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This report was prepared for the Defense Nuclear Agency under contract number DNA001-92-M-0658. The report is based on information obtained from a 40-year follow-up of people exposed to radiation due to discharges of radioactive waste from an industrial facility, the Mayak Production Association, into the Techa-Iset river system. The results of the medical follow-up have been described in a number of articles published in scientific journals in Russia. This report summarizes dosimetric and medical data within the framework of deterministic effects and, in particular, chronic radiation sickness (CRS). From 1952 to 1961, 940 people out of 28,000 exposed to radiation in the riverside communities on the Techa were diagnosed as having CRS. Conditions of exposure are described, irradiation dose computations are presented, and the clinical picture of CRS is characterized.

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Analysis of Chronic Radiation Sickness Cases in the Population of the Southern Urals

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FOREWORD

After World War II, according to current Russian arms experts, the Soviet Union rapidly accelerated its nuclear weapons program. Under the leadership of Igor Kurchatov and others at the Ministry of Medium Machine Building, plants for processing fuel for weapons were quickly set up, first near the city of Chelyabinsk in Russia and later near Tomsk and Krasnoyarsk. The first was called the Mayak Production Association. While the English translation of "mayak" is, ironically,"lighthouse," it and the other plants were supported by "secret cities," whose addresses were merely a number appended to the city name, e.g., "Chelyabinsk-70" or "Tomsk-7." Access into and out of these special areas was restricted, and workers at the plants received medical care from a system separate from that for other citizens in the region.

A committee headed by Dr. G. M. Frank established the initial safety standards in 1946. Permissible exposures to radiation were high at first, up to 0.2 rem/day or 60 rem/year. Two years later they were lowered to 0.1 rem/day or 30 rem/year. At this time a distinction was made between workers and the general population. In case of an accident, workers were allowed up to 25 rem in 15 minutes or 100 rem/year. In 1953, exposure standards were lowered to 15 rem/year for workers. Since 1962, permissible maximum exposure levels for both workers and the general population have been roughly similar to those in the United States.

Although, as one might expect, most persons received exposure below these levels, these standards were occasionally exceeded. I have spoken personally with scientists who admitted, off the record, that they sometimes left their dosimeters at home when they knew they would be exposed to higher than normal levels. Some of these individuals had one set of accurate records for their personal knowledge and one set for safety personnel. There are also anecdotes of persons being given "administrative" doses; i.e., when their actual exposures exceeded daily or annual limits, a number at or just below the standard was recorded.

Because of the long-term exposure to levels of ionizing radiation that were often orders of magnitude above those Western workers generally experienced, several individuals, according to the literature, reported symptoms of sleep and appetite disturbances, difficulties with concentration and memory, irritability, and other "soft" clinical signs. Complete blood counts, when taken, revealed pancytopenia. Symptoms would improve and counts would return to normal only when the individual was removed from sources of radiation exposure. A team of physicians headed by Dr. A. K. Guskova and Dr. G. D. Baysogolov coined the term "chronic radiation sickness" to describe these effects, which they felt to be due to the unusually high levels

of radiation received and the length of exposure. Their work is cited in this report.

Professor T. D. Lysenko, a scientist who had Stalin's confidence during the late forties and early fifties, according to published information, did not believe that exposures to ionizing radiation at levels insufficient to cause deterministic health effects would create problems for the individual later. For this and other reasons, most likely including accelerated work patterns, carelessness, and accidents, radioactive wastes less than a millicurie/liter were discharged directly into the Techa river. As this report documents, over 4,500 curies were discharged directly into the river in one particular year. The villagers downstream used the water for fishing, watering their gardens, bathing, cooking, and even drinking. They preferred it to well water. Of course they didn't know what the nature of the facility upstream was nor what was in its effluent. After a few years, medical and dosimetric investigations were carried out. Several villagers had effects similar to those of the radiation workers. Several thousand villagers were evacuated without being told why, and a few villages were completely evacuated. The practice of dumping radioactive wastes directly into the river was halted. Of the riverside people exposed, 940 were diagnosed as having "chronic radiation sickness."

In 1989, the veil of secrecy was lifted. According to its records, the International Atomic Energy Agency was notified of the accident at Kyshtym (near Mayak), where an underground tank with highly concentrated wastes exploded in 1957 and contaminated a large area. Scientists from Branch 4 of the Institute of Biophysics, now the Urals Research Center for Radiation Medicine (URCRM), were permitted to disclose the results of the dosimetric and clinical investigations conducted earlier. Dr. A. A. Akleyev, Dr. M. M. Kossenko, and Dr. M. O. Degteva visited the Armed Forces Radiobiology Research Institute (AFRRI) and presented some of their data. In June 1992, under the leadership of Professor V. N. Soyfer, a historic workshop was conducted at George Mason University in Fairfax, VA. This workshop, which was underwritten by AFRRI and the Department of Energy, brought together scientists and political figures from both the Russian Federation and the United States. As a result of those and subsequent discussions, AFRRI and URCRM collaborated in studying the effects of chronic radiation exposure on the Techa river village populations. It is hoped that the joint effort, which resulted in this report, will be the springboard for further research.

In view of the present concerns regarding human experimentation, it should be noted that no exposures of humans (or animals) to radiation were conducted as part of this study, which is a detailed retrospective review of the effects of exposures resulting from either accidental or intentional release of radioactive effluents that were considered, in the minds of the scientists at that time, to pose no health threat to those downstream. When the effects of these inadvertent or misguided releases of radioactivity became known, the practice of direct discharge of radioactive effluent was stopped, and villagers were evacuated when this appeared necessary. Although patients were not told the true nature of their illnesses (for reasons stated above), appropriate medical care, such as was available under the Soviet system at that time, was given to those affected. The data generated are unique in terms of the length and level of exposures and the large

numbers of persons involved. Dr. M. M. Kossenko and her colleagues have done an outstanding job in recording and analyzing these data, especially in view of the lapse of time, former secrecy, and other obstacles.

The mission of AFRRI is to conduct research in the field of radiobiology and related matters, which includes certain occupational, preventive, epidemiological, and environmental health aspects of medicine. This work is therefore of vital importance to AFRRI. It is our intention that the worldwide scientific community be apprised of the valuable work of URCRM and that this effort shall serve as the springboard for further collaborative research between URCRM and Western institutions, governmental and private, with similar interests.

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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CONTENTS

INTRODUCTION 1

CHAPTER 1
Brief Description of the Basin of the Techa River 3

Geographical Position and Hydrogeological Conditions 3

Water Consumption in the Riverside Communities 6

CHAPTER 2
Disposal of Radioactive Wastes into the Techa River in 1949-1956 7

Source of Radioactive Contamination of the Techa River 7

Exposure Situation on the Banks of the Techa River 7

CHAPTER 3
Doses of Radiation to the Population 11

Evaluation of Doses Due to External Exposure 11

Evaluation of Doses Due to Internal Exposure 12

Distribution of Accumulated Dose Among Exposed Populations 15

Dose Estimation Evolution: Significance of Individual Dose Uncertainty 18

CHAPTER 4
Methods Used in Diagnosing Chronic Radiation Sickness 21

Concepts of Diagnosis of Chronic Radiation Sickness 21

Diagnosis of CRS in the Population on the Techa and the Role of Visiting Medical Teams 23

Screenings to Identify Radiation Effect Cases 24

Principles of Dynamic Follow-Up . . . 26

Medical Records 27

CHAPTER 5
Characterization of Population with Diagnosed Chronic Radiation Sickness . . . 29

Time of First Diagnosis of CRS 29

Age and Sex Characteristics of the Population with CRS 30

CRS Cases in Different Communities . 32

Degree of Gravity in CRS Cases 34

CHAPTER 6
Examples of Chronic Radiation Sickness Cases: Abstracts from Case Histories 35

Cases 1 Through 3 35

Cases 4 Through 6 37

CHAPTER 7
Status of Systems and Organs in Chronic Radiation Sickness 43

Hematopoietic System 44

Nervous System 51

Skeletal System 53

Cardiovascular System 56

Alimentary Tract Status 59

Biochemical Blood Studies 60

Immune System 64

CHAPTER 8

Verification of Diagnosis of Chronic Radiation Sickness 69

Differential Diagnosis Between Chronic Radiation Sickness and General Somatic Diseases 69

Assessment of Annual Dose Rate Threshold for CRS in the Urals Population 75

Social Aspects of Diagnosis Reassessment 76

CHAPTER 9

Clinical Picture of Verified Cases of Chronic Radiation Sickness 77

"Image" of Chronic Radiation Sickness 77

Is Chronic Radiation Sickness a Specific "Strontium Disease" of the Population Exposed on the Techa? . . . 80

CHAPTER 10

Uncertainties in Prevalence Studies of Chronic Radiation Sickness for the Techa River Population 81

CHAPTER 11

Proposals for Further Research Into Chronic Radiation Sickness 83

REFERENCES 85

ABBREVIATIONS 89

INTRODUCTION

The late forties and fifties of the twentieth century were marked by unusually sharp political and military confrontations of a number of countries (primarily the Union of Soviet Socialist Republics (USSR) and the United States that led to the production and accumulation of nuclear weapons. At that time, a powerful military complex for plutonium production, later named Mayak Production Association, was established in the USSR within 100 km of the city of Chelyabinsk in the Southern Urals.

During the 40 years of operations at Mayak, significant radioactive contamination of large areas in the Southern Urals occurred both as a result of radiation accidents and from imperfect technological processes. Personnel of the Mayak production complex and about 450,000 people residing in the areas contaminated with radioactive material were exposed to increased levels of radiation.

Protracted doses of combined external and internal radiation to red bone marrow ranged from several mSv to 4 Sv. The average doses were estimated to be higher than those for the population exposed at Chernobyl and were comparable to those in A-bomb survivors in Hiroshima and Nagasaki.

These exposures resulted in the development of deleterious health effects in a large number of people. One of the most severe early effects of radiation in the areas near Mayak was chronic radiation sickness. This disease is not mentioned in the world's official statistical nomenclature of diseases, obviously because nowhere else in the world has chronic radiation at these significant dose levels been experienced.

The term, chronic radiation sickness (CRS), introduced by the Russian scientists A. K. Guskova, G. D. Baysogolov, and others, proceeded from the necessity to designate a specific term for a disease that was diagnosed in several hundred workers of the Mayak industrial complex. The same diagnosis was made for 940 residents of the riverside villages on the Techa river, into which high-level wastes from the Mayak plant had been dumped from 1949 through 1956. During the 40-year period of operations at Mayak, all studies on radiation exposure of personnel at the plant and of the off-site population, the doses of radiation exposure, and the possible health effects from radiation exposure were classified for national security reasons.

This report provides a clinical description of cases of CRS in residents of Techa riverside villages. The first three chapters are devoted to the geographical description of the Techa river, water usage patterns, radioactive waste disposal practices, dosimetry methods, and exposure rates. Subsequent chapters describe the status of organs and systems in patients for whom the diagnosis of CRS was established in the fifties and early sixties; abstracts of patients' clinical histories are also presented. In addition, this report provides a critical analysis of the degree of certainty of this diagnosis from the point of view of current knowledge of individual radiation doses received by the exposed population and on the basis of currently accepted theories of development of radiation effects. Differential diagnoses are also discussed.

This report was prepared at the Urals Research Center for Radiation Medicine (formerly Branch 4 of the Institute of Biophysics, USSR Health Ministry). It is presented by the authors as the first open scientific analysis of the issues relevant to the deterministic effects of chronic population exposure.

For patient attention to the preparation of this analysis the authors wish to express appreciation for the following contributions:

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Entered data into data base

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Entered data into data base

We believe that the investigation of CRS should be continued for the purpose of assessing the outcome of the disease for each patient and for developing an algorithm for computer-based diagnosis verification. We believe that our work will contribute to further development of the scientific basis for the need to establish global parameters to ensure radiation safety.

CHAPTER 1

Brief Description of the Basin of the Techa River

Geographical Position and Hydrogeological Conditions

The Techa river, the tributary on the right of the Iset river, flows into the basin of the Kara Sea. On the basis of Techa's hydrogeological characteristics (240 km in length, up to 2 km in width, and mean annual flow rate at the outfall about 7 m/sec), the river can be assigned to the category of small rivers [1]. Its main tributaries are Mishelyak, Zyuzelka, Baskazyk, and Shutikha. The schematic of the river system is presented in figure 1.1.

The Techa riverside area can be divided into two parts: floodland and bed characteristics. A cascade of hydraulic engineering installations are located in

Fig. 1.1. Schematic of the Techa river (approximate scale) and the villages located on its banks before radioactive contamination. See table 3.2 for complete list of villages.

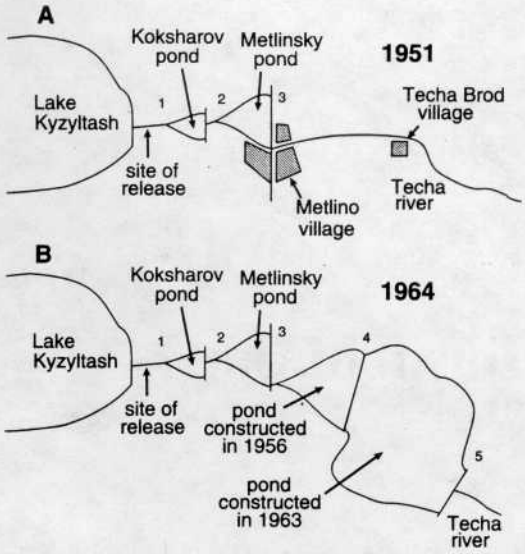

Fig. 1.2. Schematic of the upper reaches of the Techa river (approximate scale) in (A) 1951 and (B) 1964.

the upper reaches of the Techa (fig. 1.2) and include reservoir numbers 2 (Koksharov pond created in August 1951), 3 (Metlinsky pond, which already existed in 1951), 10 (dating back to 1956), and 11 (created in 1963). The stretches of the river from reservoir 11 up to the village of Muslyumovo are for the most part swampy, with a poorly marked winding bed overgrown with water plants. The width of the riverbed is 3-15 m, and the depth is 0.5-2 m; bed deposits consist of turf, silt, or clay. In its upper and middle reaches (downstream of the village of Muslyumovo), the river has a well-marked bed, its bottom consisting of layers of sand and slime, and in some places clay, sand, and gravel. The mean width and depth of the river during the summer are 22 m and 0.5-1.0 m, respectively.

Since the Techa is a river on a plain, it has few turnings: the mean value of its winding coefficient is about 1.07. The longitudinal profile of the riverbed is characterized by a slope of the average line of the bottom and the slope of the water surface along the river course, with the midstream and downstream reaches of the river having virtually the same slope as the water surface, about 0.6%. Being a river on a plain, the Techa receives its supply of water from melting snow and intensive spring floods (table 1.1).

The main source of water supply to the Techa during the summer is groundwater. During the period of floods, a backwater phenomenon develops in a tributary stream that minimizes the amount of groundwater entering the river. On the average, the fraction of groundwater entering the river is about 10% of the overall river runoff.

A comparison of the mean annual water discharge into the river and the annual level of precipitation in the area (fig. 1.3) has shown that the curve representing the water discharge is actually similar in shape to that referring to precipitation, with a year's delay in dynamics.

If we study the absolute estimates of river water discharge in dynamics (from 1948 through 1988), we are able to observe that the construction of the hydraulic engineering installations on the river in 1956 and 1964 did not cause any changes in the hydrological conditions of the river; just as under natural conditions, water discharge ranged from 2 m/sec to 10 m/sec in certain years. The minimum discharge estimates (≤1 m/sec) occurred in the drought-afflicted years 1975 and 1976.

Table 1.1. Water runoff distribution by months (percentage of annual rate).

	Month											
Village	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Muslyumovo (upper reaches of the Techa)	3.6	2.0	2.0	39.0	14.0	6.0	7.5	7.6	4.5	5.5	4.7	4.1
Pershino (lower reaches of the Techa)	2.7	2.2	1.8	41.0	15.0	6.5	6.2	6.7	5.3	5.2	4.1	3.1

Note: Contribution in spring months (April-May) accounts for about 55% of the annual runoff.

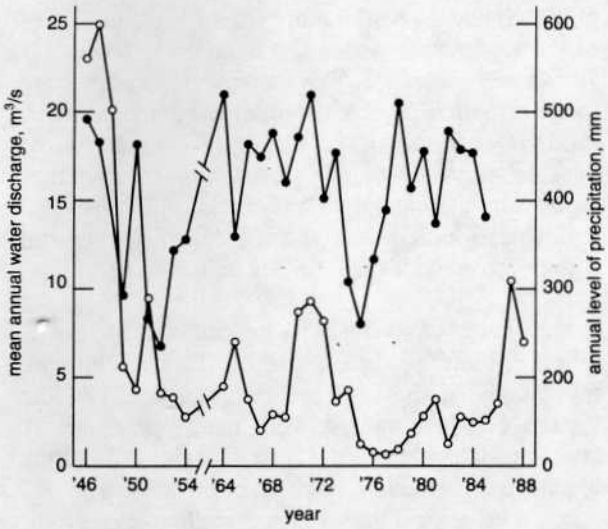

Fig. 1.3. Mean annual water discharge (o) into the Techa river and annual levels of precipitation (•).

In terms of chemical composition, the water of the Techa is classified as the carbonate-sodium type, pH 7.5-8.5, and mineralization is estimated to be about 700 mg/l at present. Data on the chemical composition of the water are presented in table 1.2. It can be seen from the table that ion concentration in the river water does not change significantly with time and averages at about 60 mg/l for Ca, 30 mg/l for Mg, 300 mg/l for HCO_3, and 40 mg/l for Cl. The most clear-cut changes were observed in the river water mineralization level and the sulfate content.

