealgia, and neurovascular dystonia of the hypotonic type persisted up to 1970. By contrast, the vertebrogenic symptom, which was infrequently and slightly manifested in the early years, occurred with higher frequency and in a more severe form in the 1970s and 1980s. The fact that this feature can be explained by the aging of CRS patients precludes a direct association between the vertebrogenic symptom and radiation exposure.

Thus, the clinical symptoms of CRS generally had clear-cut positive dynamics, and recovery in the majority of cases occurred toward the end of the 1960s.

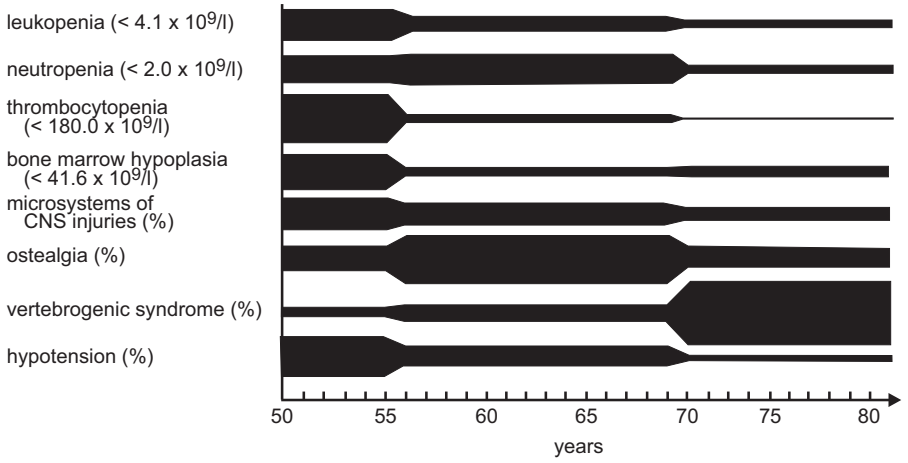

Fig. 17. Clinical symptomatology.

CHAPTER 4

Mortality of Patients with Diagnosed CRS

Information is available on 343 (36.5%) deaths in the 940 patients with diagnosed CRS: 129 (39.6%) deaths in the 326 men and 214 (34.8%) deaths in the 614 women. The sources of this information were official documents (death certificates) and reports of next of kin of those who had migrated beyond the surveyed territory. The information obtained from these sources is considered incomplete because of migration. The circumstances that caused a significant portion of the exposed population to migrate and the resultant loss of 44 individuals to early follow-up have been addressed in chapter 2 of this report. In subsequent years of migration it was impossible to trace people with CRS. Consequently, data listed below are considered tentative; they cannot be used to calculate death rates nor to analyze death causes. They do however provide information on ages and calendar dates of deaths (tables 7 and 8). Table 7 provides distribution according to the years of follow-up of known deaths among CRS patients.

The number of deaths increased with time from the beginning of exposure and is attributable to the

Table 7. Dynamics of death cases in patients with diagnosed CRS.

Years of follow-up	Deaths	Total deceased (%)
1954	1	0.3
1955–59	14	4.1
1960–64	23	6.7
1965–69	32	9.3
1970–74	45	13.1
1975–79	55	16.0
1980–84	56	16.3
1985–89	73	21.3
1990–93	43	12.5
1995	1	0.3

Table 8. Age distribution for deceased CRS patients.

Age	Deaths	% of total deceased
18	2	0.6
19	1	0.3
20–24	5	1.5
25–29	4	1.2
30–34	4	1.2
35–39	5	1.5
40–44	9	2.6
45–49	15	4.4
50–54	16	4.7
55–59	25	7.3
60–64	33	9.6
65–69	43	12.5
70–74	47	13.7
75–79	60	17.5
80–84	41	11.9
85–89	23	6.7
90–94	9	2.6
95	1	0.3

aging population. The small number of deaths in recent years (after 1990) is due to inadequate information and to the unavailability of death certificates that have not yet been retrieved from the offices of the civil registrars for these years. Increases in the number of deaths are naturally due to aging and can be seen in the data on age distribution of death cases (table 8).

Data in table 8 show that 13.3% of CRS patients died at ages under 50, and 52.7% of patients died at ages 70 and over.

Mortality from All Causes Based on Death Certificates

Death rates for patients with diagnosed CRS were studied by the cohort method in comparison to matched controls. Death certificates stored in the archives of the civil registrars confirmed the deaths. Copies were made of the death certificates for deceased residents of the surveyed territories through which the Techa flows and the clean villages to which exposed residents moved. Death certificates were made for both the deceased residents of the Techa riverside area and for the unexposed people who had lived in the same administrative districts but far from the Techa. Death certificates on deceased residents of the Kunashaksky, Krasnoarmeysky, Kaslinsky, Argayashsky, and Sosnovsky districts of the Chelyabinsk Region are available for 1950–1993 and on deceased residents of the Kataysky and Dalmatovsky districts of the Kurgan Region for 1950–1982.