The bed deposits in the upper reaches of the river from reservoir 11, upstream of Muslyumovo, consist of layers of turf, silt, and clay. There are flood swamps measuring 300 m to 2 km in width along the river shoreline; the most swampy areas are located between the villages of Nadyrov Most and Muslyumovo at the site where the river Zyuzelka flows into the Techa. The central portion of the

Table 1.2. Chemical composition of the Techa river water.

Site of observation	Year	pH	Ca mg/l	Mg mg/l	K mg/l	Na mg/l	HCO_3 mg/l	SO_4 mg/l	Cl mg/l	Mineralization mg/l
	1954	8.6	62.5	24.8	-	-	-	87.5	16.6	315
	1955	8.2	58.8	-	-	-	-	-	28.0	398
Muslyumovo	1964	-	63.2	31.2	28.5	28.5	230.6	55.4	23.4	432
	1976	-	56.0	49.0	-	-	-	-	-	880
	1986	-	66.0	52.8	-	-	-	-	-	-
	1987	-	53.6	36.6	-	-	-	-	-	-
	1964	-	58.7	51.1	26.9	26.9	214.7	56.8	30.2	-
	1980	8.5	68.5	29.9	9.6	54.7	302.6	128.2	42.5	656
Pershino	1981	8.2	62.5	33.2	9.9	57.4	309.9	132.0	39.4	654
	1982	8.5	69.7	30.4	10.2	20.0	298.3	131.0	47.2	673
	1983	8.4	62.1	28.9	-	-	299.6	464.8	45.4	1188
	1984	8.5	61.3	31.6	-	-	319.0	111.0	47.2	690
	1986	-	76.0	45.6	-	-	-	-	-	-

flood soil is composed of turf/bog soils, which give way to meadow/turf soils along the boundaries of the swamps. The turf layer is from 10 cm to 3 m thick; the turf contains a considerable amount of minerals and an increased percentage of ash (10%-35% and up to 60% in the bottom layers). Clay, sandy loam, and less frequently sand compose the underlying layer of the turf. Bed deposits in the middle and lower reaches of the river are composed of sandy silt/gravel. The dry floodplain, measuring 200-500 m in width, is composed of meadow/turf soils.

Studies on the mechanical composition of the soils have shown that the sandstone bed deposits and the sandy loam soils of the floodplains are characterized by a higher content of large particles (0.25 mm to 1 mm), while the fine particles (<0.01 mm) are uniformly distributed over the vertical profile, with content being determined by the type of soil.

Water Consumption in the Riverside Communities

Research carried out in the fifties showed that the sanitary and hygienic characteristics of the river water were well within the limits permissible at that time. The Techa riverside was chosen as a place for building settlements and agricultural works, largely because of the good taste of the water, availability of fertile floodlands, a convenient bank line, and the fact that the average river water level did not actually change throughout the year.

In 1950, there were 25 settlements on the banks of the Techa within the boundaries of the Chelyabinsk province and 14 settlements within the boundaries of the Kurgan province. The diagram in figure 1.1 shows the spacing of the settlements, which were mostly small villages and hamlets typical of agricultural zones in the Urals. Within the boundaries of the Chelyabinsk province, population size by settlements was as follows: 13 settlements with up to 300 residents, 6 settlements with 300-500 residents, and 6 settlements with over 1,000 residents.

Ethnic Tartars and Bashkirs prevailed in the population of the upper reaches of the Techa, while the inhabitants of the settlements downstream of the village of Muslyumovo were mainly Russian. A characteristic feature of Techa villages is that they are laid out parallel to the river, often on both banks. According to local tradition, private houses are built of logs, while schools, shops, and storehouses are built of brick or stone. There is no clear functional differentiation between the districts of the settlements.

The river was the main source of drinking water. There were no wells in small and medium-size villages. In larger villages, some of the families had wells in their yards. River water was used for irrigating kitchen gardens, laundry, and other domestic needs.

The economic status of the riverside territories may be defined as typically agricultural, widely used for running small private farms that produced food (milk, meat, potatoes, and other vegetables). The Techa floodlands and meadows were mainly used as pastures and hayfields. In summer, the river was the habitat of waterfowl. People fished in the river for a considerable part of their daily subsistence, and also used it for watering cattle.

CHAPTER 2

Disposal of Radioactive Wastes into the Techa River in 1949-1956

Source of Radioactive Contamination of the Techa River

The Mayak Production Association is located in the Chelyabinsk region (eastern side of the Southern Urals) within 15 km of the town of Kyshtym, at the upper reaches of the Techa river and a number of interconnected lakes. Mayak was the first and the most important military radiochemical installation in the country. Construction of the first Mayak buildings dates back to 1945. The first plutonium production reactor of the graphite-moderated type, the so-called A facility, was put on line in 1948. In all, there were five graphite-moderated reactors and one heavy-water-moderated reactor. The water for cooling purposes was taken from nearby Lake Kyzyltash. Chemical reprocessing of irradiated fuel started in 1948. Technology for recovering plutonium and uranium was based on the process of precipitation of irradiated plutonium and uranium from solutions of highly radioactive fission products. The separation process resulted in the release of high-level wastes with a sodium nitrate concentration over 100 g/l and sodium acetate concentration amounting to 60-80 g/l. (See Cochran and Norris [2] for a brief description and history of Mayak.)

Exposure Situation on the Banks of the Techa River

Volumes of dumps and their radionuclide composition. During 1949-1956, Mayak released 7.6 x 10^7 m^3 liquid wastes with 10^{17} Bq (2.7 x 10^6 Ci) of uranium fission products into the Techa. About 95% of these releases occurred between March 1950 and November 1951. The average daily release during this period was 1.6 x 10^{14} Bq (4,300 Ci) with the composition of the radionuclides as follows: ^{90}Sr (11.6%); ^{89}Sr (8.8%); ^{137}Cs (12.2%); isotopes of rare earth elements (26.8%); ^{95}Zr and ^{95}Nb (13.6%); ^{103}Ru and ^{106}Ru (25.9%). In the subsequent 5 years the releases into the river system decreased sharply, totaling 3.5 x 10^{14} Bq (9,500 Ci) per year in 1952 and ranging from 2 x 10^{13} to 8 x 10^{13} Bq (500 to 2,000 Ci) annually during 1953-1956 (fig. 2.1). In 1956, the riverbed of the Techa was dammed, and the penetration of radioactive substances to the lower parts of the river decreased

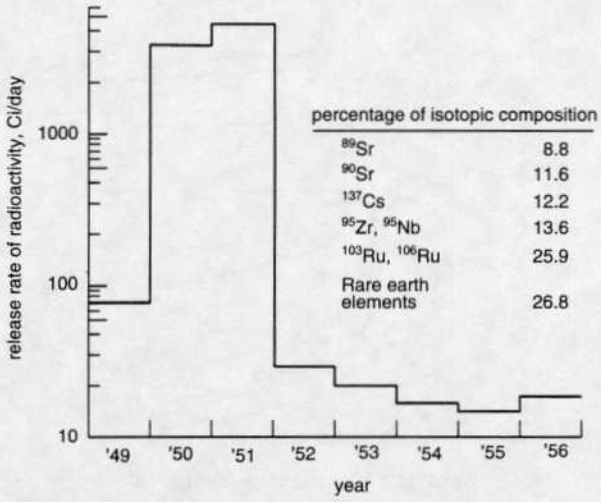

Fig. 2.1. Average amount of radioactivity released per day into the Techa river from 1949 to 1956, and the radionuclide composition of the release .

to approximately 2 x 10^{10} Bq (0.54 Ci) per day. The construction of another dam in 1963 effectively isolated the contaminated upper Techa.

In summary, the contamination of the Techa-Iset river system was caused mostly by the massive releases in 1950-1951, and 23.8% of the released activity consisted of the long-lived radionuclides ^{137}Cs and ^{90}Sr.

Concentration of radionuclides in river water. The releases led to radioactive contamination of the Techa, Iset, and Tobol rivers, with the most serious contamination on the banks of the Techa. At the confluence of the Techa and Iset rivers, the concentration of radionuclides decreased by a factor of about 10 (mostly as a result of dilution), and at the confluence of the Iset and Tobol rivers, the concentration was reduced further by another factor of 10. Systematic measurements of radionuclide concentrations in river water, sediments, and floodplain soils, measurements of gamma ray exposure rates, and determinations of the radionuclide composition in the contaminated areas began in the summer of 1951. The values of the specific activity in the water of the Techa below the site of release for the years 1951-1955 are shown in figure 2.2. From 1951 to 1952, the concentration of radionuclides in the river water decreased sharply. Subsequently, the decline was slower. About 70% of the radionuclides released in 1950-1951 ended up in the sediments of the Koksharov and Metlinsky ponds in the upper reaches of the Techa and about 10% in the sediments of the parts of the river within approximately 80 km of the site of release. In subsequent years, the contaminated sediments became a source of secondary contamination of the river water.

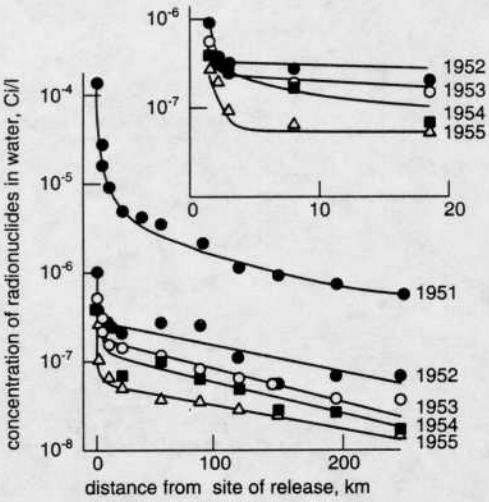

Fig. 2.2. Total beta radioactivity of the river water (average annual values per liter of water) in the early fifties as a function of the distance from the site of release.

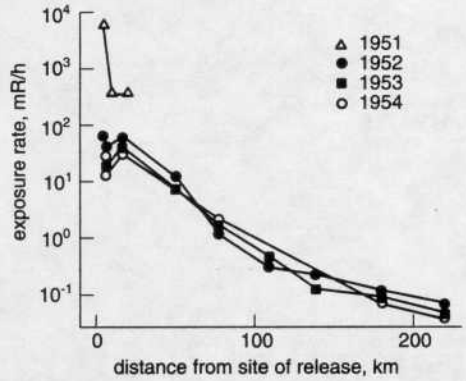

Fig. 2.3. Results of gamma ray exposure rate measurements along the Techa river in the early fifties.

Gamma-field levels in the riverside areas. Figure 2.3 shows measured gamma ray exposure rates along the water edge of the Techa. The main source of gamma radiation was the radioactive silt, with no appreciable shielding by the water layer near the bank strip (fig. 2.4). After the sharp decline in

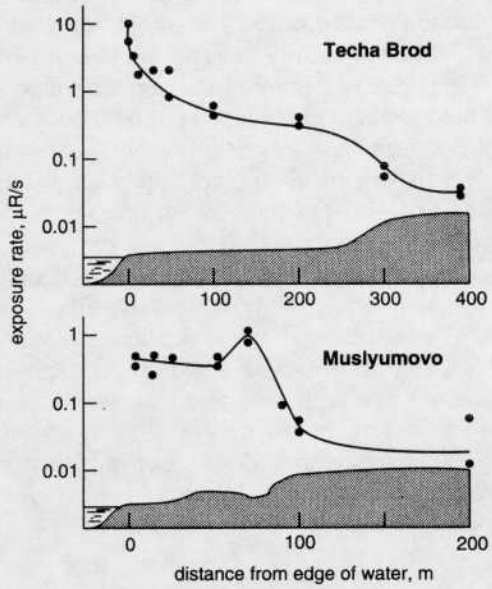

Fig. 2.4. Results of exposure rate measurements (summers of 1954 and 1955) as a function of distance from the edge of the water in the villages of Techa Brod (18 km downstream from the site of release) and Muslyumovo (78 km downstream). Shore topography is shown in lower parts of panels. A sharp decrease in exposure rate corresponds to the border of the territory flooded in 1951.

releases at the end of 1951, the gamma ray exposure rate changed very little and appeared to be due to ^{137}Cs and its long half-life as the main contributor.

Results of the measurements are available in technical reports of the working team that made the measurements under the direction of Professor Alexander Marey (1907-1987) of the Institute of Biophysics, Moscow. These reports do not provide sufficient detail to assess the accuracy of the measurements, but they are the only source of information on gamma radiation levels along the Techa river during the early fifties. On the upper reaches of the Techa, measurements began in the summer of 1951, and in subsequent years were taken in specific reference sites two to five times a year. Since 1952, measurements have been taken yearly along the whole river.

Implementation of protective measures. Due to the contamination of the river system, 124,000 people who lived near the banks of the Techa and Iset rivers were exposed to radiation. Radiation levels were highest near the site of the release, and 28,100 inhabitants in the regions of Chelyabinsk and Kurgan received doses that may have had significant health effects. Incidence of exposure was not only determined by external exposure but was also determined by water consumption because the river was the main and sometimes the only water supply for drinking and other uses. There were few wells. They were used only by a portion of the population and then not for all purposes since well water was inferior to river water in terms of taste. The river was used for fishing, watering cattle and agricultural crops, breeding waterfowl, laundering, and bathing.

An extraordinary flood in April and May of 1951 led to radioactive contamination of the land adjacent to the river. The floodlands were used by some of the inhabitants for cattle breeding and growing hay. Up to this time, radionuclides had been ingested mainly with water; after the flood, food was contaminated, especially milk and vegetables from flooded kitchen gardens.

In 1953, river water for domestic use—drinking, fishing, breeding waterfowl, and bathing—was banned. The most contaminated areas of the floodlands were excluded from agricultural use. Simultaneously, the construction of wells began but with some interruptions. By the end of 1954, all inhabitants and their cattle on the Techa had been provided with water from underground wells; however, no explanation of the restrictions on use of river water was given, and consumption of river water and its use for other household needs continued on a reduced level until 1956 when a special "river militia" was created to enforce the restrictions in the settlements.

During the first years of contamination, there were 39 settlements on the banks of the Techa river (see table 3.2). In 1953, the evacuation of the village of Metlino began. Metlino happened to be in the most unfavorable situation because it was located on the bank of the Metlinsky pond (fig. 1.2), only 7 km below the site of release. The last of the 1,200 inhabitants of the village were evacuated in 1956. From 1956 to 1960, about 6,300 inhabitants of other settlements were relocated to areas removed from the contaminated river.

According to our calculations, the major exposures occurred between 1950 and 1956. However, a multitude of factors changed during this period, and these changes in amount of radioactivity released, radionuclide composition, hydrogeological conditions, and protective measures made the reconstruction of radiation doses to the exposed population a difficult and complex task.

CHAPTER 3

Doses of Radiation to the Population

Evaluation of Doses Due to External Exposure

The absorbed doses due to external exposure in different settlements along the Techa were estimated on the basis of measurements of gamma ray exposure rates (a) along the banks of the river, (b) on the shore within a few hundred meters of the water, (c) in specified areas of villages, and (d) inside some of the houses. On the basis of these measurements, we reconstructed the average levels of exposure at relevant sites in each of the riverside villages for each calendar year.

The average period of time spent by inhabitants of the different settlements at each of the specified sites with different dose rates was estimated by Professor Melkhior Saurov, Institute of Biophysics, Moscow, who had monitored typical life patterns of different age groups among the inhabitants of the riverside villages in the sixties. On the basis of his analyses, the average annual absorbed doses from external exposure for different age groups in each village were calculated. The results are provided in table 3.1. The technical reports by Professor Saurov did not provide information on the variation in life patterns, and we were therefore not able to estimate the distribution of doses from external exposure;

Table 3.1. Levels of external irradiation for different age groups of inhabitants in Techa riverside villages.

		Average annual absorbed doses, 10^{-2} Gy		
Village	Distance from the site of release (km)	Children (born in 1944-1950)	Teenagers (born in 1935-1943)	Adults (born before 1935)
Metlino	7	106.0	213.0	101.0
Techa Brod	18	99.0	197.0	93.0
Asanovo and Nazarovo	33	71.0	143.0	68.0
Nadyrovo	50	32.0	65.0	30.0
Muslyumovo*	78	5.8	11.0	5.4
Brodokalmak*	109	2.5	4.5	2.4
Russkaya Techa*	138	1.9	3.2	1.9
N. Petropavlovka*	148	1.8	3.1	1.8

*Village currently exists.

instead we used average values for specified age groups and specified settlements. Average whole-body absorbed doses from external exposure that depend on the distance along the Techa river from the site of release are given in figure 3.1.

The highest dose rates occurred in 1951, but the levels in 1950 were not much lower if one assumes that gamma radiation levels in those first years were proportional to the annual releases of fission products into the river. The accumulation of doses due to external exposure ended effectively in 1956 when all inhabitants in the upper regions of the Techa were resettled and when the contaminated floodlands were fenced off. The inhabitants of the village of Metlino received the highest cumulative doses due to external exposure. The overall average dose for the year 1951 alone was estimated to be 0.5-1.0 Gy, but the variation of gamma dose levels was such that individual exposures were estimated to be between 0.05 and 2.0 Gy. In the lower regions of the river in the Kurgan territory (more than 150 km below the site of release), doses due to external exposure did not exceed 0.01 Gy per year, even in the period of massive releases.

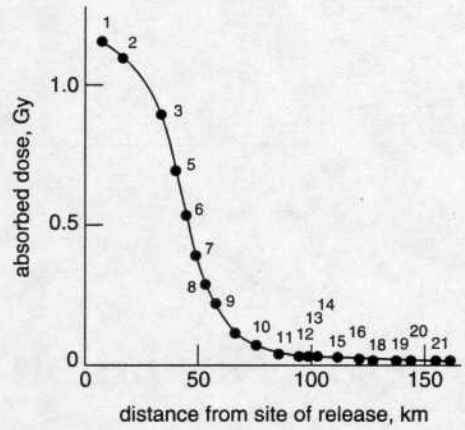

Figure 3.l. Average cumulative, whole-body-absorbed doses from external radiation as a function of the distance along the Techa river downstream from the site of release. • = mean values for settlements, calculated by considering age distributions. Numbers 1-21 = like-numbered settlements in figure l.l.

Evaluation of Doses Due to Internal Exposure

Incorporation of ^{90}Sr in the human body. To calculate tissue doses due to incorporated radionuclides, it is necessary to know the kinetics of their accumulation in different organs and tissues. Among the radionuclides released into the Techa river, ^{90}Sr was the main contributor to internal exposure; ^{90}Sr is accumulated in the skeleton and retained there for many years. Since 1960, scientists from Branch 4 of the Institute of Biophysics, located in Chelyabinsk, have measured beta activity on the surface of the teeth of inhabitants of settlements on the Techa river; this was made possible with detectors that could make such measurements in the mouth of a person. Since 1974, inhabitants of the settlements have also been examined for ^{90}Sr and ^{137}Cs body burdens using a whole-body counter [3]. More than 23,000 measurements were made on about 12,000 people. To measure ^{90}Sr, a phoswich detector was used to measure the bremsstrahlung of the yttrium beta rays. The results of ^{90}Sr measurements of the total body burden and in tooth enamel showed a clear dependence on the year of birth. As seen in figure 3.2, the maximum ^{90}Sr content in the body was observed in those who were teenagers (13-15 years old) during the period of massive releases. The maximum content of ^{90}Sr in tooth enamel was seen in those who were born in 1950, i.e., those who received the maximum concentrations in the first years of life. Dose reconstruction had a twofold base: beta measurements of teeth were used to deduce the yearly levels of intake of ^{90}Sr in different villages and in different age classes. These distributions of intake were then used to

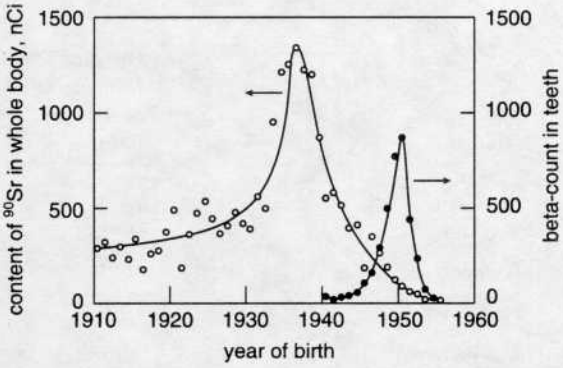

Figure 3.2. Average values of whole-body-counter measurements (o) and beta-count rates of teeth (•) for different age cohorts of residents of Muslyumovo. Left curve: our model calculation on the basis of mean ^{90}Sr intake levels shown in figure 3.3. Right curve: cubic spline circumscribing age dependence of beta-count rates in teeth.

estimate, on the basis of whole-body measurements and a model of age-dependent strontium metabolism, the doses due to incorporated ^{90}Sr and other incorporated nuclides. Both steps of the procedure were somewhat complex and are detailed in our other papers [4-6].

Evaluation of ingestion rates of ^{90}Sr using beta-measurements of teeth. The method of reconstructing ^{90}Sr intake using beta measurements of teeth was developed by Vyacheslav Kozheurov in 1978. It is largely based on the fact that the uptake of ^{90}Sr into tooth enamel has a sharp peak in childhood, and that there is almost complete retention once strontium is contained in the enamel.

As seen in figure 3.2, enhanced beta levels were detectable among those who were children during the period of radioactive releases. The principle of the computations was to express the average values of the observations for the different age cohorts in terms of a comparatively simple model that contains unknown dietary contents of strontium for each year and unknown age-dependent uptake factors, and to determine these unknown parameters in terms of a least square fit of the model to the data. As an example of the results obtained, figure 3.3 shows the ingestion levels of ^{90}Sr for different age cohorts of the population of the village of Muslyumovo for relevant years.

Incorporation of radionuclides in the first 3 years that corresponded to the highest intake rates occurred mostly with water, and ingestion levels of

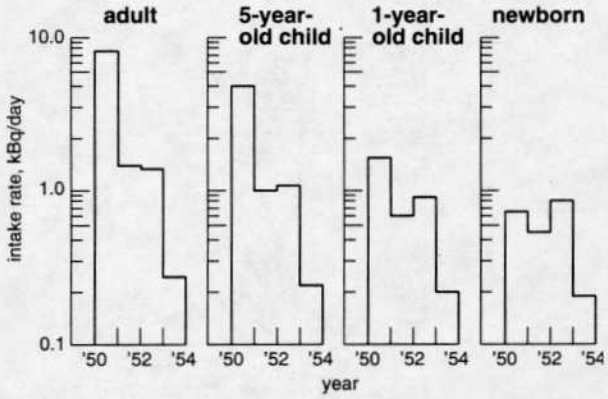

Fig. 3.3. Annual levels of ^{90}Sr intake reconstructed on the basis of tooth measurements for different age cohorts of Muslyumovo residents; "adult" includes those more than 10 years old [7].

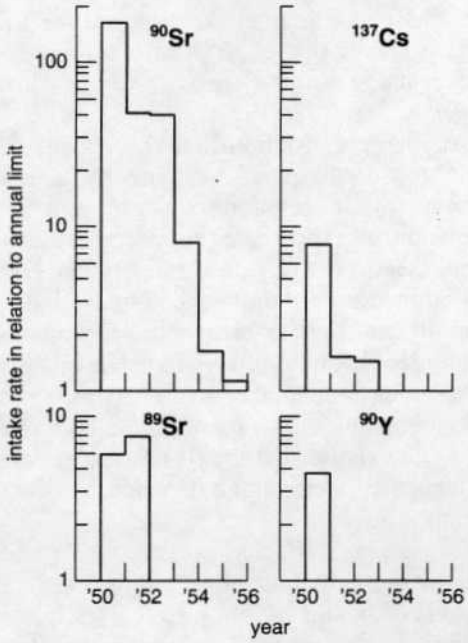

Fig. 3.4. Annual intake levels of major dose-forming radionuclides for adult residents of Muslyumovo in relation to modern Russian limits of intake for the members of a "restricted group of the population" (group B in the Russian regulatory document "Norms of Radiation Safety").

other nuclides were therefore derived from the ingestion of ^{90}Sr scaled in terms of radionuclide composition of the river water. It was thus established that ^{89}Sr and ^{137}Cs were also involved. Figure 3.4 shows the annual ingestion levels of predominant radionuclides for adults in the village of Muslyumovo.

Model of age-dependent strontium metabolism in humans. The detailed model for uptake and retention of strontium in the human body has been described by Degteva and Kozheurov [6]. It was designed to fit data from measurements of long-term retention of ^{90}Sr in the population along the Techa river, but we also used information supplied in various earlier studies. For a 40-year-old adult the generalized model corresponds to Marshall's model [7]. In our studies, the model served to bring the measurements together into a relatively simple framework and thus offset the absence of reliable information on the initial period of strontium ingestion along the Techa river. The essence of the model is an expression for the retention function R(x, t) of the strontium ingested at age x that is taken up and

remains in the human skeleton at time t after the ingestion. See figure 3.5 for strontium retention for different ages.

The content of strontium in the bones was calculated for purposes of internal dosimetry by integrating the product of the retention function and the corresponding ingestion rate. As described in the previous section, the relative ingestion rates were determined according to age at intake in the different villages by the beta measurements of teeth. Scaling to absolute values was achieved on the basis of the measurements of strontium in the skeleton. The computed curve for the ^{90}Sr body burden in figure 3.2 shows that the fit is adequate and that it reflects the essential age dependence of strontium metabolism.

This suggests that the absorbed doses in RBM and in cells of bone surfaces were correctly calculated with the help of the model. Dose factors from earlier publications [8, 9] were used to compute the doses in RBM and bone surfaces from the strontium content in bone.

Apart from the osteotropic ^{90}Sr and ^{89}Sr, a certain dose contribution is also due to ^{137}Cs, which is almost uniformly distributed in the entire body. For evaluation of doses due to incorporated ^{137}Cs, a metabolic model from Publication 30 of the International Commission of Radiological Protection was used [10]; the retention function was modified, however, to take into account the dependence of the excretion rate constant on age.

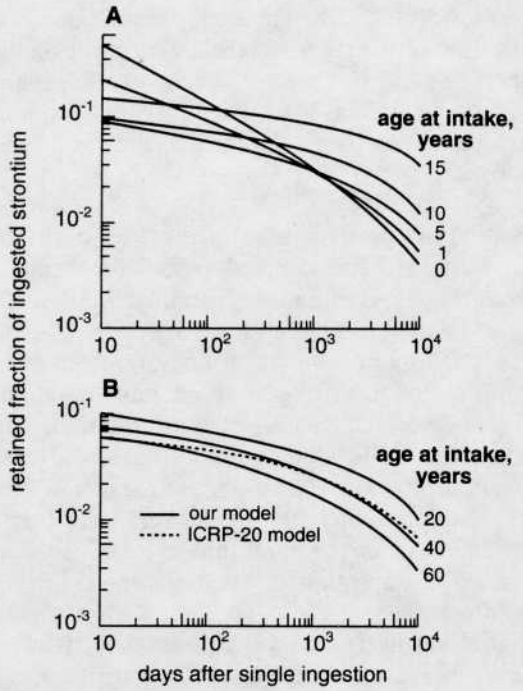

Fig. 3.5. (A) Retention function for newborns, infants of one year, children of 5 and 10 years, and adolescents of 15 years. (B) Retention function for adults of 20, 40, and 60 years in comparison with ICRP-20 retention function [7].

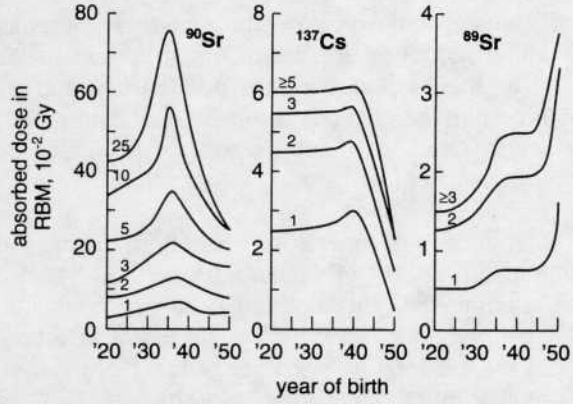

Fig. 3.6. Age profiles of absorbed doses in RBM calculated using models described in chapters 8-10. Input intake levels correspond to the mean values for Muslyumovo residents. Numbers at each curve indicate years of dose accumulation from the onset of intake.

Evaluation of doses due to incorporated radionuclides. The estimated doses due to incorporated radioactivity versus year of birth are summarized in figures 3.6 and 3.7 for RBM and

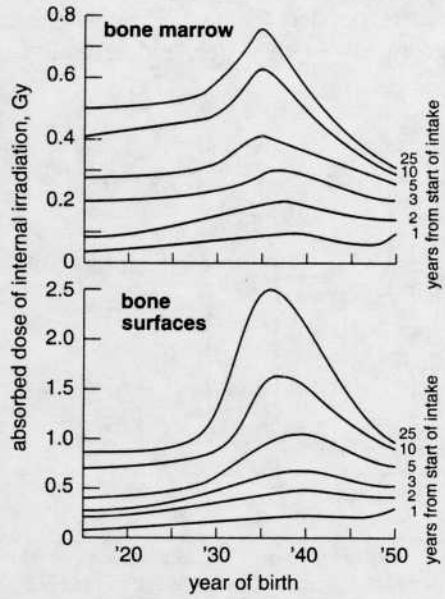

Fig. 3.7. Age profiles of total doses from radionuclides (^{90}Sr + ^{89}Sr + ^{137}Cs) in RBM and bone surfaces of Muslyumovo residents.

cells of bone surfaces according to year from start of intake. These figures show that the youngest age groups were most highly exposed initially. After a few more years there is a distinct maximum of dose for those who were in their teens during the period 1950-1951 of maximum releases of uranium fission products. It was this part of the population that proved to be the critical group in terms of accumulated doses. The highest levels were found in the first years of exposure, and 80%-90% of all doses due to internal exposure were accumulated within the first 10 years. For investigating health effects, the variation of doses due to internal exposure had to be determined as a function of the distance along the river. Measurements of body-content of ^{90}Sr in the inhabitants of the settlements in question were analyzed in detail. This analysis showed that variations of the mean doses due to internal exposure in the inhabitants (corrected for age) reflected two factors: first, with increasing distance from the point of release the radionuclide concentration in the river water was reduced, especially due to dilution of the water by tributaries; and second, substantial differences in body burdens occurred due to the different degrees of providing individual settlements with clean water from underground wells during the period of major radioactive releases. In some villages there were no wells, and all inhabitants consumed the river water; other settlements had nearly enough wells to provide everybody with clean water. A further factor may have been national traditions; there is, for instance, much higher tea consumption among the Tartar and Bashkir populations. Figure 3.8 reflects these various factors and shows the mean values of the doses due to internal exposure of RBM for different villages in the order of their distances from the point of release. The values are average values for individual villages that were determined from whole-body-counter measurements, but they are standardized for age.

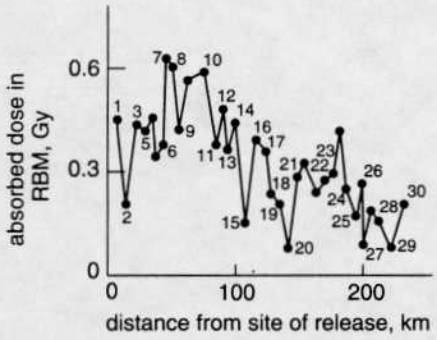

Fig. 3.8. Average RBM doses from radionuclides for residents of different villages. Values correspond to mean levels of whole-body-counter measurements adjusted for age distribution of each village. Scattering mainly reflects fractions of population who drank well water or river water in 1950-1951, which varies for different villages. A time period of 25 years was taken for calculating cumulative doses. Numbers at points identify settlements listed in figure 1.1.

Distribution of Accumulated Dose Among Exposed Populations

Entire Techa river population. Table 3.2 gives the overall results on doses due to incorporated radionuclides and doses due to external irradiation. The absorbed doses in bone differ substantially from those in other tissues because of the high contribution of strontium. This difference increases with the distance from the site of release, in agreement with the increasing relative contribution of incorporated radioactivity. Figure 3.9 shows the distribution of the entire population of 28,100 people that was studied in terms of doses due to internal and external exposure of RBM. More than half of the Techa river population (74%) received doses of less than 0.5 Gy. The median dose was 0.25 Gy, and the mean dose was 0.4 Gy. Such a result is characteristic for many exposure situations. Relatively few people, principally those who inhabit the area close to the source of radioactive contamination, receive substantial doses; lower doses occur in a larger number of people. In this case, only an estimated 8% of the entire population received doses to the RBM greater than 1 Gy, while about 1% received doses that were estimated to be greater than 2 Gy. Preliminary assessment places an upper limit of the range of doses at approximately 4 Gy; however, this may be an underestimation for certain critical groups. Our analysis was restricted to determining average doses in different settlements and different age classes. It would be beneficial to direct further research at improving individual dose estimates.

Cohort of persons with CRS. The approach to individual dose estimates for CRS patients was based on the ratio between measured individual ^{90}Sr content in the skeleton or the teeth and the mean value for the corresponding age group. Multiplication of this coefficient by the corresponding mean dose (taking into account the date of individual diagnosis) yields "individual dose of internal exposure." For persons without individual measure-

Table 3.2. Average organ-absorbed doses (external and internal) for residents of Techa riverside villages (period of dose accumulation = 25 years).

Village	Distance from site of release (km)	Population	Organ-absorbed doses, 10^{-2} Gy				
			RBM	BS	ULI	LLI	Other tissue
Metlino	7	1,242	164.0	226.0	133.0	146.0	127.0
Techa Brod	18	75	127.0	148.0	117.0	121.0	115.0
Asanovo and Nazarovo	33	898	127.0	190.0	97.0	110.0	90.0
M. Taskino	41	147	110.0	168.0	81.0	93.0	75.0
Gerasimovka	43	357	98.0	163.0	66.0	79.0	59.0
Geologorazvedka	45	238	75.0	122.0	52.0	61.0	46.0
Nadyrov Most	48	240	70.0	118.0	47.0	56.0	41.0
Nadyrovo	50	184	95.0	180.0	53.0	70.0	44.0
Ibragimovo	54	184	85.0	170.0	43.0	60.0	34.0
Isayevo	60	434	59.0	119.0	30.0	42.0	23.0
Podsobnoye Khoz.	65	487	63.0	141.0	25.0	41.0	17.0
Muslyumovo*	78	3,230	61.0	143.0	21.0	37.0	12.0
Kurmanovo	88	1,046	38.0	88.0	13.0	23.0	7.5
Karpino	96	195	48.0	115.0	15.0	29.0	7.8
Zamanikha	100	338	36.0	85.0	12.0	22.0	6.3
Vetroduyika	105	163	44.0	106.0	14.0	26.0	7.1
Brodokalmak*	109	4,102	14.0	31.0	5.2	8.7	3.3
Osolodka	125	362	34.0	83.0	10.0	20.0	4.9
Panovo	128	129	38.0	91.0	12.0	23.0	5.7
Cherepanovo	137	222	25.0	59.0	7.7	15.0	4.0
Russkaya Techa*	138	1,472	22.0	53.0	7.1	13.0	3.7
Baklanovo	141	480	7.5	17.0	3.1	4.9	2.1
N. Petropavlovka*	148	919	28.0	68.0	8.7	17.0	4.3
2-Beloyarka	155	386	31.0	75.0	9.4	18.0	4.6
Lobanovo*	163	626	22.0	53.0	7.1	13.0	3.7
Anchugovo*	170	1,093	26.0	63.0	8.1	16.0	4.1
Verkhnyaya Techa*	176	979	29.0	70.0	8.9	17.0	4.4
Skilyagino*	180	492	40.0	90.0	12.0	23.0	5.8
Bugayevo*	186	1,074	25.0	60.0	7.8	15.0	4.0
Dubasovo*	200	703	16.0	37.0	5.3	9.6	3.0
Bisserovo*	202	465	26.0	63.0	8.1	16.0	4.1
Shutikha*	203	1,109	8.0	18.0	3.2	5.2	2.2
Progress	207	205	17.0	40.0	5.6	10.0	3.1
Pershino*	212	1,143	15.0	34.0	5.0	9.0	2.9
Ganino and Markovo	215	220	12.0	29.0	4.4	7.7	2.7
Klyuchi*	223	1,309	7.5	17.0	3.1	4.9	2.1
Zatecha*	237	1,135	17.0	40.0	5.7	11.0	3.2

*Village currently exists.
Note: RBM = red bone marrow; BS = bone surface; ULI = upper large intestine; LLI = lower large intestine.