Death certificates include coded information on places of residence and principal causes of death as defined in ICD-9 [13]. Information from paper documents was entered into a computer bank in which the death registry was compared with the registry of the exposed population and, for the purposes of this study, with the registry of CRS patients. Comparisons were made with family name, given name, patronymic, birth date, and place of birth. If all these parameters coincided, the death certificate was assigned the same systemic number as the CRS patient. When there was a deviation in the data, the death certificate was included in the control cohort.

The unexposed residents of the same surveyed territories of the same administrative districts were the control or comparison cohort. Such "regional" control met the requirements for compatibility with the study cohort. The members of the two cohorts lived in the same administrative districts, same geographic and climate zones, were involved in the same type of agricultural production, were in similar social conditions, and had similar ethnic structures. Data on age and sex composition of the control cohort were derived from records of regional statistical offices. Information on deaths in the control cohort was individualized.

It should be noted that the analysis presented below is based on so-called crude (nonstandard) estimates. Age-specific compatibility of the cohorts was ensured by excluding the age cohort 0–14 years from the control group; the same age cohort is absent in the CRS study group. Each of the report sections that addresses mortality contains age-specific death rates.

The use of the cohort method allowed estimation of death rates for CRS patients who lived in the surveyed territory until death—570 of the 940 CRS cases met these requirements. Death certificates confirmed 221 deaths.

Coefficients of all causes of death for the CRS cohort and the controls are provided in table 9.

Table 9. Death rates from all causes.

Characteristics	Patients with CRS		Controls
Years of follow-up	1950–1989	1950–1990	1950–1982
Age cohorts (years)	18–90	18–90	15–90
Person-years	19,192	20,011	994,125
Death cases	194	221	11,674
Mortality coefficient $x10^{-3}$	10.11	11.04	11.74
90% confidence intervals	8.76–11.59	9.60–12.56	11.50–11.97

It is evident that the general mortality rate is slightly lower (statistically insignificant) in CRS patients in the period 1950–1989 when compared to the unexposed group. However, an increase of a year in the follow-up time results in an increased death rate for CRS patients and draws this rate closer to the respective estimate for controls.

Age-Specific Mortality Characteristics

Age-specific mortality characteristics of patients with diagnosed CRS were calculated for the period 1950–1993 and of control cohorts in 1950–1982 (table 10).

Death rates for all causes in patients aged 15–49 were lower for patients with CRS versus controls, and a statistically significant decrease in death rates was noted in age groups 15–19 and 30–39. Death rates for CRS patients (50 years and older) were substantially higher than for matched controls.

Table 10. Age-specific mortality parameters.

	Mortality rates x 10^{-3} and 90% confidence intervals	
Age groups (years)	Subjects with CRS	Controls
15–19	0.34 (0.04–1.23)	1.60 (1.34–1.98)
20–29	1.63 (0.65–3.36)	2.64 (2.40–2.90)
30–39	0.79 (0.21–2.02)	4.07 (3.79–4.36)
40–49	5.58 (3.36–8.70)	6.39 (6.04–6.76)
50–59	33.10 (22.77–46.47)	10.47 (9.95–11.00)
>60	480.00 (408.48–560.64)	39.25 (38.34–40.19)
All ages	11.04 (9.63–12.56)	11.74 (11.50–11.97)

Dependence of Mortality Rates on Dose

Mortality rates from all causes in different dose groups are presented in table 11 and figure 18. The highest death rate was in the group with the average dose to the RBM of 1.32 Gy, and it proved to be much higher than in the group with the lowest dose. Calculation of linear regression showed a positive value of the dose coefficient to be equal to 3.97 per 1000 per 1 Gy. The death rate of CRS patients therefore does increase with dose.

Table 11. Dose dependences of mortality rates.

Dose groups, Gy to RBM	Average dose, Gy to RBM	Number of cases	Number of person-years	Mortality coefficient x10^{-3} (90% confidence intervals)
<0.2	0.14	52	5,045	10.31 (7.69–13.50)
0.2–0.4	0.3	73	7,075	10.32 (8.05–12.98)
0.4–0.7	0.53	48	4,778	10.05 (7.40–13.32)
0.7–1.0	0.78	14	1,449	9.66 (5.27–16.23)
1.0–1.5	1.32	30	1,398	21.46 (14.48–30.69)
>1.5	2.16	4	265	15.09 (4.11–38.64)