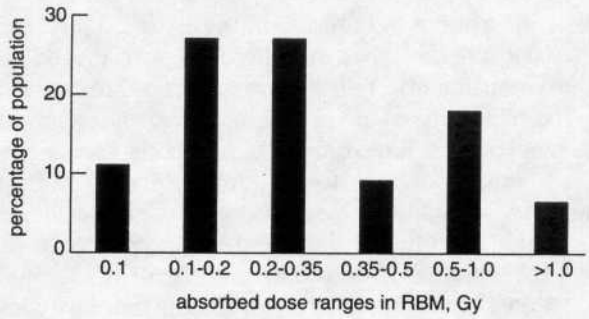

Fig. 3.9. Approximate distribution of total RBM doses in the Techa river population. Total absorbed dose in RBM is the cumulative dose of external radiation + cumulative (25-year) dose of internal radiation ($^{90}Sr + ^{89}Sr + ^{137}Cs$). Total doses were calculated for each age group of each village, and these groups were then gathered into six large groups in accordance with the bounds of RBM dose intervals.

ments, mean internal doses accumulated to the date of diagnosis for corresponding age group and settlement were ascribed.

Age-, time-, and settlement-specified mean values were taken as "individual doses due to external irradiation" for persons with CRS. Table 3.3 presents the accumulated doses in the cohort of persons with CRS.

As seen, the picture is similar in general to the dose distribution for the entire population, but a small displacement to the right is observed (63.3% of the people received doses less than 0.5 Gy, and 82.1% received less than 1.0 Gy). It should be noted also that the period of dose accumulation for the cohort in table 3.3 is considerably shorter than for the entire population. Nevertheless, about 18% of CRS patients had received doses to the RBM that were greater than 1.0 Gy by the time of diagnosis.

ICRP Publication 41 [11] states that the thresholds for nonstochastic effects of ionizing radiation depend on dose rate rather than on accumulated dose. The following threshold values were accordingly set up for chronic radiation conditions: 0.4 Sv per year for the suppression of hematopoiesis and 1.0 Sv per year for lethal aplasia of bone marrow. Table 3.4 presents maximum annual doses in RBM in CRS patients. Because the rate of dose accumulation was uneven over time, the maximum annual values for each patient were taken. As seen, about 85% of the patients were exposed to dose rates of less than 0.4 Gy per year, and only one patient received more than 1 Gy.

Table 3.3. Accumulated dose in RBM of CRS patients.

Dose interval, Gy	Number of patients	Percentage
<0.1	82	8.72
0.1-0.2	144	15.32
0.2-0.3	163	17.34
0.3-0.4	102	10.85
0.4-0.5	104	11.06
0.5-0.6	46	4.89
0.6-0.7	46	4.89
0.7-0.8	38	4.04
0.8-0.9	23	2.45
0.9-1.0	24	2.55
1.0-1.5	120	12.77
1.5-2.0	27	2.87
>2.0	21	2.23

Thus, we have three possible versions for interpreting findings on dose distribution in the cohort of persons with CRS:

(1) Some individual dose assessments are incorrect.

(2) Some diagnoses are incorrect.

(3) The presence of other harmful factors besides ionizing radiation caused the thresholds for nonstochastic effects in RBM in this cohort to be lower than the ICRP-41 values [11].

Table 3.4. Maximum annual dose in RBM of CRS patients.

Dose interval, Gy/year	Number of patients	Percentage
<0.1	457	48.6
0.1-0.2	218	23.2
0.2-0.3	84	8.9
0.3-0.4	38	4.0
0.4-0.5	99	10.5
0.5-1.0	43	4.6
>1.0	1	0.1

Each of these versions must be examined, and the possible sources of errors in dose assessment and diagnoses are considered below.

Dose Estimation Evolution: Significance of Individual Dose Uncertainty

Significance of strategy of dose assessment. The first assessment of population doses in settlements on the Techa river was made in 1956 by Dr. Alexander Marey (1907-1987). The main task at that time was to estimate exposure levels for critical groups and to take protective measures. It was dangerous to people's health to underestimate exposure levels in those conditions. Besides, there was insufficient knowledge about radionuclide metabolism in the human body and quantitative parameters for dose calculations. For these reasons the first assessments of doses were very high (18-28 Sv) to the bone tissue for Muslyumovo residents (it should be noted that, in the fifties and sixties, the dose in rad was multiplied by a factor of 5 to obtain the equivalent dose in rem; this was intended to take into account uneven distribution of ^{90}Sr in bone). Perhaps, some of the physicians who were involved in the investigation of the population at that time were informed of the values of dose estimates but were inclined to diagnose any health impairment in patients who received high doses as CRS. After the sixties, the main goal of investigators became the correlation of biological effects observed in the population with the levels of radiation doses. In such conditions, overestimation of doses could become the cause of underestimation of risk coefficients per unit of dose, so all subsequent dose estimates were lower. The principal strategy in dose reassessment was to arrive at the most accurate estimates of probable doses and to evaluate their reliability.

Sources of uncertainty in dose assessments. It is important to identify the main sources of uncertainty in dose assessments: incomplete initial data, insufficient accuracy of measuring techniques in the fifties, and imperfect concepts and models used for dose evaluation. It is obvious that in retrospective studies we cannot do anything about the initial data. Data were specifically related to external doses that were based on gamma-field measurements in periods of massive release (1951-1956) and the findings of life-pattern monitoring in the sixties. These sets of data are described in technical reports that do not give sufficient details that might be used to evaluate the reliability of the data. Therefore, under current concepts, we have only data points that are mean-in-group estimates for external doses. A current study will connect measurements of radionuclides in objects in the environment with exposure to external gamma fields into the same data set. We will reconstruct the uncertainty in gamma fields by computer simulation and evaluate the uncertainty in individual external doses by means of stochastic modeling of life patterns. Internal dose assessments are based on a a multitude of measurements of ^{90}Sr in the whole body and the teeth, and we have enough statistics to evaluate the distribution of individual ^{90}Sr contents [3]. The usefulness of whole-body counting for reconstructing doses of ^{90}Sr intakes received decades earlier is confirmed by Toohey *et al.* [12]. For our current concept of internal dose reconstruction we suggest the use of (1) the same age-dependent relative intake rates for the entire Techa river population, (2) the same radionuclide composition of ingested radioactivity for the entire Techa river population, and (3) the same age-dependent values of parameters in biokinetic and dosimetric models. Thus we neglect the difference in radionuclide composition of intake that was dependent on the water supply source and do not take into account individual variability in metabolic parameters. The work on reassessing internal doses has started, and the analysis of the approaches to individual doses are provided in the paragraphs below.

Approaches to assessing individual internal doses. The first approach to assessing individual doses for residents on the Techa river—"mean-in-group"—is described in sections entitled "Evaluation of Doses Due to External Exposure" and "Evaluation of Doses Due to Internal Radiation" at the beginning of this chapter. These estimates were used for constructing dose distribution in the entire population. But the significant heterogeneity in measured levels of individual ^{90}Sr body burdens within each age group for every settlement restricts the possibilities to use such assessments for particular samples of individuals along the Techa, for instance, in the cohort of persons with CRS.

Another approach to dose assessment is based on the ratio of individual ^{90}Sr content in the skeleton or the teeth and the mean value for an age group. Multiplying this coefficient by the corresponding

mean dose yields "individual dose." The defect in the methodology of this approach, which gives a point and not an interval dose estimate, consists of the following: the principal factor determining dose variations (specifically in age) is the variation in radioactive water consumption. Because measurement of ^{90}Sr dates dozens of years after ^{90}Sr intake, these variations are overlapped, for example, by variations in excretion rate, tooth formation rate, etc. It should also be mentioned that we measured ^{90}Sr content either in the compact bone matter or in the teeth, and the doses, for example, to the bone marrow were obtained mainly at the expense of radionuclide content in the spongy matter of the bones. Thus, this approach can bring about a distortion of the actual absorbed dose distribution. It is also impossible to determine the dose for those in whom no ^{90}Sr content had been measured, because of death for example, and also for those whose radioactivity levels were too low to be detected by the time measurements were conducted, especially for a considerable number of elderly people on the lower Techa river.

Neither approach takes into account the differences in isotope composition and the dynamics of radionuclide intake in the groups that used clean and radioactive drinking water. The basic concept we are going to use to revise internal doses is "family ecology."

We assume that all persons living in a private house use a common source of drinking water, drink milk from the same cow, eat vegetables from the same kitchen garden. Food composition is also assumed to be the same, as the residents usually have their meals together and eat the same food. The attitude toward sanitary and safety measures (prohibited use of river water, evacuation, recommendations to use the water of the wells, etc.) is common for all members of the family. The community of ethnic traditions is also essential. It is the difference in specific dietary activity on some private farms that accounts for much of the measured content variance. In view of the above, a correlation must exist: members of families whose specific dietary activity was above mean values will also show measured contents exceeding mean values, and families with low specific dietary activity will show low (on the average) measured contents. The coefficient of variations connected by the group correlation must be the same. Therefore, the mean relative contents for a family as a whole and the individual variations should be considered. Our tentative assessment of 20 families confirmed that the variability coefficient remains constant and is about 40%. Thus it becomes possible to estimate the ^{90}Sr content in individuals for whom no measurements were previously made on the basis of their having lived in the same house with those in whom such measurements were made. An internal family variability coefficient may be used as the measure of uncertainty. Thus the problem of uncertainty in individual dose estimates has not been solved in this study. We hope that a new approach to individual dose assessments, development of radionuclide transport models in the river system, development of a model for intake reconstruction as well as metabolic models will provide more well-founded conclusions concerning individual dose estimates in our further studies.

CHAPTER 4

Methods Used in Diagnosing Chronic Radiation Sickness

Concepts of Diagnosis of Chronic Radiation Sickness

Terminological aspects. The question of CRS as a separate clinical entity has not yet been resolved by organized medicine. In the *International Classification of Diseases* (ICD) [13] and the *Guide to International Statistical Classification of Diseases, Trauma, and Death Causes* [14], radiation effects and their early reactions and late manifestations are listed in the section devoted to accidents, poisoning, and trauma, but no mention is made of CRS. Updated versions of the ICD take into account new achievements in medical science such as the discovery of previously unknown etiologic factors of some diseases (for example, AIDS) but do not contain the term "chronic radiation sickness."

The oversight may be due to the fact that nowhere else but in Russia did such prolonged effects of significant rates of ionizing radiation occur in man, with a more or less uniform dose distribution in the body resulting in the development of a pathological process. At that time, priority was given to keeping secret the fact that an off-site population was being exposed for several years to an open source of ionizing radiation at considerable rates. Information on the radiation releases and their health effects was classified and that may be the reason why cases of this pathological condition with a clearly outlined etiology, definite pathogenesis, and dynamics of clinical symptomatology were not included in ICD nomenclature. In the USSR, the ICD was not recognized until 1966. Data on chronic overexposure of the work force at the plants that produced plutonium for weapons and processed radioactive waste materials causing the radiation accidents in the Urals and their effects first appeared in the open press in 1990 [15, 16]. However, the difficulties in creating a list of radiation effects, CRS in particular, were not only due to the secrecy that had existed until 1990—the very essence of this pathological condition had not yet been elucidated with enough detail.

The term "chronic radiation sickness" appeared in publications of the thirties and forties, and it most often signified either long-term results of an acute radiation exposure [17, 18] represented by leukemia, skin cancer, or cataract, or it signified a localized radiation trauma manifested by burns, radiation ulcers, or hyperkeratosis, most often resulting from locally applied high doses of radiation. Later it became clear that an acute radiation effect does not assume the form of CRS with time.

Definition and classification of CRS. All countries except the USSR (currently Russia) still consider that the response to repeated or long-term exposures to small doses of ionizing radiation may be manifested by a hematopoietic reaction, most commonly by moderate leukopenia. Such shifts in the blood-forming system were recorded for the participants in the Radium Project and for roentgenologists who began working in the thirties and continued working for many years. These changes were considered a reaction to radiation (a biological response of the organism to radiation) and not a separate clinical entity. The authors of the clinical classification of various forms of radiation sickness in the USSR were A. K. Guskova and G. D. Baysogolov [19, 20].

Before that, according to the authors of the monograph [20], radiation pathology [21, 22] was only referred to as "some amorphous general form of radiation disease."

A. K. Guskova and G. D. Baysogolov [20] gave the following definition of the notion of CRS: "Chronic radiation sickness is a complex, clearly outlined clinical syndrome occurring as a result of the long-term exposure of the organism to radiation, single or total doses of which regularly exceed the dose permissible for professional exposure." This definition does not quantitate the permissible irradiation doses for plant personnel. According to the radiation safety standards adopted in the USSR, these norms were different at different times.

> "Chronic radiation sickness is characterized by a certain dynamics of the clinical course directly related to radiation load formation, a combination of slow build-up of radiation affections and signs of compensatory processes and adaptive reactions. Individual symptoms and even clinical syndromes are not characteristic exclusively of radiation sickness but their very sequence may be considered as a characteristic feature allowing to distinguish chronic radiation sickness as a separate clinical entity. As a rule, a correct, well-grounded diagnosis of chronic radiation sickness caused by general irradiation does not present a great difficulty and may be established at any therapeutic or prophylactic institution.
>
> "Two variants of chronic radiation sickness are distinguished: (1) one with a developed clinical syndrome resulting from general external irradiation or incorporation of isotopes uniformly distributed in the body; and (2) the other with a clinical syndrome manifested mainly by affections of individual organs and systems due to internal or external irradiation." [20]

In their classification of CRS, the authors distinguished three degrees of gravity. It was emphasized, however, that the distinction of degrees of gravity of CRS is to a certain degree a matter of convention. CRS of first degree of gravity (mild) is characterized by neuroregulatory disorders in different organs and systems (cardiovascular system in particular), presence of unstable moderate leukopenia, and less frequently thrombocytopenia. The second degree (medium gravity) is associated with more pronounced regulatory disorders accompanied by the development of functional insufficiency of digestive glands and the cardiovascular and nervous systems, and signs of anatomic damage of radiosensitive tissues, hypoplastic status of hematopoiesis, changes in the myelin of the CNS conduction tracts, and disturbances of some metabolic processes. The third degree of gravity (severe) is characterized by destructive processes in the hematopoietic tissue, atrophic changes in the mucous membrane of the gastrointestinal tract, myocardial dystrophy, disseminated encephalomyelosis with a mild course, and, in cases of weakened general immunity, infectious/septic complications.

CRS is also classified according to the stages of development. Development of the first stage coincides with the period of accumulation of most of the total irradiation. The second stage is the stage of recovery, and it usually starts 3 to 12 months after cessation of irradiation or after a significant decrease in irradiation levels to levels of permissible doses or below. During this stage, the cycle of major destructive changes is usually over, and repair processes predominate. The third stage includes outcomes and sequelae of CRS; the outcomes may be a complete recovery (cure), recovery with a complicating defect, or progression of the disease toward leukemia, hypoplastic anemia, or tumors in different locations.

CRS in personnel of Mayak nuclear complex. The classification of CRS described above was established in the early sixties [20], but the working scheme of classification and periodization [19] of CRS was applied in practice as early as 1950 by physicians serving personnel who were producing plutonium for weapons at Mayak. The scheme came into being as a response to the needs of everyday practical work at the time when some of the workers of the plant were exposed to radiation at annual doses of 2.0-4.5 Gy [23]. The diagnosis of CRS was made for 1,596 workers, 632 of whom developed the disease by 1954. One of the specialists in radiation medicine who had been working in Mayak's health care system since the early fifties wrote, "I have available data on the course of CRS in 1,355 workers of type "A" plants (first production-type reactors) and type "B" plants (for separation of irradiated uranium). In 1949-1954 these persons were exposed to a significant over-irradiation. The doses of the total gamma-radiation received per

working day often amounted to over 3-12 rem or more, and the total doses received during 2-4 years of work were 200-600 rem or more. In addition, all of them were exposed to a wide spectrum of radionuclides." [24, 25]

Maximum annual doses ranged from 0.4 to 4.5 Gy, with the total dose of external gamma irradiation amounting to 1.0-9.33 Gy over 0.8-6 years of work. The distribution of accumulated doses in a representative group of workers with the diagnosis of CRS was as follows:

1.0-2.0 Gy	31.8%
2.01-4.0 Gy	44.6%
4.01-6.0 Gy	18.8%
6.01-9.33 Gy	4.8%

Women accounted for 36.6% of workers with diagnosed CRS.

Among the clinical manifestations of CRS, the most common were disorders of the hematopoietic system, chiefly changes in morphological composition of the peripheral blood, manifested by cytopenia (leukopenia, thrombocytopenia, neutropenia). The erythrocyte count was found to be reduced but did not fall below the lower limits of the physiological norm. At maximum annual doses ranging from 1.01 to 2.0 and from 2.0 to 4.0 Gy, the incidence of bone marrow hypoplasia during the period of development of CRS was 16% and 32%, respectively. Within 5-10 years after exposure to radiation, most of the patients' values characterizing morphological composition of peripheral blood had returned to normal limits, but in 7.3% of cases a moderate hypoplasia of the bone marrow was noted. The syndrome of impaired neurovascular regulation was documented in 78%, asthenic syndrome occurred in 58%, and the organic CNS affection syndrome of an encephalomyelosis type was noted in 24% of patients with diagnosed CRS. During the period of development of CRS, chronic gastritis was diagnosed in one fourth of the patients, mainly associated with hyposecretory disorders.

In two cases, CRS led to the development of aplastic anemia 2-4 years after radiation exposure started [25]. Development of leukemia resulting from CRS was observed in 11 workers at Mayak; in 7 cases acute leukosis led to fatal outcomes in the years 1952 through 1961 [25, 26]. The mean age of persons who died of leukosis was 38.1 years.

Doshchenko [24] gives a description of a case of CRS developing into acute leukosis (hemocytoblastosis) in the young worker Alexander Aliyev. He had been working at the atomic industry enterprise for 6 months and had received a total dose of external radiation of 668 rem. The initial period of the disease was characterized by hypoplasia of hematopoietic tissue (moderate leukopenia and pronounced thrombocytopenia in the peripheral blood), and the second stage of the disease was manifested by poorly differentiated leukosis that caused the patient's death at the age of 29.

Diagnosis of CRS in the Population on the Techa and the Role of Visiting Medical Teams

The first examinations of exposed people living in the Techa riverside villages were conducted by the same specialists who established the diagnosis of CRS in the workers at Mayak.

As indicated above, over the 2 years after releases of radioactive wastes into the Techa, no measurements of radionuclide content in the river water and bed deposits and no measurements of gamma background levels on the banks of the river and in the riverside settlements were made. According to the information given by the corresponding service of the facility, releases of radioactive wastes started in the fall of 1949. Specialists first visited the Techa area with the purpose of assessing the radiation situation in the summer of 1951.

Even the first measurements showed that in some areas on the shores of Metlinsky Pond (the village of Metlino was located 7 km from the site of releases of radioactive wastes) the gamma background level amounted to 5 R/hour. In this connection, suspicions arose as to the probability of radiation-induced pathological conditions occurring in the inhabitants of the riverside villages who had been exposed to an open source of ionizing radiation, the river, for 2 years by that time.

In order to carry out medical examinations of the population, visiting teams of physicians of the Medico-Sanitary Department No. 71, which provided medical services to the workers of the plant, were organized. In the summer of 1951, a part of the population of the village of Metlino was examined. A year later, a second visit of specialists was organized to conduct a follow-up examination of Metlino residents and also to examine the population of some other villages located in the lower reaches of the Techa. It was at that time that the first cases of CRS were diagnosed in the exposed off-site population.

In spite of the fact that the majority of the physicians of the visiting teams had gained a certain clinical experience in diagnosing and treating CRS, correctly diagnosing radiation effects in the exposed population presented a considerable difficulty for them. First, in contrast to the workers at Mayak, the off-site population had no individual dosimeters, and no information on radiation levels was available to the physicians. The fact of exposure of the population to a radiation source was recorded on the basis of personal interviews that contained the following questions:

- How long had the resident been living in the village;
- At what distance from the river was the house situated;
- Was river water (or well water) used and for what purposes (drinking, cooking, watering the cattle);
- Whether he/she had bathed in the river;
- Whether fish were caught in the river; and
- Whether the kitchen garden was flooded with river water during floods.

The answers were recorded in the residents' medical records. Second, in contrast to workers at Mayak, information on the basic state of health of the population before exposure started was very scarce. People of all ages were irradiated in the riverside villages: children and teenagers, professionally active people, and elderly people. Many of them had general somatic diseases diagnosed not by doctors but by paramedical personnel who provided medical services to the residents of the villages. Medical records containing information on such conditions had not been preserved as a rule.

The program for visiting examinations usually included (a) questioning patients about any complaints relative to their health, (b) recording any past diseases, (c) assessing general health (pediatric status for children), (d) assessing neurological status, (e) gynecological examinations for women, and (f) peripheral blood analysis including counts of all corpuscular elements.

Information on radioactive contamination of the river and the territory of the villages, external irradiation of the residents, and ingestion of radionuclides was concealed from the population. The people did not understand why these mass medical examinations were given, so they often gave inadequate descriptions of their complaints.

The diagnosis of CRS presented considerable difficulty for physicians because they were aware of the significant contamination of the territory but lacked information on individual levels of exposure and basic health.

Screenings to Identify Radiation Effect Cases

There were certain periods in the history of establishing the new clinical entity "chronic radiation sickness" and individual dose assessment methodology when the condition was diagnosed with different degrees of certainty. With growing expertise in assessing individual irradiation levels, improved observation of the exposed population, and the accumulation of data obtained by comparing their state of health with unexposed populations living under approximately the same conditions, the diagnosis of CRS became more substantiated. During these periods, the question of the expediency of a retrospective reassessment (revision) of previously established diagnoses was repeatedly raised in view of new information appearing. Decisions about the consistency of the diagnoses were in most cases made on a collegial basis. To have a clear notion of radiation effects in the Southern Urals a detailed description of the methods used for diagnosing radiation-induced pathology in different periods and at different institutions should be known.

The period from 1950 through 1951 had the highest annual dose rate and a lack of diagnosed cases of radiation effects because specialists were completely unaware of the off-site population exposure and did not conduct any purposeful observations. Any cases of possible radiation-related illnesses would have been classified in general somatic diseases.

During 1952 and 1953, radiation exposure from external radiation and from incorporation of long-lived radionuclides was going on. Visiting teams of medical specialists with a certain expertise in diagnosing radiation effects at Mayak conducted the first medical observations of the population in the upper reaches of the Techa, and it was at that time that the first isolated cases of CRS were diagnosed.

From 1954 to 1956, a significant decrease in discharges of radioactive wastes into the Techa, a cessation of radionuclide ingestion with drinking water, and a reduction in annual dose rates were observed. Two specialized dispensaries established at that time had to provide follow-up examinations and treatment for the irradiated population. These two institutions employed medical specialists without any expertise in radiation medicine. However, thanks to the establishment of these institutions, mass prophylactic examinations of the population were made and, as a result, a larger number of CRS cases were diagnosed.

To accurately and retrospectively assess the situation in 1954-1956, we must consider that, in addition to objective symptoms that formed the basis for diagnosing CRS, both the individuals examined and the physicians who made the diagnoses were influenced by certain emotional and psychological factors. It is in these years that a number of protective and hygienic measures aimed at reducing radiation rates and abating the impact of radioactive contamination were carried out. These measures included providing a water supply from ground sources (wells), prohibiting the use of river water by fencing off the river and its floodlands with barbed wire, using "river militia" patrols, and evacuating the population from a number of riverside villages. At the same time, the exposed population was still kept in the dark about the reasons for taking all those measures. The people were naturally worried by the lack of explanation and the necessity to abandon their habitual ways of life. Mass medical surveys intensified their suspicions that their life and health were endangered. Such was the sociopsychologic situation in which radiation effects were revealed and diagnosed.

Judging by the reports prepared at that time, 1,159 cases of CRS were diagnosed; the condition was recorded in every fourth individual examined. In some communities in the upper reaches of the river and in the village of Metlino in particular, the disease was diagnosed in 64.7% of examined adults and in 63.1% of examined children. However, there were a considerable number of diagnosed cases of CRS (in about 5.5% of examined individuals) recorded in the communities of the lower reaches of the Techa as well as in the Iset riverside area.

Verification of the irradiation rate was eventually accomplished. Environmental monitoring carried out every year suggested that the external dose accumulated in individuals residing in those localities could hardly exceed 20 rem; it actually averaged about 3 rem. It became possible to tentatively estimate the presence of radionuclides in the human organism by using the method for measuring the number of beta-radiation impulses in the excreta; it was thus demonstrated that the doses received by the residents of the lower Techa and the Iset riversides could hardly be regarded as the threshold for CRS.

The "control" cohorts composed of nonirradiated people living under similar social and hygienic conditions became a component of the structure of follow-up studies. Attempts were made to single out the most typical manifestations of radiation pathology by comparing findings of the examinations for both exposed and control cohorts.

Residents of the riverside communities were evacuated from 1957 to 1961. During this period the annual dose rate was estimated only on the basis of radionuclides incorporated in the body, and it was considerably lower than in the earlier periods. Mass dynamic prophylactic examinations of the exposed population were continued, but only isolated cases of CRS were detected.

There was a growing awareness that it was practically impossible to substantiate the diagnosis of CRS without taking into account the individual irradiation dose, i.e., a reliable diagnosis of CRS could not be made on the basis of only the findings of examinations conducted by the medical staff of outpatient departments or by visiting medical

teams. Consequently, no diagnoses were made after 1956 solely on the basis of examinations conducted by outpatient and visiting consultants. If the condition was evaluated as suggestive of CRS, the patient was referred to a specialized dispensary for a detailed examination (including individual dose estimation) and treatment. Sometimes the choice was made between the two Moscow clinics: the clinical department of the Institute of Biophysics (Clinical Hospital No. 6) and the Nutrition Institute. The diagnosis of CRS was either confirmed or rejected by experts at these institutions. Thus, medical examinations assumed the character of screenings.

Principles of Dynamic Follow-Up

In the absence of information on individual doses of irradiation, even an inpatient examination (especially if performed only once) did not guarantee against mistakes in diagnosing radiation effects. A case of CRS diagnosed by the experts of the Institute of Biophysics can serve as an example.

Extract from Case History

> Patient R., born in 1932. Hospitalization lasted from 3 December 1956 to 16 January 1957. She is a resident of a village situated approximately 700 km (downstream) of the contamination source. However, the amount of radioactive substances ingested with drinking water and food exceeded the permissible limits tenfold in this area.
>
> Patient's complaints: General weakness, increased fatigability, headaches (beginning in 1954), anorexia. Evaluation of the patient's objective symptoms revealed moderate hypotonia and insufficiently developed subcutaneous fatty layer.
>
> Laboratory findings: The myelogram showed normal findings. Peripheral white blood cell count was 3,100-3,700 x 10^9/l, thrombocyte count was 225-268 x 10^9/l. Radiochemical studies of urine and stools yielded negative results.
>
> Conclusion: In view of the patient's past history, clinical findings, laboratory findings, obvious exposure to radioactive substances in doses exceeding permissible limits, we consider it unreasonable to exclude a possible role of radioactive substances in the development of the pathological process in this patient.
>
> Diagnosis: Stages I and II of CRS.
>
> Concurrent diagnosis: Cystitis, slight bile duct dyskinesia.

According to findings obtained in later periods, it is unlikely that the exposure rates exceeded the natural background by 1-2 cSv in the area where the patient lived. The tenfold increase in the permissible dose, which was recorded in the patient's case history, was 5 cSv, since the dose limit for a restricted portion of the population was determined to be 0.5 cSv.

The patient's complaints and the objective signs fit well into the symptomatology of the general somatic diseases she had. There was no reason for making the diagnosis of CRS. It is obvious that in this case, as A. K. Guskova and G. D. Baysogolov wrote in their book [20], the diagnosis was influenced by an "insufficiently critical attitude of the researchers who assigned every pathological process in exposed persons to CRS manifestations, the more so because they had no detailed information on dose levels available. Our clinic was not free of such errors either."

With an increasing understanding of the difficulties of diagnosing CRS, it became clear that a conclusive diagnosis should be based not only on a detailed examination at the inpatient department but due consideration should also be given to the findings on dynamic follow-up. A new kind of hospital record form for patients with suspected CRS was introduced, the patient's attendance card. It was used for registering the patient's follow-up visits to the hospital. Patients were invited to undergo follow-up examinations (or treatment, if necessary) every 6 months during the initial course of the disease and annually thereafter.

Dose verification brought about the necessity to revise the CRS cases diagnosed earlier. Such reassessments were mainly performed from 1959 through 1964 by a commission of medical specialists and were based on all relevant medical and dosimetric information. The leading experts in radiation medicine with experience in diagnosing ra-

diation effects in personnel of the Mayak facility were engaged in analyzing the certainty of diagnosis in CRS cases in the population irradiated on the Techa and Iset. As a conclusion to this analysis they wrote, "taking into account a comparatively low radionuclide body burden and the fact that CRS, especially in its first stage, has no specific features inherent to only this clinical entity, such a high morbidity rate seems doubtful."

The case ascertainment analysis made it possible to identify a number of erroneous, insufficiently grounded CRS diagnoses. It concerned, in particular, the 128 cases of CRS diagnosed in Iset riverside residents.

Medical Records

The information about the presence of CRS in an individual patient was entered into three medical documents: individual outpatient card (medical record book), patient's case history, and patient's attendance card. The latter document was aimed at establishing control over the regularity of follow-up examinations and contained the date of the next medical examination the patient had to undergo.

The documents containing medical records have been retained in the archives of the Urals Research Center for Radiation Medicine since 1951. The archives also contain abstracts from case histories of those patients who underwent treatment at Clinical Hospital No. 6 in Moscow. However, to ensure secrecy, the diagnosis was not indicated as "chronic radiation sickness." The abbreviation ABC (astheno-vegetative syndrome) was used to designate CRS, or it was recorded as "specific effect," "specific injury," or indicated on the title page of the patient's card in a codified form as "st. 1", which signified stage 1 of CRS. The meaning of this conventional marking was known to the medical personnel of the clinic.

None of the previous diagnoses of CRS was deleted; the information on the new diagnosis and the date of its establishment was just written next to the earlier date. This information allowed an analysis of the dynamics of the patient's condition. However, over the 40 years, the paper of the medical records has worn out, and the records have become illegible in some cases.

Unfortunately, up to the present time, data on the medical follow-up of the total exposed population have not been entered into a computer because of technical and financial conditions. Within the framework of this report, a portion of information from the medical records of patients with diagnosed CRS has been entered into a computer.

CHAPTER 5

Characterization of Population with Diagnosed Chronic Radiation Sickness

After a review of all types of existing medical records (case histories, outpatient cards, medical follow-up cards), it was possible to confirm the diagnosis of CRS in 940 individuals exposed to radiation in the villages on the Techa river[1]. This number did not include cases in which the diagnosis of CRS was first suspected and then ruled out because further investigations, usually conducted at an inpatient department, failed to confirm the diagnosis.

Time of First Diagnosis of CRS

Although radioactive releases into the Techa river started in the fall of 1949, radiation exposure in the riverside villages was not assessed until the summer of 1951. At that time, the first medical examinations were made of some of the residents of Metlino, a village situated 7 km from the release site. CRS was suspected in some of the residents who were examined. The first diagnosed cases of CRS date back to 1952. Table 5.1 and figures 5.1 and 5.2 show the years when cases of CRS were diagnosed.

Table 5.1. Diagnoses of CRS, 1952-1973.

Year	CRS cases	Percentage of diagnoses established
1952	16	1.70
1953	36	3.83
1954	33	3.51
1955	253	26.91
1956	287	30.53
1957	128	13.62
1958	125	13.30
1959	24	2.55
1960	3	0.32
1961	6	0.64
1962	10	1.06
1963	8	0.85
1964-69	9	0.96
1970-73	2	0.21
Total	940	100.00

Only 5% of the total number of 940 cases of CRS were diagnosed during the first 3-4 years of radiation exposure at the highest annual dose rates. The highest number of cases were registered in 1955 and 1956 when access to the river was already restricted and body intake of radionuclides in the riverside villages was sharply reduced.

Would it be reasonable to assume that the data cited above confirm a specific character of the disease course, i.e., that the symptoms of CRS developed in later periods as a result of accumulating substantial doses even though by that time dose rates on the Techa were already reduced? The assumption may be valid, but while analyzing the dates of CRS

[1]After these 940 individuals were identified and studied, we elected to redefine the criteria for establishing a diagnosis of CRS (see chapters 9 and 10). Only 66 of the 940 cases meet these revised criteria. Reasons for continuing to apply the diagnosis of CRS to the entire group are discussed in chapter 8 in the section entitled Social Aspects of Diagnosis Reassessment.

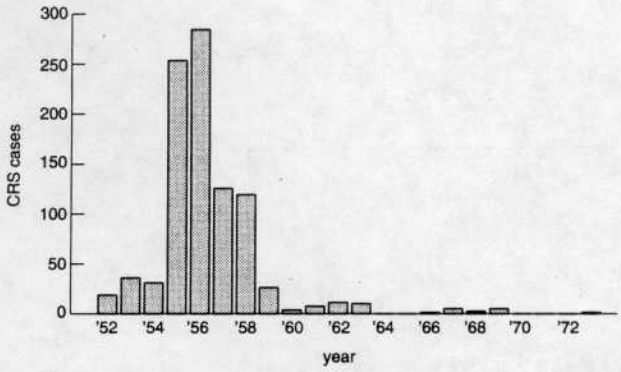

Fig. 5.1. Time of diagnosis of CRS.

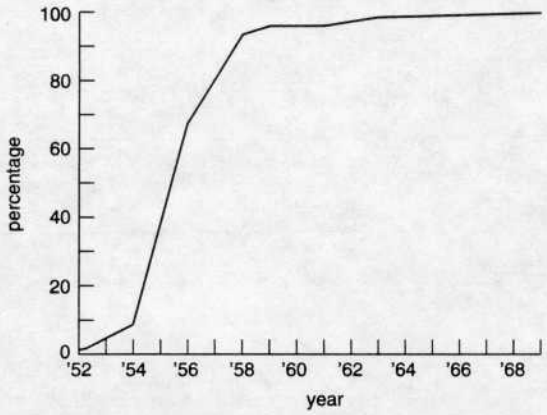

Fig. 5.2. Time of diagnosis of CRS (accumulation curve), 1952-1969.

diagnosis, only isolated CRS cases could be diagnosed before mass medical examinations of the population started. Such examinations became routine in 1954 when two specialized medical institutions were established for rendering medical services to the irradiated population: Dispensary I in the Chelyabinsk region and Dispensary II in the Kurgan region. One of the purposes of the examinations was to decide whether resettling the residents of the riverside villages was advisable. Table 5.2 provides the number of persons examined and those diagnosed with CRS in the first 10 years after exposure started (data were derived from annual medical reports).