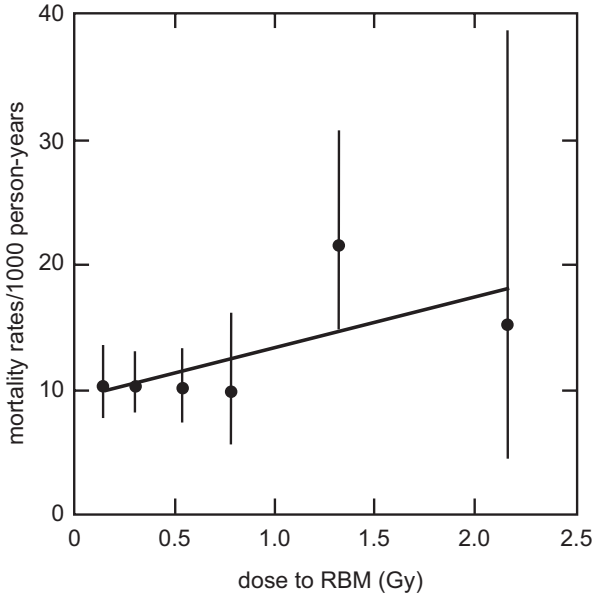

Fig. 18. Dependence of all causes of mortality on dose.

Excess death risk from CRS was calculated by using the AMFIT software program elaborated by Preston, Lubin, and Pierce [14]. The results of the calculations are provided in the appendix.

A relative risk model was used to analyze the dose-response relationship. The mortality rate at zero dose was 11.04/1000 or 1104/100,000 person-years of the dose coefficient. The attempt to assess the value of the linear dose coefficient was unsuccessful because the model parameters differed too much from actual parameters. By using the model with the quadratic dose, $I = 1(a + bD^2)$, the value of 0.371 for coefficient b was obtained. The quality of approximation may be assessed on the basis of the standard coefficient error equal to 0.168 and the value p equal to 0.027.

The calculations show that age at exposure did not play an important role in expression of radiation effect.

Mortality Structure

The highest death rates in CRS patients and in the unexposed people of the comparison group (controls) were associated with blood circulation disorders (ICD-9 class 7: 44% in patients with CRS and 45% in controls). Neoplasms ranked second among causes of death: 25% for all deaths for the CRS cohort and 16% for controls. Respiratory diseases (ICD-9 class 8), digestive diseases (ICD-9 class 9), urogenital tract impairment (ICD-9 class 10), and trauma (ICD-9 class 17) were almost similar in the CRS cohort and the controls. Some disease classes were not represented in the mortality structure for the CRS cohort, and extensive mortality rates associated with the same classes were less than 0.5% for the control group. Causes of death for CRS patients versus controls are provided in table 12.

There were differences between the cohorts in death rates associated with two disease classes. Higher death rates associated with neoplasms (ICD-9 class 2) were noted for the CRS cohort in comparison to controls (24.89% and 16.17%, respectively). Extensive death rates were associated with symptoms, signs, and inadequately defined conditions (ICD-9 class 16) and were higher for unexposed subjects. Some differences were observed in extensive death rates associated with infectious diseases: 3.17% for the CRS cohort and 5.77% for the unexposed control group.

Mortality rates (x 10^{-5}) were calculated and are listed in table 13.

Statistically significant differences between the cohorts were established for two disease classes: patients with CRS had higher death rates associated with neoplasms and lower rates with inadequately defined conditions versus controls.

Mortality from Leukemia and Solid Cancers

Due to higher cancer-related death rates in CRS patients this pathology is addressed in more detail.

There were 25 cancer deaths in men with CRS. The death rate and its 90% confidence intervals accounted for 369.22 (238.88–546.44) x 10^{-5}. The same causes led to 30 deaths in women, and the death rate was estimated to be 226.59 (152.95–324.02) x 10^{-5}. These sex-related differences in

Table 12. Mortality structure.

	CRS patients		Controls	
ICD-9 classification*	Number of cases	%	Number of cases	%
1. Infectious diseases	7	3.17	674	5.77
2. Neoplasms	55	24.89	1,888	16.17
3. Diseases of the endocrine system	1	0.45	41	0.35
4. Blood diseases	-	-	20	0.17
5. Psychiatric disorders	-	-	29	0.25
6. Disorders of the nervous system	1	0.45	83	0.71
7. Blood circulation disorders	98	44.34	5,313	45.51
8. Respiratory diseases	26	11.76	1,231	10.54
9. Diseases of the digestive system	5	2.26	258	2.21
10. Diseases of the urogenital system	2	0.90	105	0.90
11. Pregnancy complications	-	-	47	0.40
12. Skin diseases	-	-	8	0.07
13. Diseases of the osteomuscular system	-	-	16	0.14
14. Congenital anomalies	-	-	7	0.06
15. Perinatal pathology	-	-	50	0.43
16. Inadequately defined conditions	2	0.90	506	4.33
17. Trauma	24	10.86	1,398	11.98
Total	221		11,674	

*International Classification of Diseases, Ninth Edition.

Table 13. Mortality rates for CRS patients and control group.