In 1955 and 1956, CRS was seldom diagnosed at an inpatient department; most cases were diagnosed during visits for periodical outpatient health surveys. In later years, the diagnosis, as a rule, was made on the basis of dynamic assessment of symptoms recorded during an examination conducted at an inpatient department. An important point is that

Table 5.2. Medical examinations and CRS diagnoses during the first decade after exposure.

Year	Medical examinations	CRS patients
1950	0	0
1951	453	0
1952	320	16
1953	578	36
1954	1,513	33
1955	*	253
1956	3,165	287
1957	3,049	128
1958	3,011	125

*Not recorded.

35 of the 38 persons in whom the diagnosis of CRS was made from 1960 through 1973 (10 years after exposure) were not older than 19 when the exposure started. In the sixties, irradiated children had reached the age of puberty and sexual maturity. Sometimes the symptoms of radioactive exposure became more pronounced during the period of age-specific changes in endocrine function.

Age and Sex Characteristics of the Population with CRS

Of the 940 cases diagnosed as having CRS, 326 were men (34.7%) and 614 were women (65.3%). Because women accounted for the larger portion (57.1%) of the total number of the exposed population, it would seem more rational to establish a correlation between the number of men and women with diagnosed CRS and the number of men and women in the irradiated population as a whole (figure 5.3). Thus, men with CRS accounted for 2.56% of the exposed male population, and the respective value for women was 3.62%.

There seem to be no sufficient grounds for drawing any definite conclusions as to the differences in radiosensitivity between the exposed men and women on the basis of the data cited above.

Data on age distribution in the exposed population when CRS was diagnosed are shown in table 5.3 and figures 5.4 to 5.8.

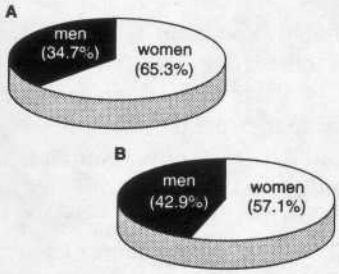

Fig. 5.3. (A) Percentage of men and women with diagnosed CRS. (B) Percentage of men and women in the exposed Techa population as a whole.

The highest incidence of CRS was registered in persons aged 40-49 (figure 5.4). In children and adolescents, CRS was diagnosed in 101 cases, 10.7% of all diagnosed cases. According to physicians who did the examinations, diagnosis verification presented much more difficulties in children than in adults. Children are often unable to give a clear account of their painful sensations, and it was impossible to obtain even anamnestic information on some of them. The physicians had to rely mainly on diagnostic criteria such as hematologic findings, i.e., on such changes in the hematologic status that could not be attributed to the effect of any somatic disease in the examined child.

In persons aged 60 or more, 35 cases of CRS (3.7%) were diagnosed. Difficulties in making the diagnosis of CRS in this group of patients were attributable to the presence of general somatic pathology, a high incidence of geriatric disorders.

To determine age groups most susceptible to radiation effects, a comparison of age distributions in the

Table 5.3. Age at time of CRS diagnosis.

Age group (years)	CRS patients	Percentage of CRS cases
0-4	0	-
5-9	18	1.9
10-14	83	8.8
15-19	141	15.0
20-29	160	17.0
30-39	182	19.4
40-49	200	21.3
50-59	121	12.9
60-69	28	3.0
Over 69	7	0.7
Total	940	100.0

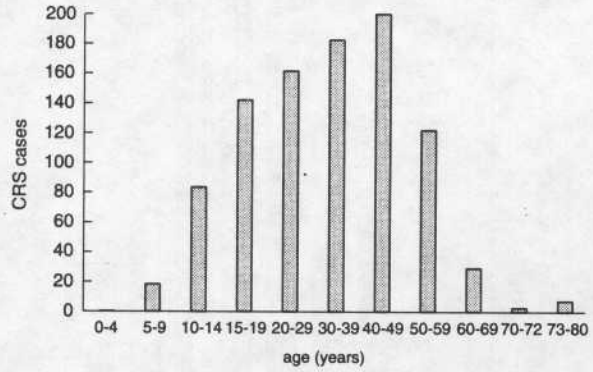

Fig. 5.4. Ages of patients at the time of CRS diagnosis.

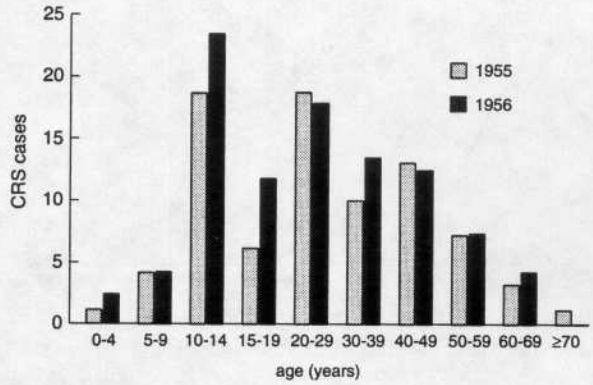

Fig. 5.5. Ages of men with CRS diagnosed in 1955 and 1956.

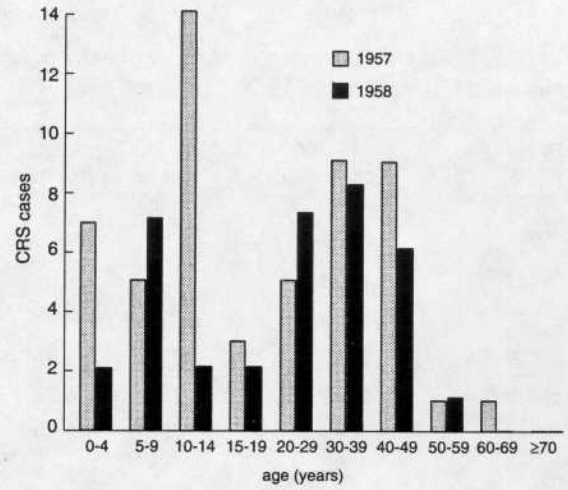

Fig. 5.6. Ages of men with CRS diagnosed in 1957 and 1958.

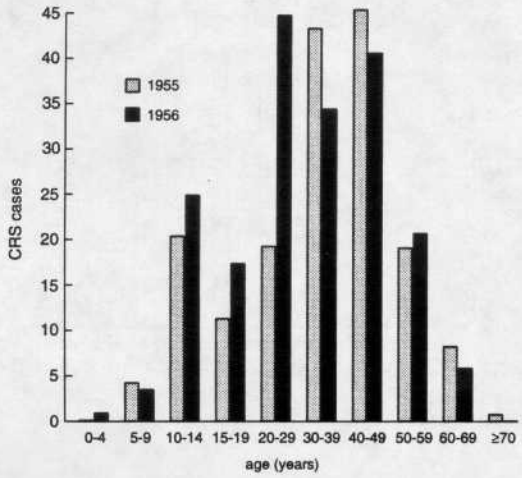

Fig. 5.7. Ages of women with CRS diagnosed in 1955 and 1956.

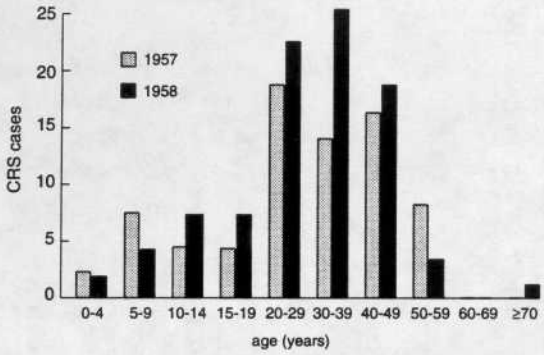

Fig. 5.8. Ages of women with CRS diagnosed in 1957 and 1958.

irradiated population and the population with CRS was made. The findings are shown in table 5.4.

The highest percentage of CRS cases was documented in people 30-49 years old at the time of the highest annual dose rates (in 1952). However, radiation effects were quite often detected in teenagers of 10-14 years old, which is representative of this age group that, according to observations, spent twice as much time on the river as adults did, and consequently received doses of external irradiation twice as high as the doses that adults received. Because of age-specific features of metabolism the body intake of radioactive substances was most significant in those who had reached the age of adolescence before exposure started.

Table 5.4. Age distribution in exposed Techa population and CRS patients, 1952.

Age group (years)	Irradiated persons	CRS patients Number	CRS patients Percentage
0-4	4,792	40	0.83
5-9	1,979	51	2.58
10-14	3,235	131	4.05
15-19	2,641	80	3.03
20-29	5,467	178	3.26
30-39	2,897	180	6.21
40-49	3,324	183	5.50
50-59	2,309	73	3.16
Over 59	3,070	24	0.78

The health surveys that were conducted did not include the exposed population as a whole, and it was therefore thought logical to present findings on age distribution for both the whole exposed population covered by examinations and those whose CRS was diagnosed during these check-ups. Findings of the survey conducted by Dispensary I (Chelyabinsk region) in 1957 may serve as an example (table 5.5). CRS was quite often diagnosed in adolescents in 1957, just as in other years.

CRS Cases in Different Communities

As pointed out above, mean doses of radiation exposure decreased in individual riverside villages along the Techa, beginning with those located at the uppermost reaches of the river near the release site down to the lowest reaches at the confluence of the Techa and Iset rivers. Estimates of mean doses of external irradiation for the villages, mean equivalent doses to the RBM, number of residents, and number of persons with diagnosed CRS are provided in table 5.6.

Table 5.5. Age distribution in examined population and in CRS patients, 1957.

Age group (years)	Patients followed up	CRS cases diagnosed	Percentage of CRS patients
Under 14	103	39	37.9
15-18	101	5	5.0
19-20	57	2	3.5
21-30	195	24	12.3
31-40	184	22	12.0
41-50	153	26	17.0
Over 50	200	10	5.0

Note: Age groups correspond to those in the report on the findings of medical surveys conducted in 1957.

Table 5.6. CRS cases in villages on the Techa.

Village	Distance from release site (km)	Mean dose of external irradiation (10^{-2} Gy)	Mean equivalent dose to RBM (10^{-2} Gy)	Residents in 1950-52	CRS cases
Metlino	7	122.0	164.0	1,272	107
Techa Brod	18	113.0	127.0	81	0
Asanovo and Nazarovo	33	86.0	127.0	1,017	1
M. Taskino	41	71.0	110.0	135	13
Gerasimovka	43	54.0	98.0	384	29
Geologorazvedka	45		75.0	273	2
Nadyrov Most	48	38.0	70.0	304	17
Nadyrovo	50	38.0	95.0	193	23
Ibragimovo	54	28.0	85.0	189	23
Isayevo	60	19.0	59.0	449	7
Podsobnoye Khozyastvo	70	11.0	63.0	560	6
Muslyumovo	78	6.8	61.0	3,321	153
Kurmanovo	88	3.9	38.0	1,084	129
Karpino	96	3.1	48.0	207	2
Zamanikha	100	2.9	36.0	357	64
Vetroduyika	105	2.7	44.0	178	10
Brodokalmak	109	2.8	14.0	4,214	44
Osolodka	125	1.5	34.0	384	14
Panovo	128	1.9	38.0	135	12
Cherepanovo	130	1.5	25.0	235	6
Russkaya Techa	138	2.2	22.0	1,506	37
Baklanovo	143	1.5	7.5	502	12
N. Petropavlovka	148	2.2	28.0	938	64
2-Beloyarka	155	1.5	31.0	395	34
Lobanovo	163	1.5	22.0	648	31
Anchugovo	170	1.5	26.0	1,177	4
Verkhnyaya Techa	176	1.5	29.0	1,110	17
Skilyagino	180	1.5	40.0	508	2
Bugayevo	186	1.5	25.0	1,193	6
Dubasovo	200	1.5	16.0	777	2
Bisserovo	202	1.5	26.0	525	0
Shutikha	203	1.5	8.0	1,229	26
Progress	207	1.5	17.0	216	0
Pershino	212	1.5	15.0	1,192	0
Ganino and Markovo	215				
Klyuchi	223	1.5	7.5	1,561	2
Zatecha	237	1.5	17.0	1,265	29

Data in figure 5.9 compare the number of residents in each settlement with the number of patients with diagnosed CRS. In the villages located in the upper reaches of the river where examinations of the population were conducted regularly, CRS was diagnosed in 5%-17% of the exposed population. Total incidence of CRS in the residents of the Techa riverside within the boundaries of the Chelyabinsk region amounted to 4.55%, and for exposed residents of the Kurgan region, it was 1.41%.

No direct correlation between the mean dose to the RBM in residents of individual villages and the rate of CRS diagnosis could be clearly observed. In some villages located in the upper reaches of the Techa, in the village of Asanovo for instance, only isolated cases of CRS were diagnosed. This may be explained by the fact that medical surveys conducted by visiting teams over the years 1951 to 1958 were not extended to the residents of this village.

Except for several villages on the upper Techa river, the mean doses to the exposed population did not reach the values (1-1.5 Sv per year) considered to be threshold levels for developing clinical manifestations. However, it should be noted that dose variations in residents of one settlement reached two orders of magnitude; in certain age groups, in particular those who were adolescents at the time exposure started, the doses were at least twice as high as doses to adults. Therefore, while mean values of doses to the whole body and RBM in adults did not reach threshold levels, thresholds may have been reached in certain individuals.

Degree of Gravity in CRS Cases

Classification of CRS needs an identification of the degree of gravity of the disease. Cases of functional disorders in physiological systems of the organism, which are easily reversed by removing patients from radiation exposure conditions, were usually determined to be CRS of first degree of gravity. In cases of second degree of gravity, functional disorders were combined with organic changes persisting for a long time.

The distribution of CRS by degree of gravity in the 940 cases was as follows:

First degree of gravity	898 cases (95.5%)
Second degree of gravity	42 cases (4.5%)

All the CRS cases with second degree of gravity were diagnosed from 1952 to 1957, the period of maximum yearly dosages.

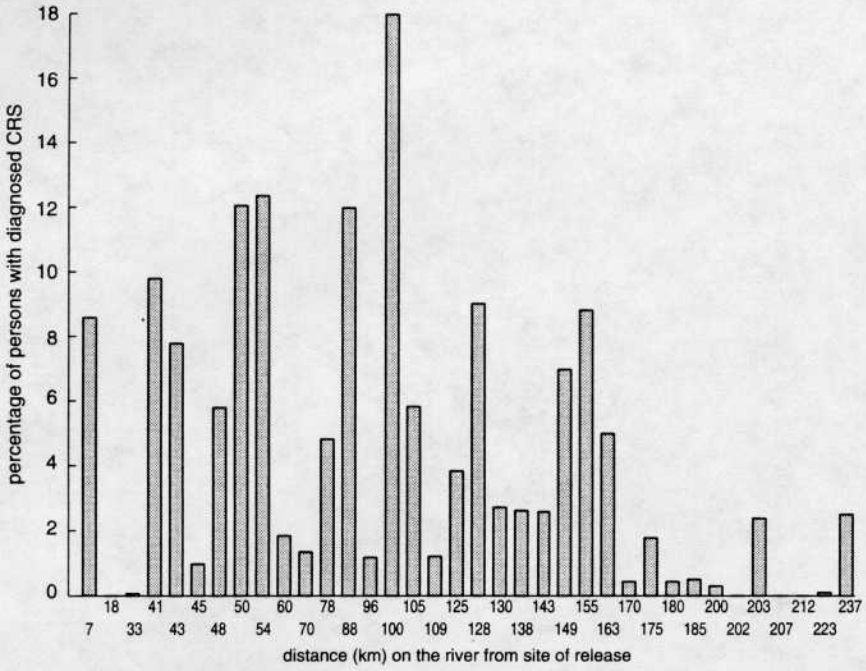

Fig. 5.9. Distribution of cases of CRS among residents of villages on the Techa river.

CHAPTER 6

Examples of Chronic Radiation Sickness Cases: Abstracts from Case Histories

Cases 1 Through 3

Chronic radiation sickness (CRS) was diagnosed in three members of one family. Twin daughters, born in 1944, were followed up at our clinic since 1955. Clinical investigations of the other four members of the family without CRS are also presented.

Family E. resided in Metlino, the village nearest the site of radioactive waste discharge on the Techa. The family's house was located 50 m from the river. The members of the family used river water for all their needs: drinking, cooking, bathing, laundry, etc. The five children spent most of their time on the river in summer. In 1956, the family was evacuated from Metlino to the town of Kyshtym.

Father, E.P.M., born in 1912. Radiation history shows that body content of ^{90}Sr, measured in 1976 with a whole-body counter, was 416 nCi. The dose of external gamma irradiation was 1.22 Gy, the estimated average for Metlino residents. No symptoms of CRS were recorded throughout the entire follow-up period. He died at the age of 69 from impairment of cerebral blood supply.

Case 1: Mother, E.T.T., born in 1910. Radiation history shows that she was a resident of Metlino from 1934 through 1956. Her external radiation dose, estimated as an average for Metlino residents, was 1.22 Gy. Body content of ^{90}Sr measured with a whole-body counter in 1974 was 229 nCi. She was a normal child at birth. Her development and growth proceeded normally in childhood. Her menses started at the age of 16. She married at 24 and had four normal pregnancies. One of the pregnancies (1944) resulted in the birth of twins. In April 1942, she suffered an acute illness with high temperature and loss of consciousness. Subsequently, dyskinesia and myasthenia with numbness of the left arm and leg developed. At times, the patient had attacks accompanied by loss of consciousness. The disease was diagnosed as meningoencephalitis. In 1954, the patient developed erosion of the cervix uteri. At follow-up examinations, the patient complained of general weakness, irritability, headaches, vertigo, occasional syncopes, hair shedding, pain in the pericardial area and joints of the upper and lower extremities, and dyspnea on walking. Findings on physical examinations were weight loss and a decreased leukocyte count of 2,800-3,800/mm^3, which were the reasons for referring the patient to Clinical Hospital No. 6 in Moscow.