	CRS		Controls	
ICD-9 classification*	Cases	Mortality rate**	Cases	Mortality rate
1. Infectious diseases	7	5.0 (14.03–72.10)	674	67.8 (62.71–73.16)
2. Neoplasms	55	274.8 (206.92–357.79)	1,888	189.9 (181.16–198.82)
3. Diseases of the endocrine system	1	5.0 (0.13–27.85)	41	4.1 (2.94–5.56)
4. Blood diseases	-	-	20	2.0 (1.22–3.08)
5. Psychiatric disorders	-	-	29	2.9 (1.94–4.18)
6. Disorders of the nervous system	1	5.0 (0.13–27.85)	83	8.3 (6.61–10.29)
7. Blood circulation diseases	98	489.7 (398.13–595.96)	5,313	534.4 (519.44–549.36)
8. Respiratory diseases	26	129.9 (84.82–190.95)	1,231	123.8 (116.99–130.98)
9. Diseases of the digestive organs	5	25.0 (8.10–58.25)	258	25.9 (22.79–29.01)
10. Diseases of the uro-genital system	2	10.0 (1.21–36.10)	105	10.6 (8.64–12.90)
11. Pregnancy complications	-	-	47	4.7 (3.45–6.35)
12. Skin diseases	-	-	8	0.8 (0.34–1.58)
13. Diseases of the osteomuscular system	-	-	16	1.6 (0.91–2.59)
14. Congenital anomalies	-	-	7	0.7 (0.28–1.44)
15. Perinatal pathology	-	-	50	5.0 (3.70–6.59)
16. Inadequately defined conditions	-	10.0 (2.21–36.10)	506	50.9 (46.57–55.48)
17. Trauma	24	119.9 (76.86–178.65)	1,398	140.6 (132.87–148.61)
Total	221	1104.3 (962.69–1257.46)	11,674	1174.0 (1150.0–1197.48)

*International Classification of Diseases, Ninth Edition.
**Mortality rates per 100,000 person-years, and 90% confidence intervals in parentheses.

death rates are not statistically significant. Table 14 shows age-specific death rates for the CRS group and controls.

As expected, cancer mortality rates increased with age for controls and reached 602 deaths per 100,000 for the oldest age cohort.

In patients with CRS, only one case of cancer was registered in an 18-year old, and no cancer cases were diagnosed in age cohorts 20–29 and 30–39. Most cancer deaths in CRS patients occurred in the age group 60 and older: 6 cases occurred at ages 60–64, 14 at ages 65–69, 7 at ages 70–74, 10 at ages 75–79, and 2 at ages 80–84. This age distribution of cancer death cases shows higher death rates for older age groups (50–59, 60 and older) in the CRS group versus controls.

The structure of cancer mortality is presented in table 15.

An increased rate of cancer mortality for the CRS group can be attributed to slightly higher rates of cancer of the following types: (a) cancer of the intestines, liver, and pancreas (summarized), (b) breast cancer, (c) cancer of the urogenital organs, and (d) leukemia. Differences in death rates approaching statistically significant values were only observed for cancer of the urogenital organs. Statistically significant differences were noted for leukemia.

Among patients with CRS there were 5 leukemia death cases: 1 case of acute undifferentiated leukemia, 3 cases of chronic myeloid leukemia, and 1 case of chronic lypmphocytic leukemia. The patients' ages at death were 18, 44, 65, 70, and 77.

Table 14. Age-related mortality rates.

	Patients with CRS			Controls		
Age groups	Cases	Number of person-years	Rate $x10^{-5}$	Cases	Number of person-years	Rate $x10^{-5}$
15–19	1	5,905	16.93	5	84,123	5.94
20–29	-	4,303	-	13	175,500	7.41
30–39	-	5,076	-	90	202,429	44.50
40–49	3	3,405	88.13	217	192,236	112.88
50–59	12	997	1203.61	420	149,990	280.02
>60	39	325	12000.0	1,143	189,847	602.06
All ages	55	20,011	274.8	1,888	994,125	189.9

Table 15. Cancer mortality.

		Patients with CRS		Controls	
Cancer site	ICD-9 code*	Number	Rates**	Number	Rates
Lip, oral cavity, pharynx	140–149	1	5.0 (0.12–27.85)	25	2.51 (1.62–3.71)
Esophagus	150	3	14.99 (3.09–43.77)	142	14.28 (12.02–16.84)
Stomach	151	13	64.96 (34.55–111.08)	652	65.58 (60.20–70.83)
Other digestive organs	152–159	9	44.97 (20.6–85.44)	231	23.24 (20.21–26.52)
Trachea, bronchi, lung	162	6	29.98 (11.0–65.36)	358	36.0 (32.33–39.92)
Bones	170	0	0	28	2.82 (1.87–4.09)
Skin	172, 173	1	5.0 (0.12–27.85)	11	1.11 (0.55–1.99)
Female breast	174	3	14.99 (3.09–43.77)	34	3.42 (2.37–4.78)
Uterus	179–180, 182	5	24.98 (8.09–58.2)	174	17.50 (15.10–20.30)
Other uro-genital organs	183–189	6	29.98 (11.0–65.36)	92	9.25 (7.45–11.34)
Lymphoma	200–203	1	5.0 (0.12–27.85)	12	1.21 (0.63–2.12)
Leukemia	204–208	5	24.98 (8.09–58.20)	36	3.62 (2.53–5.01)
Other	170–171, 190–199	2	9.99 (1.21–36.06)	93	9.35 (7.54–11.45)
All sites		55	247.82 (206.92–357.79)	1,888	189.89 (181.16–198.82)

*International Classification of Diseases, Ninth Edition.
**Mortality rate per 100,000 person-years; 90% confidence intervals in parentheses.

Table 16. Dependence of cancer mortality on dose.

Dose groups Gy to RBM	Average dose Gy to RBM	Number of cases	Number of person-years	Mortality rate $x10^{-3}$ (90% confidence intervals)
<0.2	0.14	10	5,045	198.22 (95.15–364.72)
0.2–0.4	0.30	19	7,075	268.55 (161.67–418.94)
0.4–0.7	0.53	18	4,778	376.73 (223.40–595.23)
0.7–1.0	0.78	1	1,449	69.01 (1.73–384.39)
1.0–1.5	1.32	6	1,398	429.18 (111.59–935.61)
>1.5	2.16	1	265	377.36 (9.43–2101.9)

Dose dependences of cancer mortality are shown in table 16 and figure 19.

It was impossible to trace a clear-cut dose dependence. The lowest coefficient value was found in the group with an average dose to the RBM of 0.78 Gy; the highest cancer mortality rate was registered in the cohort group with an average dose of 1.32 Gy. The small number of analyzed cases resulted in a very wide range of confidence intervals and consequently in considerable uncertainty of mortality coefficient values. However, approximating the mortality rate dependence on absorbed dose using a linear regression equation produces the following values: $I = 211 + 86.03D$, i.e., a positive but not high inclination angle of the approximating curve.

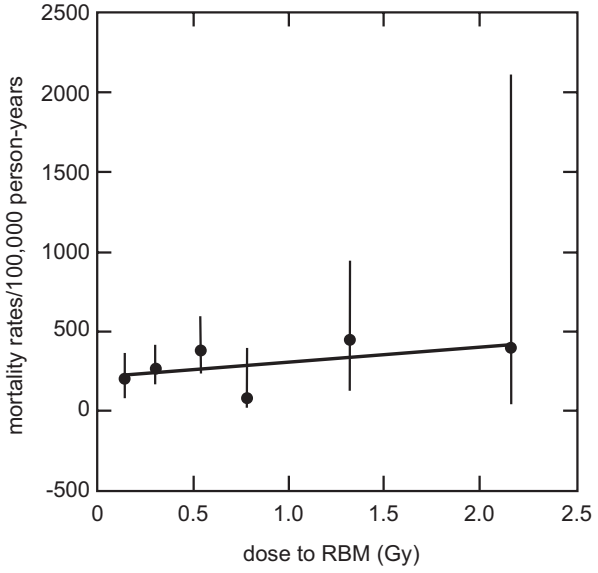

Fig. 19. Dependence of cancer mortality on dose.

Analysis of Mortality Rates for Patients with Verified Diagnoses of CRS

Chapter 9 of the first report [1] provides an analysis of the cases of CRS in exposed residents in the Urals and the clinical picture of CRS in patients whose diagnoses had been verified. Of the 940 cases initially diagnosed as CRS, 66 cases were validated with sufficient certainty. The dose rate to the RBM in these patients was approximately 1 Gy, and typical clinical manifestations that diminished with dose rate were present. The age composition of this group indicates that many were exposed in childhood or adolescence. Thus, among the 66 verified cases, there were 46 patients (69.7%) whose ages at exposure were 19 and under, 18 patients (27.3%) were 20–39 years old, and only 2 patients (3%) were over 40.

Deaths in these 66 cases were analyzed for the period 1950 to 1992. The 16 deaths (24.2% of the 66 cases) during this period occurred during the following years:

1954–1959, 2 deaths,

1960–1969, 1 death,

1970–1979, 3 deaths,

1980–1989, 7 deaths, and

1990–1992, 3 deaths.

Number and percentage of deceased patients by age were as follows:

one patient 19 years old (6.25%),

one patient 22 years old (6.25%),

one patient 30–39 years old (6.25%),

four patients 40–49 years old (25%),

one patient 50–59 years old (6.25%),

one patient 60–69 years old (6.25%), and

seven patients 70 years old and older (43.75%).

Causes of death for confirmed cases of CRS are presented in table 17. Deaths were reported by the next of kin in 5 cases but the exact causes of death cannot be provided because the death certificates were not available.

Six of the 16 deaths (37.5%) were due to neoplasms—a higher percentage than the percentages for the total CRS group and for controls.

Table 17. Causes of death for verified CRS cases.