The patient's case history during that hospitalization (1 December 1956 through 10 January 1957) indicated that she was severely emaciated. Heart borders were within age-specific norms. Heart sounds were dull. There was a systolic murmur at the apex on auscultation. The pulse was rhythmic, medium-full, with 76-82 beats per minute. The arterial pressure was 105/60 mm of mercury. On palpation of the abdomen, no tenderness was revealed. The liver and spleen were not enlarged. The examination of the patient's neurological status revealed tenderness of the upper trigeminal and both occipital points bilaterally. There was a marked asthenia of the left arm. Tonic convulsions of the muscles on the left side of the neck in the standing position with outstretched arms and periodical generalized convulsions of the torsion spasm type were

observed. The patient's finger-nasal reflex was normal, and there was a marked intention tremor of the fingers. The patient was steady in Romberg's position. A quick expiration of abdominal reflexes, particularly on the left, was noted. There was hypoesthesia on the left. Patient's blood count of 3 December 1956 was 3,700,000 erythrocytes; 3,700 leukocytes with a differential 4% eosinophils, 16% immature neutrophils, 34% segmented neutrophils (total neutrophils: 1,800/mm^3), 32% lymphocytes, 14% monocytes; 155,000 thrombocytes; and 12% reticulocytes. Erythrocyte sedimentation rate was 25 mm/hour. Erythrocyte anisocytosis was noted on blood smear examination. Subsequent blood counts revealed fluctuations in the number of leukocytes from 3,300 to 5,700, in neutrophils from 1,500 to 2,900, and in lymphocytes from 900/mm^3 to 1,500/mm^3. The myelogram of 29 December 1956 showed 39,500 myelokaryocytes. Erythroblastopoiesis was characterized by a decreased number of polychromatophil erythroblasts and an increased number of oxyphilic ones, as well as by a lack of proerythroblasts. RBM reticulocytes made up 14%. Myelopoiesis was characterized by a decreased number of segmented neutrophils. The number of reticular cells, plasmatic cells, and monocytes was increased. Urinalysis was normal. Analysis of stools revealed no helminth ova. Analysis of the patient's stomach juice showed her total acidity was 32; free hydrochloric acid, 14; and bound hydrochloric acid, 12. On the roentgenoscopic examination of the patient's stomach and duodenum no organic changes were disclosed, only stomach hypotonia was observed. An increase in the content of lactic acid in the patient's blood was recorded. Quick's assay, reflecting an antitoxic liver function, was estimated to be 4.9%. Takata-Ara reaction was slightly positive. Total blood protein count was 8.1 g %. Albumin-to-globulin relationship was 1.43. The content of 17-ketosteroids in the total urine excreted daily was 5.065-7.14 mg per day.

Conclusion of the ophthalmologist: stage-4 trachoma, bilateral corneal opacification, hypermetropia, presbyopia, lens sclerosis.

Conclusion of the otolaryngologist: atrophic rhinitis.

Conclusion of the gynecologist: menopause with a marked climacteric syndrome; senile colpitis.

Clinical diagnosis: stages I and II of CRS with signs of premature aging and acute weight loss, leukopenia, and neutropenia. Concomitant diseases: residual signs of past meningoencephalitis with epileptic seizures; stage-4 trachoma.

The patient was given general sustaining therapy, including 40% solution of glucose intravenously, vitamins B_1 and C, sodium nucleate, and five 3-day courses of vitamin B_{12} at the daily dose of 50 g. In addition, she received a course of testosterone propionate. She was also given a massage of the chest, left arm, and leg.

During hospitalization, the patient's general condition improved, her weight increased by 3 kg, and headaches diminished. However, the patient's work ability was found to be reduced. Referral to the Regional Experts Commission on Work Capacity was recommended to identify the stage of disability.

Over the subsequent years, the patient was followed up and treated in the Clinical Department of Branch 4 of the Institute of Biophysics. The following somatic disorders were diagnosed: hypofunction of the adrenal gland system in 1964; chronic coronary insufficiency and cerebrovascular sclerosis in 1972; in 1973, multiple myeloma was suspected on the basis of findings of protein immunophoresis that showed the presence of an extra protein fraction in the zone of beta globulins. Subsequent studies failed to confirm the diagnosis of multiple myeloma. Diffuse pneumosclerosis was diagnosed in 1975, chronic heart ischemia and immature senile cataract in 1985, and inflammation of the right lung and a suggestion of the presence of degeneration foci in the lungs in 1986 when the patient was referred for treatment to a pulmonological center.

Son, E.E.P., born in 1938. No individual dosimetric studies were made for him. In 1949, he fell ill with lymphogranulomatosis (Hodgkin's disease) and died of the disease in 1964.

Case 2: E.V.P., first of twin daughters born in 1944, weighed 1,990 g at birth. She spent much time on the Techa riverbanks in her childhood. The dose of external gamma radiation she received was about 2 Gy; in 1980, her body content of ^{90}Sr, measured on a whole-body counter, was 218 nCi.

She was a weak child, and in comparison to her peers, her physical development was retarded. Since childhood she complained of headaches associated with fatigue and weather changes. For this reason, she started attending school at the age of 9.

She progressed poorly at school because of frequent headaches, general weakness, and poor memory. She completed seven forms with considerable difficulty. She was then employed to deliver telegrams by the local post office. By the end of her workday, she usually felt manifest tiredness and had headaches. She had difficulty in doing any domestic tasks, including those requiring the least physical effort. She had to give up her job because of her poor health, and as she was not entitled to old-age pension (she had not yet attained that age), she had practically no means for living.

During the pubertal period from 1966 through 1967, her asthenic syndrome was especially pronounced. Her secondary sexual characteristics were found to be underdeveloped. Given the disorders of the nervous system (uniform hyperactivity of tendon reflexes, eyelid and finger tremor), susceptibility to leukopenia and neutropenia (1.62-2.6 x 10^9/l) in the peripheral blood, the condition was diagnosed as CRS. Concomitant diseases were bilateral chronic sinusitis, chronic hypertrophic rhinitis, and bile duct dyskinesia.

In 1973, her condition improved, and the peripheral blood count normalized. However, her asthenia, vascular regulation disorder, and susceptibility to hypotonia persisted.

Case 3: E.G.P., second of twin daughters born in 1944, was followed up from 1955, and the state of her health was similar to that of her sister. The dose of external gamma radiation she received from 1950 to 1951 was about 2 Gy. Body content of ^{90}Sr was 233 nCi in 1980.

She weighed 1,900 g at birth. She was a weak child and was often ill. She spent a lot of time on the riverbanks of the Techa. She went to school when she was 9 years old. Her progress at school was just satisfactory. She completed eight forms and entered a medical school but was unable to study because of headaches and general weakness. She then worked as a winder at a radio manufacturing plant. She usually felt very tired by the end of her workday. Her medical history included flu, parotitis, measles, scarlet fever, and frequent respiratory infections. CRS was diagnosed in 1967 when her complaints of asthenia-type symptoms increased and underdevelopment of secondary sexual characteristics was noted. She began to menstruate at 16. Armpit hairs were absent. At 23, her physical development corresponded to that of a 16-year old. She did not marry. Arterial hypotonia was recorded at 90/50-100/70 mm Hg. There was a slight exophthalmos and insufficient ocular convergence on the right. Hyperactive knee-jerk reflexes were noted. Some blood counts showed neutropenia under 2.3 x 10^9/l. Karyologic examinations did not reveal any changes in the structure and number of chromosomes. No pathologic changes were noted in sternal bone marrow. Concomitant diseases were purulent sinusitis on the right and hypertrophic rhinitis. By 1973, the patient's condition stabilized, but asthenic symptoms persisted.

E.E.P., daughter, born in 1947. According to her mother, hair on the girl's head did not grow until she was 4. She was a weak child and went to school when she was 10. At the age of 11, she was thoroughly examined: certain nervous system disorders were noted as represented by persistent red dermographism and tremor, but there were no abnormalities in peripheral blood count. General somatic diseases were chronic gastritis, chronic cholecystitis, hypertrophic rhinitis, and granular periodontitis. She completed seven forms with much difficulty, and was then employed as a nurse assistant at a kindergarten. She married and gave birth to a normal girl.

Son, E.V.P., born in 1950. On examination, no signs of radiation disease were detected. He took a negative attitude to medical examinations. He was an unskilled worker.

Comments. Of the seven members of family E. who were exposed to external irradiation at doses from 100 to 200 cSv with incorporated uranium fission products, three members developed CRS characterized by bone marrow hematopoiesis inhibition and asthenic syndrome, and, in the cases of childhood exposure, by infantilism. One member of the family who was 12 years old when exposure started, died of lymphogranulomatosis (Hodgkin's disease), which was diagnosed before the onset of radiation exposure.

Cases 4 Through 6

Case 4: M.E.N., born in 1941. Radiation history shows that the patient was born in the village of Kurmanovo and resided there permanently until 1960 when all inhabitants were evacuated and the

village was pulled down. Her house was located within 100 m of the river Techa. The family used the river water for all needs, including cooking and drinking, up to 1953. As a result of the first measurement on a whole-body counter in 1975, body content of ^{90}Sr was estimated to be 605 nCi. The average dose of external irradiation for Kurmanovo inhabitants was 7 cGy.

The patient had been followed up since October 1955 at the Urals Research Center of Radiation Medicine, formerly Branch 4 of the Institute of Biophysics. At that time, CRS was suspected on the basis of the following findings: epistaxis, ostealgic syndrome, asthenia, and moderate peripheral blood neutropenia (2.0-2.8 x 10^9/1). The patient was referred to the Institute of Biophysics in Moscow.

She was admitted to the clinic of the Institute of Biophysics on 28 December 1955. Objective findings on admission were infantilism and the absence of menstruation, and that the patient looked younger than her age.

Conclusion of the neuropathologist: evidence of endocrine insufficiency and vascular regulation dysfunction; sinusitis with secondary trifacial nerve neuralgia.

Conclusion of the otolaryngologist: bilateral chronic catarrhal otitis.

Conclusion of the ophthalmologist: stage-4 trachoma; bilateral myopic astigmatism.

Conclusion of the gynecologist: pronounced genital infantilism.

Blood count findings: 4.6 x 10^{12}/l erythrocytes, 5.6 x 10^9/l leukocytes, 2.7 x 10^9/l segmented neutrophils, 2.6 x 10^9/l lymphocytes; differential showed 2% eosinophils and 4% monocytes; 230 x 10^9/1 thrombocytes.

During the first month of the patient's stay at the clinic, her condition was satisfactory. On 31 January 1956, the patient's condition deteriorated. She developed quinsy and significant hepatomegaly, and her peripheral blood leukocyte count decreased to 0.4 x 10^9/l. A myelogram that day showed a scarcity of cellular elements in the bone marrow, absence of granulocytes, and large numbers of decayed cells and plasmocytes. Taking into account the peripheral blood count findings and the disease course, the results of the bone marrow investigation were consistent with the diagnosis of agranulocytosis.

As a result of therapy administered (antibiotics, hemotransfusion), the patient recovered from the agranulocytic crisis. However, with peripheral blood leukopenia of 1.7-2.8 x 10^9/l and neutropenia of 0.3-0.5 x 10^9/l, toxic granularity and erythrocyte anisocytosis persisted. Attending physicians were of the opinion that, in spite of the 5-month hospitalization and intensive treatment, there was no marked improvement in the patient's condition. As before, the main abnormality was represented by hematopoietic disorders manifested by persistent leukopenia within the range of 1.7-2.8 x 10^9/l with neutropenia (0.3-0.5 x 10^9/l), lymphocytosis, toxic granularity, and erythrocyte anisocytosis, indicating inhibited hematopoiesis.

Diagnosis on discharge was stage-II CRS with pronounced hematopoietic disorders, pronounced genital infantilism, endocrine abnormalities combined with vegetative dysfunction, stage-4 trachoma, and bilateral myopic astigmatism.

Repeated agranulocytic crises occurred in 1964 and subsequent years. They occurred in a number of cases in response to certain pharmacological preparations; sometimes their cause could not be identified.

The most severe agranulocytic crisis occurred in 1971. The patient was admitted to the clinic on 10 July with septic temperature elevation and signs of necrotic changes in the oral mucous membranes. Granulocytes were completely absent in peripheral blood from 11 to 16 July, and leukocyte count was 0.6-1.2 x 10^9/l. By the time neutrophil-type cells began to appear in the peripheral blood, the patient had developed sepsis. *Corynebacteria* resembling *Listeria* in morphologic properties were cultured from the patient's peripheral blood, RBM, and oral mucous membranes.

Key symptoms in the clinical course of sepsis were injury of bone tissue and cartilage. Development of chondrolysis was followed by the disappearance of cartilaginous tissue in the symphysial and intervertebral areas. Damage to the cartilaginous tissue caused a change of the shape of the patient's nose. She developed acute manifestations of diffuse osteoporosis involving mainly pelvic bones. An increased content of blood alkaline phosphotase

was noted. The content of calcium in the urine was elevated.

Most of the prescribed antibiotic preparations proved to be ineffective. Only levomycetine (chloramphenicol) improved the patient's condition. However, effective doses of this drug led to the development of leukopenia. Anabolic hormones were added to antibacterial therapy.

By March 1972, the patient's condition improved considerably: ostealgia subsided, and blood counts and temperature normalized. The pathological changes in the bone and cartilage tissues resulted in ankylosis of the hip joints and spine, a decrease in the patient's height by 6 cm, and disability.

Comments. This case exemplifies the development of CRS in a 14-year old girl whose exposure started at the age of 9. Body content of ^{90}Sr that was measured 25 years after intake of uranium fission products was estimated to be 605 nCi. With the background of reduced hematopoietic potential, the patient developed recurrent agranulocytosis, which resulted in sepsis and invalidism.

Case 5: M.N.G., born in 1910. Irradiation history showed that from 1945 through 1956 the patient was a resident of Metlino, the village located near the dumping site of the radioactive waste on the Techa. The mean dose to the RBM was 1.22 Gy for the inhabitants of this settlement. Daily urinary ^{90}Sr counts varied from 21 to 92 pCi. The patient did not undergo individual measurements with a whole-body counter since such examinations were only started in 1974. However, the other members of his family, whose dietary habits were the same as his, underwent measurements for ^{90}Sr. His son's (M.B.N., born in 1929) ^{90}Sr body content was estimated to be 226 nCi in 1976, and his daughter's (S.G.N., born in 1937) estimate was 1,830 nCi.

The patient's growth and development proceeded normally in childhood. He had typhoid fever at the age of 17 and malaria at the age of 22. The onset of chronic gastritis was documented at the age of 29. At 39, the patient developed a gastric ulcer for which he was operated on in 1943. In 1953, he underwent an operation for chondroma of the left lung. From 1966 on, he was monitored by a urologist for prostate adenoma.

The diagnosis of stage-I CRS was established in 1953 on the basis of the patient's complaints of pain in the bones of the legs and arms and the findings of peripheral blood counts. Beginning in 1952, leukopenia (2.85-5.6 x 10^9/1), neutropenia (1.9-4.0 x 10^9/l), and intermittent thrombocytopenia (82.0-198.0 x 10^9/1) were recorded. From that time on, the patient repeatedly underwent treatment at Branch 4 of the Institute of Biophysics and at Clinical Hospital No. 6 in Moscow. The patient was pronounced incapacitated for work (group II invalid) by the Regional Experts Commission on Work Capacity.

The diagnosis of chronic myeloid leukosis was established in March 1966 (16 years after radiation exposure started) when the patient sought medical advice for exacerbation of his lumbar osteochondrosis. Peripheral blood analysis revealed leukocytosis (9.2-148.0 x 10^9/l) and the presence of myeloblasts, promyelocytes, and myelocytes. A total RBM hyperplasia of myeloid tissue that filled up all bone marrow spaces was revealed upon trephine biopsy. Bone trabeculae were thin with cracks and microfractures, and calcareous protein conglomerates with surrounding fibrous tissue bundles occurred rather frequently in the bone marrow. Cytostatic therapy controlled tumor growth in the bone marrow. The disease lasted for 5.5 years. The patient died in December 1971 of progressive leukemia complicated by interstitial pneumonia.

Comments. This patient was exposed to radiation in the upper reaches of the Techa with a resultant dose to the RBM in excess of 1 Gy and developed CRS characterized by hematopoiesis inhibition. Within 16 years of the start of exposure and 12 years after the diagnosis of CRS was established, chronic myeloblastic leukosis developed and brought about the patient's death.

Case 6: Zh.N.D., born in 1935. Irradiation history shows that the patient resided in the village of Metlino near the point where radioactive wastes were discharged into the Techa. According to Lemberg et al. [27], external radiation at the patient's residence was 0.1 R/day. Her growth and development proceeded normally as a child. At the age of 6, she suffered pneumonia. From the age of 15, she drank the water and ate food contaminated with uranium fission products.

The patient began complaining of weakness, headaches, and dizziness 1.5-2 years after the exposure started. A year later stomatorrhagia developed. Skin vasomotor reactions and tachycardia were ob-

served. During the 3-year period, moderate anemia (3.1-3.5 x 10^{12}/l erythrocytes), moderate leukopenia (4.0 x 10^9/l), moderate relative (47%) and absolute (1.9 x 10^9/1) neutropenia, stab neutrophils (10%), and monocytosis (14%) were recorded. Thrombocytopenia was present at 133 x 10^9/l. In subsequent years, the patient's peripheral blood counts were generally normal.