Causes of death	Number of deaths	Percentage
Infectious diseases		
Tularemia	1	6.25
Neoplasms	6	37.5
Lymphoma	1	
Cancer of facial skin (with metastasis)	1	
Malignant tumor of the brain	1	
Chronic myeloleukemia	2	
Acute leukemia	1	
Diseases of the nervous system		
Disseminated sclerosis	1	6.25
Respiratory diseases		
Bronchial asthma, cardiopulmonary insufficiency	1	6.25
Trauma and poisoning	2	12.50
Overexposure to cold	1	
Suicide	1	
Unknown causes	5	31.25

Life Span in Patients with Diagnosed CRS

The average life span for a cohort of people can be correctly estimated either after the death of all members of the cohort or on the basis of life expectancy tables [15]. Neither of the two approaches is currently applicable to CRS patients. The first approach cannot be applied because some of the patients were still alive as of 1995. Life expectancy tables could not be constructed because of the lack of the classic age distribution in the sample analyzed—as a rule, CRS was not diagnosed in children.

At the same time, the results of a 45-year follow-up of patients with CRS provided the age at death for each deceased patient. The average age for 129 men with CRS was 62.29 years (51.95–74.12), and the average age for 214 women was 70.22 years (61.02–80.12).

For age cohorts in which about 50% of their original number had died it is possible to estimate median life expectancy—the time by which half the number of the followed-up cohort died since the beginning of exposure (1950).

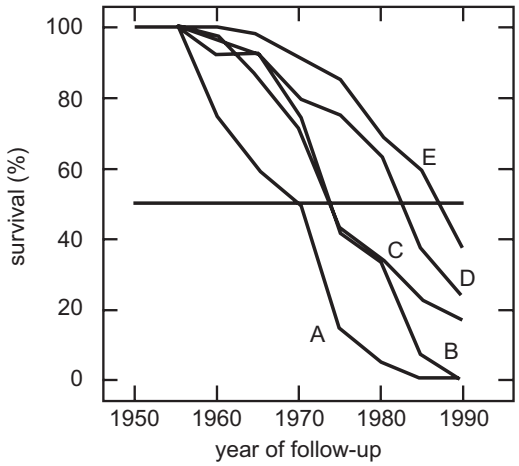

Fig. 20. Dynamics of survival for CRS patients:
A, subjects born in 1880 and earlier;
B, subjects born in 1891–1895;
C, subjects born in 1896–1900;
D, subjects born in 1901–1905; and
E, subjects born in 1906–1910.

Table 18 and figure 20 show life expectancy dynamics for the members of different age cohorts.

Table 18. Life expectancy dynamics for CRS patients.

Age by 1950	Percentage of patients alive by year								
	1950	1955	1960	1965	1970	1975	1980	1985	1990
>60	100	100	75	60	50	15	5	0	0
59–55	100	100	92	92	75	42	33	8	0
54–50	100	100	97	86	71	43	34	23	17
49–45	100	100	96	92	80	75	64	47	24
44–40	100	100	100	98	92	85	70	58	37
39–35	100	99	98	94	92	88	78	70	59

Time periods from the beginning of exposure (1950) to the year by which 50% of a given age cohort had died were as follows:

20 years for subjects born in 1890 and earlier (aged 60 or older in 1950),

24 years for subjects born in 1891–1895 (59–55),

24.4 years for subjects born in 1896–1900 (54–50),

33.5 years for subjects born in 1901–1905 (49–45), and

37.3 years for subjects born in 1906–1910 (44–40).

Life expectancy estimates for patients with CRS correlate with the calculated average life span estimates obtained by M. M. Saurov et al. [16] on the basis of mortality data for the entire exposed population. According to the data of this publication, the average life expectancy was 16 years for patients over 60, 25 years for patients aged 50–59, and 35 years for patients aged 40–49.

CHAPTER 6

Consequences of CRS

This report and the report of 1994 (1) on the deterministic effects of protracted radiation exposure were prepared and published under the sponsorship of AFRRI. The term "chronic radiation sickness" was designated by Russian researchers. The symptom complex that formed the basis for a CRS diagnosis was observed in workers at the Mayak plant that produced weapon-grade plutonium and also in residents of nearby villages who were exposed to discharges of radioactive wastes into the river Techa.

CRS was induced by chronic radiation exposure to sufficiently high doses, generally more than 1 Gy per year, for many months or years. The most typical manifestation of the disease was the disturbance of hemopoiesis, represented in some patients by RBM hypoplasia, leukopenia, neutropenia, and thrombocytopenia in the peripheral blood and, in some instances, by later development of leukemia. Hemopoietic disturbances developed almost at the same time as the signs of immune insufficiency.

Other symptoms of CRS were organic injury to the nervous system manifested by micronecrotic changes in the myelinic membrane of the nerve conductors at significant exposure doses as well as by disturbed vascular and cardiac regulation, inhibited secretion of gastric glands, and asthenia.

In cases where dose accumulation occurred as a result of exposure to a combination of external gamma radiation and incorporation of long-lived Sr-89 and Sr-90 isotopes, key symptoms were ostealgia and metabolic disorders of osteogenesis, accompanied in some instances by the development of osteomyelofibrosis. These deterministic symptoms were characterized by fairly distinct dynamics, and their intensity diminished, as a rule, following cessation of exposure or significant reduction in dose rates.

The diagnosis of CRS was made in 1,268 nuclear workers of the Mayak facility and in 940 residents of the Techa riverside area.

As stated above, the diagnosis of CRS was erroneous in a number of cases. Diagnoses were made at a time when even approximate estimates of individual exposure doses were nonexistent. In the course of dynamic follow-up of CRS patients, physicians who made the diagnoses in the past had to admit to diagnostic mistakes in 199 cases. Most mistakes occurred because CRS was confused with a general somatic disease simulating CRS or with a singular transitive response to radiation exposure and not as a clear-cut symptom complex of a specific disease.

It should be noted that no algorithm exists for diagnosing CRS. Some researchers who have studied CRS [17] maintain that the CRS symptom complex may sometimes be represented by only a few of its signs, and that the symptoms may be manifested with different intensity and may be transitive or long-standing.

Today, 45 years later, data that have accumulated from the follow-up of CRS patients over the years have helped describe in this report the dynamics of the principal symptoms of the disease and its outcomes.

The key symptom of the condition was impairment of the hemopoietic system. The existence of hematological problems in the followed-up CRS patients is confirmed by the following observations: (a) dependence of the number of cellular elements in the

peripheral blood on dose accumulated in the RBM (decrease in leukocyte, neutrophil, and thrombocyte counts with dose), and (b) distinct dynamics of blood parameters—clearly manifested reduction in the number of cellular elements at the highest dose rates and a subsequent normalization with decrease in dose rate.

Currently there are no patients with clinical symptoms of CRS. If we assume that the diagnoses of CRS were adequately substantiated, we have to conclude that the 674 cases that were traced by us did end in recovery.

The average duration of the disease was 7.35 years, and the recovery time was directly dependent on the exposure dose. At doses in excess of 700 mSv to the RBM, repair processes lasted for more than 9 years. The duration of the disease was presumably dependent on the patient's age at exposure. According to data cited in this report, the longest courses of CRS were noted in patients born in 1935–1939. It must be emphasized that individuals who were adolescents at the beginning of exposure absorbed the highest doses to the RBM.

Data on the 343 deceased of the total 940 CRS patients are available. The mortality rate for CRS patients calculated according to the methods of epidemiological analysis was found to be within the same range as the rate for unexposed controls (11.04 and 11.74 per 1,000, respectively).

Although a certain increase in death rate proportional to dose squared was noted, patients with diagnosed CRS were dying at more advanced ages compared to matched unexposed controls.

The most common death causes for both exposed patients and control subjects were diseases associated with disorders of blood circulation. Among patients with CRS diagnosed earlier, neoplasms accounted for 55 deaths. The cancer death rate for CRS patients was 274.8 (206.9–357.8), which was higher than the respective rate of 189.9 (181.2–198.8) for the comparison group.

A statistically significant increase in leukemia incidence was noted in patients with diagnosed CRS: one case of acute nondifferentiated leukemia, three cases of chronic myeloid leukemia, and one case of chronic lymphoid leukemia. The cases of acute nondifferentiated leukemia and chronic myeloid leukemia should obviously be regarded as outcomes of chronic exposure in patients who received significant doses to the RBM and developed hemopoietic hypoplasia shortly after the beginning of exposure.

However, it should be noted that the increased cancer mortality rate for patients with CRS did not result in life span shortening. As a rule, such patients developed tumors at advanced ages: 11% of cases at ages 60–64, and 60% of cases at ages over 65. The average age at death of 129 male patients who had CRS was 62.29, and the average age for 214 women was 70.22, which was not much lower than the respective values for unexposed members of the matched age cohorts.

Data on A-bomb survivors [18,19] also point to the fact that life span shortening unrelated to cancer occurrence is highly questionable. Calculations of life expectancy, if they involve eliminating cancer as the cause of death, increase life expectancy by only 2 years. The conclusion about an increased incidence of cancer that does not entail life span shortening correlates with the data cited above in spite of the fact that it was made by us in a relatively small-sized CRS group.

Thus, CRS diagnosed in a number of Techa riverside residents was found to be associated with higher cancer and leukemia death rates in particular but did not cause significant life span shortening.

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Appendix

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              Written by Dale L. Preston and Donald A. Pierce
                     DOS Protected Mode 80387 version
                 Single precision workspace size - 500000

use rez input @

BSF file created by DATAB           on    4/28/1996 13:41

Input from rez.bsf
1004 records read                   1004 records used
                                       0 records rejected
Workspace for 300 variables.          13 are currently defined.
Up to 287 new variables can be created
fit @

        Iter      Step     Deviance
          0         0      3376.454
          1         3      2426.953
          2         2      852.1215
          3         0      797.4037
          4         0      724.3001
          5         0      720.9407
          6         0      720.9298
          7         0      720.9298

   Piece-wise exponential regression model

   Product additive excess model {TO*(l + Tl + T2 +...)}

   CASES is used for cases
   PYR is used for person years

                          Parameter Summary Table
        # Name             Estimate     Std. Error     Test Stat.     P value
Log-linear term 0
1 %CON..............         7.007         0.06727         104.2      < 0.001
       Deviance     =       720.930       df = 1003
       Pearson Chi2 =       2560.37

ci@

                          95.00% Confidence Bounds
        # Name             Estimate      Std. Error       Lower        Upper
Log-linear term 0
1 %CON ..............         7.007       0.6727E-01        6.875        7.139
       EXP (estimate)        1104.           1.070         968.0        1260.
```

```
line 1 dose*dose @
fit@

        Iter      Step    Deviance
          0         0     720.9298
          1         0     713.5369
          2         0     713.2260
          3         0     713.2236
          4         0     713.2235

   Piece-wise exponential regression model

   Product additive excess model {TO*(1 + T1 + T2 +...)}

   CASES is used for cases
   PYR is used for person years
```

Parameter Summary Table

#	Name	Estimate	Std. Error	Test Stat.	P value
Log-linear term 0					
1	%CON.....	6.890	0.08378	82.24	< 0.001
Linear term 1					
2	DOSE * DOSE.....	0.3710	0.1679	2.209	0.027

Deviance = 713.224 df = 1002
Pearson Chi2 = 2177.85

```
line 1 +dose @
fit @

        Iter      Step    Deviance
          0         0     713.2235
          1         0     713.2202
          2         0     713.2201

   Piece-wise exponential regression model

   Product additive excess model {TO*(l + Tl + T2 +...)}

   CASES is used for cases
   PYR is used for person years
```

Parameter Summary Table

#	Name	Estimate	Std. Error	Test Stat.	P value
Log-linear term 0					
1	%CON.....	6.880	0.1870	36.79	< 0.001
Linear term 1					
2	DOSE * DOSE.....	0.3511	0.3492	1.005	0.315
3	DOSE.....	0.03935	0.6522	0.06034	> 0.5

Deviance = 713.220 df = 1001
Pearson Chi2 = 2179.54

```
line 1 -dose @
line 1 +dose*dose*dose @
fit @
```

Iter	Step	Deviance
0	0	724.3283
1	0	713.3280
2	0	713.2242
3	0	713.2235
4	0	713.2235

Piece-wise exponential regression model

Product additive excess model {TO*(l + Tl + T2 +...)}

CASES is used for cases
PYR is used for person years

Parameter Summary Table

# Name	Estimate	Std. Error	Test Stat.	P value
Log-linear term 0				
1 %CON.....	6.890	0.08378	82.24	< 0.001
Linear term 1				
2 DOSE * DOSE.....	0.3711	0.1679	2.209	0.027
Deviance =	713.224	df = 1002		
Pearson Chi2 =	2177.84			

ci@

95.00% Confidence Bounds

# Name	Estimate	Std. Error	Lower	Upper
Log-linear term 0				
1 %CON.....	6.890	0.8378E-01	6.726	7.054
EXP (estimate)	982.5	1.087	833.7	1158.
Linear term 1				
2 DOSE * DOSE.....	0.3711	0.1679	0.4190E-01	0.7002

```
line 1 +age@
fit@
```

Iter	Step	Deviance
0	0	713.2235
1	1	713.1075
2	0	713.0699
3	0	713.0240
4	0	713.0222
5	0	713.0221

Piece-wise exponential regression model

Product additive excess model {TO*(1 + T1 + T2 +...)}

CASES is used for cases
PYR is used for person years

Parameter Summary Table

# Name	Estimate	Std. Error	Test Stat.	P value
Log-linear term 0				
1 %CON.....	7.049	0.3916	18.00	< 0.001
Linear term 1				
2 DOSE * DOSE.....	0.3167	0.1907	1.660	0.097
3 AGE.....	-0.002237	0.004933	-0.4535	> 0.5
Deviance =	713.022	df = 1001		
Pearson Chi2 =	2085.92			

end

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This report was prepared at the Urals Research Center for Radiation Medicine, Chelyabinsk, Russia, under a contractual agreement with the Defense Nuclear Agency (DNA001-95-C-0156) and presents a further summary of research data on the deterministic effects in the population exposed to radiation from discharges of radioactive wastes by the Mayak radiochemical facility into the river Techa in the Urals. The first report, "Analysis of Chronic Radiation Sickness Cases in the Population of the Southern Urals," was published by the Armed Forces Radiobiology Research Institute, Bethesda, Maryland (Contract Report 94-1) and provided the exposure conditions, exposure dose assessment, clinical picture of chronic radiation sickness diagnosed in 940 exposed residents, and differential diagnoses of the disease.

This report summarizes the data on the dynamics of chronic radiation sickness, analyzes the processes of restoration of disrupted functions, and describes the outcomes of long-term effects.

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