Within 5 years of the first contact with radioactive substances and following an attack of lacunar angina, the patient developed hemorrhagic phenomena (petechial skin eruption, hemorrhages into the retina of the right eye, vaginal discharge tinged with blood), hepatomegaly, and progressive cytopenia (1.4 x 10^{12}/l erythrocytes, 1.3 x 10^9/l leukocytes). A month later, a loud systolic murmur was heard at the base of the heart. The liver was palpable 4 cm below the costal margin. There was tenderness of the inferior margin of the liver on palpation. The spleen was not enlarged. Tendon and periosteal reflexes were very high with an extended excitation zone and had organic character. There were multiple old and fresh hemorrhages in the eye fundi around the ocular nerve papillae. The patient was administered a complex of antibiotic, antihemorrhagic, hematopoietic, and symptomatic preparations.

Short-term periods of relative improvement of the patient's general condition were followed by periods of aggravation of symptoms, such as temperature elevation, progressive anemia, skin hemorrhages, uterine and intestinal bleeding, necrotic changes in the fauces, and hypoxic brain edema. The patient's leukocyte count was 0.7-3.5 x 10^9/l, and only during the preterminal period did it rise to 7-12 x 10^9/l. Simultaneously, the mature neutrophil count steadily decreased to 6%-7%. From the moment of initiation of treatment, both juvenile neutrophil-type cells (promyelocytes, myelocytes) and nondifferentiated cells (hemocytoblasts, myeloblasts) were revealed.

Four sternal punctures were performed on days 34 and 112 of the disease. The punctate analysis revealed a very small number of myelocytes (20-40 x 10^9/l), while the percentage of reticular cells was rather high. Increased percentages of hemocytoblasts and myeloblasts and degenerative changes in RBM cells were also noted.

The patient died within 5 months of the onset of the clinical manifestations of the terminal stage of leukemia, which was combined with bilateral pneumonia and pulmonary edema.

Postmortem samples of the patient's organs and tissues were taken to estimate the content of radioactive substances in the body. The radiometric analysis included preliminary ashing of the tissues by heating with nitric acid (bones were burned in a furnace), and the activity of the preparations obtained was measured using an end-type counter. As a result of the measurements, an adjustment was introduced for natural ^{40}K radioactivity. With the deduction of this value, the net activity of beta isotopes in the cadaver was 30.2 Ci. The contents of beta-radioactive substances in the organs and tissues are shown in table 6.1.

Tentative calculations based on the mean daily dose of permanent radiation exposure equal to 0.1 R and periodic stays in the immediate vicinity of the river in summer months with an elevated gamma-field (minimum rate 100 μR/sec) have shown that within 5.5 years the total dose of external radiation could have amounted to 330 R.

Table 6.1. Contents of beta-radioactive substances in organs and tissues in patient Zh.N.D.

		Activity	
Organ/ tissue	Weight of organ/tissue (g)	1 g tissue, decays/min	Per organ (μCi)
Skeleton	7,426	9 ,018.0	30.1656
Liver	1,910	2.66	2.3 x 10^{-3}
Lungs	1,540	8.47	5.9 x 10^{-3}
Kidneys	320	3.66	0.5 x 10^{-3}
Spleen	230	0	0
Muscles	21,859	4.73	46.5 x 10^{-3}
Brain	1,040	2.80	1.3 x 10^{-3}
Stomach	311	1.70	0.2 x 10^{-3}
Small intestine	700	4.67	1.5 x 10^{-3}
Large intestine	700	13.18	4.2 x 10^{-3}
Pancreas	47	5.40	0.1 x 10^{-3}
Bladder	109	5.13	0.3 x 10^{-3}
Blood	4,009	2.71	4.9 x 10^{-3}
Heart	260	2.67	0.3 x 10^{-3}

Note: total activity, 30.2336.

The dose of internal radiation to the skeleton was calculated by taking into account radionuclide content and effective half-life values, which were assumed to be 43.2 days for ^{89}Sr and 1,700 days for ^{90}Sr.

The total radiation dose received throughout the patient's lifetime was estimated to be 750 R. Bone marrow microscopy indicated relatively abundant cellular elements in the bone marrow; prevalence of reticular cells of various sizes with rounded, oval, and less frequently, irregular nuclei, and a slightly basophilic cytoplasm; and relatively numerous smaller cells, resembling microhemocytoblasts in shape, with compact nuclei and narrow cytoplasmic belts. Gigantic cells with 2-3 nuclei as well as erythroblasts and plasmatic cells were not infrequent; mature granulocytes and their precursors were not found.

Comments. For the first 5 years from onset of exposure to uranium fission products, the health status of Zh.N.D. was generally satisfactory, although symptoms of CRS (hematopoietic function inhibition, mostly that of leukopoiesis and thrombopoiesis) were present.

A sharp deterioration of the patient's health began with angina, temperature elevation, necrotic changes in the fauces, and symptoms of hemorrhagic diathesis. At the same time, a rapid progression of peripheral blood abnormalities was observed.

The condition could be assigned to one of the two types of hematopoietic effects that are similar in clinical symptomatology: aplastic anemia and acute leukemia. It is obvious that the principal factor responsible for causing the disease was exposure, both external and internal, to uranium fission products.

CHAPTER 7

Status of Systems and Organs in Chronic Radiation Sickness

Descriptions of the hematopoietic, nervous, skeletal, cardiovascular, digestive, and immune systems and the findings of biochemical blood studies in patients with CRS are provided in this chapter. The information presented will make it easier to understand the clinical manifestations of CRS and the incidence of individual symptoms and syndromes.

With the aim of detecting radiation injuries in exposed populations, standard follow-up protocols were developed, and periodic medical examinations for different groups of exposed people were established. Therapeutic, pediatric, neurologic, and gynecologic assessments as well as comprehensive blood analyses were a compulsory part of mass medical surveillance in the territories contaminated with radioactive material. In-depth examinations of hospital patients were done using more sophisticated diagnostic methods.

A number of invasive diagnostic methods, such as cytologic studies of bone marrow, bone structure studies based on *in vivo* trephine biopsy, aspiration biopsy of the gastric mucous membrane, veloergometry, and other methods, were used when appropriate. Diagnostic methods have been improving over the 40-year follow-up of the exposed population. These natural improvements over the years have complicated the presentation of the results of the long-term follow-up of patients with CRS according to a standard scheme. To outline the complex symptoms of CRS, the clinical symptoms of patients with CRS were compared by incidence and severity to similar manifestations in nonexposed controls and sometimes in exposed individuals who did not have CRS. To confirm the radiation-induced development of the effect, the symptoms in the three patient groups who differed in exposure doses were separately analyzed. As a rule, the incidence and severity of symptoms were compared with the dose accumulated in the bone marrow, a critical organ, and the analysis of bone pathology took into account the dose to bone surfaces. To analyze the dynamics of manifestations of CRS, the symptoms were analyzed at different time intervals over a 40-year period. The symptoms of CRS were therefore analyzed wherever possible on the basis of the following three groups that differed in doses accumulated in RBM by the time the diagnosis of CRS was established:

Group 1: below 0.5 Gy
Group 2: 0.5 to 1.0 Gy
Group 3: above 1.0 Gy

Although the International Commission on Radiological Protection (ICRP) [11] has given preference to dose rate rather than to total dose in establishing the threshold dose for nonstochastic effect manifestations in cases of highly fractionated irradiation, we grouped the patients on the basis of accumulated dose estimates for the following reasons:

- more or less equal numerical distribution of patients in the groups,
- dependence of severity of deterministic effects on dose, and
- a closer relation of the length of persistence of the effect with accumulated dose.

In addition, four time periods of manifestation of effects were set:

- 1951-1955, period of CRS development,
- 1956-1959 and 1960-1969, periods of stabilization and recovery, and
- 1970 and later years, periods of long-term consequences and outcomes of CRS.

Hematopoietic System

Peripheral blood studies. For all patients with diagnosed CRS, a full morphologic analysis of the peripheral blood in dynamics was made: erythrocyte, reticulocyte, thrombocyte, and leukocyte counts; hemoglobin level; and ESR. Conventional laboratory methods were used for peripheral blood studies.

Visiting teams of physicians determined hemoglobin levels with a Salie's hemometer in the first years of the follow-up and, later, more accurately at inpatient departments using automated cell counters. During visiting examinations, erythrocyte and leukocyte counts were made in Goryayev counting chambers; in hospital surroundings, electronic counters "Celloscope" and "Pikoskoln" were used for this purpose. Leukocyte count was made per 100-200 cells stained according to Pappenheim's method, thrombocytes and reticulocytes were counted on smears stained by Alexeyev's method, and ESR was estimated by Panchenkov's method. At outpatient departments, blood was collected from fingers during the the course of the day, while at inpatient departments it was collected in the morning when stomachs were empty.

Blood study findings were analyzed for two groups: all patients with diagnosed CRS (940 cases), and all CRS patients without any evidence of conditions that could have influenced their peripheral blood status (tables 7.1 and 7.2). Blood count findings for patients with CRS were compared with respective

Table 7.1. Mean values of peripheral blood parameters for patients with CRS ($\bar{x} \pm \sigma$).

	Period of follow-up (years)					
	1951-1955			1956-1959		
	Dose to RBM (Gy)					
Parameter	<0.5 (639)	0.5-1.0 (508)	>1.0 (958)	<0.5 (2,024)	0.5-1.0 (858)	>1.0 (677)
Hemoglobin M, g/l	135.9 ± 16.57	119.1 ± 19.08	135.7 ± 21.47	134.8 ± 18.12	128.2 ± 18.82	138.1 ± 20.62
Hemoglobin F, g/l	121.1 ± 17.15	121.2 ± 6.23	118.9 ± 15.45	121.0 ± 17.00	122.1 ± 16.15	121.3 ± 15.28
Erythrocytes M, 10^{12}/l	4.4 ± 0.45	4.0 ± 0.73	4.5 ± 0.63	4.4 ± 0.51	4.5 ± 0.51	4.5 ± 0.67
Erythrocytes F, 10^{12}/l	4.2 ± 0.43	4.1 ± 0.42	4.1 ± 0.47	4.2 ± 0.43	4.2 ± 0.42	4.1 ± 0.47
Reticulocytes, °/oo	3.7 ± 2.51	4.1 ± 3.43	2.9 ± 2.20	4.3 ± 3.28	5.3 ± 4.28	5.2 ± 3.74
Leukocytes, 10^9/l	5.9 ± 1.58	5.5 ± 1.71	5.2 ± 1.52	5.5 ± 1.51	5.8 ± 1.92	5.6 ± 1.56
Total neutrophils, %	50.9 ± 10.19	51.9 ± 11.92	55.7 ± 9.89	50.9 ± 10.96	50.9 ± 11.70	51.8 ± 10.73
Total neutrophils, 10^9	3.0 ± 1.12	2.9 ± 1.19	2.8 ± 1.13	2.8 ± 1.15	3.0 ± 1.55	2.9 ± 1.10
Stab neutrophils, %	9.8 ± 5.22	9.6 ± 5.41	8.3 ± 5.47	8.7 ± 5.49	10.0 ± 6.21	8.7 ± 5.10
Lymphocytes, 10^9/1	2.2 ± 1.11	2.0 ± 0.92	1.7 ± 0.98	2.0 ± 0.76	2.0 ± 0.78	2.0 ± 0.71
Eosinophils, %	3.6 ± 2.69	3.5 ± 2.76	3.2 ± 2.60	3.5 ± 2.70	3.8 ± 2.77	3.2 ± 2.68
Monocytes, %	7.9 ± 3.46	7.2 ± 3.38	6.3 ± 2.98	8.4 ± 3.63	8.3 ± 3.61	7.6 ± 3.70
Thrombocytes, 10^9/1	223.1 ± 67.22	212.8 ± 61.65	198.7 ± 53.39	243.8 ± 62.26	246.0 ± 62.52	243.0 ± 55.78
ESR, mm/hr	11.1 ± 8.07	10.8 ± 8.28	10.9 ± 8.87	10.9 ± 8.65	10.5 ± 8.66	11. 0 ± 8.80

Continued on next page.

Table 7.1. Mean values of peripheral blood parameters for patients with CRS ($\bar{x} \pm \sigma$) (continued).

	Period of follow-up (years)					
	1960-1969			≥1970		
	Dose to RBM (Gy)					
Parameter	<0.5 (1,747)	0.5-1.0 (907)	>1.0 (913)	<0.5 (1,839)	0.5-1.0 (1,058)	>1.0 (1,435)
Hemoglobin M, g/l	135.0 ± 17.32	137.3 ± 20.21	131.3 ± 21.07	138.2 ± 17.45	136.2 ± 19.92	131.6 ± 20.22
Hemoglobin F, g/l	121.5 ± 16.78	121.6 ± 16.80	120.9 ± 15.43	123.9 ± 16.75	121.1 ± 16.02	119.1 ± 16.12
Erythrocytes M, 10^{12}/l	4.5 ± 0.50	4.5 ± 0.54	4.3 ± 0.62	4.6 ± 0.45	4.5 ± 0.55	4.4 ± 0.59
Erythrocytes F, 10^{12}/l	4.2 ± 0.42	4.2 ± 0.46	4.1 ± 0.43	4.3 ± 0.41	4.2 ± 0.42	4.1 ± 0.46
Reticulocytes, °/oo, %	5.6 ± 4.68	6.3 ± 5.46	5.5 ± 4.41	5.6 ± 4.88	6.0 ± 5.15	5.9 ± 4.11
Leukocytes, 10^9/l	5.7 ± 1.68	8.6 ± 16.72	5.8 ± 1.87	5.9 ± 1.77	6.3 ± 4.87	6.1 ± 2.14
Total neutrophils, %	51.4 ± 10.30	51.6 ± 14.14	51.8 ± 10.18	57.5 ± 9.20	56.8 ± 9.88	57.5 ± 8.64
Total neutrophils, 10^9	2.9 ± 1.24	5.0 ± 11.97	3.0 ± 1.32	3.5 ± 1.38	3.7 ± 4.16	3.5 ± 1.39
Stab neutrophils, %	5.3 ± 3.42	6.1 ± 4.60	5.2 ± 3.44	3.6 ± 2.82	3.5 ± 2.70	3.7 ± 2.95
Lymphocytes, 10^9/l	2.0 ± 0.72	2.0 ± 0.88	2.0 ± 0.90	2.0 ± 0.65	2.0 ± 0.71	2.0 ± 0.67
Eosinophils, %	3.8 ± 3.23	4.0 ± 3.43	3.8 ± 2.70	2.7 ± 2.42	2.7 ± 2.57	2.4 ± 1.96
Monocytes, %	7.8 ± 3.34	7.8 ± 3.65	7.9 ± 3.00	5.2 ± 2.81	5.7 ± 3.05	5.6 ± 2.79
Thrombocytes, 10^9/l	267.1 ± 64.80	276.7 ± 81.22	266.6 ± 58.71	269.1 ± 54.39	269.7 ± 55.25	264.3 ± 46.63
ESR, mm/hr	14.5 ± 9.64	14.5 ± 10.83	14.6 ± 10.16	16.3 ± 11.11	15.0 ± 10.69	15.5 ± 11.05

Note: The number of follow-up patients for each dose is indicated in parentheses.

Table 7.2. Mean values of peripheral blood parameters for patients with CRS and comparison groups.

	Patients with CRS				Irradiated people		Healthy people	
	Period of follow-up (years)							
	1951-1955	1956-1959	1960-1969	≥1970	1951-1955	1956-1960		
Parameter	(586)	(890)	(718)	(794)	[30]	[59]	[18]	[28,29]
Erythrocytes M, 10^{12}/l	4.3 ± 0.04	4.4 ± 0.02	4.5 ± 0.03	4.8 ± 0.04	4.2	4.4	4.5	4.7
Erythrocytes F, 10^{12}/l	4.1 ± 0.03	4.1 ± 0.02	4.2 ± 0.05	4.2 ± 0.02	4.0	4.2	4.2	4.2
Hemoglobin M,g/l	115.2 ± 0.87**	134.4. ± 0.65**	141.5 ± 0.73	145.8 ± 0.99	107.0	126.1	117.0	148.1
Hemoglobin F, g/l	107.6 ± 1.0**	121.3 ± 0.6**	124.5 ± 0.72	127.6 ± 0.57	99.2	115.0	108.0	129.9
Reticulocytes, °/oo	2.6 ± 0.24*	4.9 ± 0.33*	5.3 ± 0.03*	5.9 ± 0.02*	2.6	2.5	8.0	7.0
Thrombocytes, 10^9/l	193.0 ± 4.12**	242.2 ± 4.8	277.4 ± 5.05**	258.2 ± 2.26	206.6	239.0	250.0	247.0
Leukocytes, 10^9/l	5.2 ± 0.12**	5.1 ± 0.05**	5.5 ± 0.06**	5.8 ± 0.07**	6.2	6.6	6.5	6.4
Neutrophils, 10^9/l	2.7 ± 0.04**	2.8 ± 0.04**	3.0 ± 0.04**	3.3 ± 0.05**	3.5	-	4.0	3.94
Stub neutrophils, %	8.7 ± 0.23**	8.7 ± 0.18**	5.1 ± 0.15**	3.3 ± 0.10	-	-	4.0	3.5
Lymphocytes, 10^9/l	1.8 ± 0.02	2.0 ± 0.02	1.9 ± 0.02	1.9 ± 0.04	2.0	1.7	1.7	2.1
Lymphocytes, %	35.2 ± 0.4**	37.7 ± 0.38**	35.7 ± 0.35**	33.6 ± 0.36*	32.4	-	26.0	28.9
Eosinophils, %	3.4 ± 0.14**	3.6 ± 0.12**	4.0 ± 0.10**	3.6 ± 0.16	3.4	3.4	3.0	2.7
Monocytes, %	7.2 ± 0.13	7.7 ± 0.22	7.5 ± 0.15	5.8 ± 0.08	6.4	7.5	6.0	5.9

Notes: Degree of statistically significant differences versus controls: *P <0.05; **P <0.01.
The number of follow-up patients for each dose is indicated in parentheses; literary source is indicated in brackets.
Cases with diseases affecting blood count findings were excluded from the study.

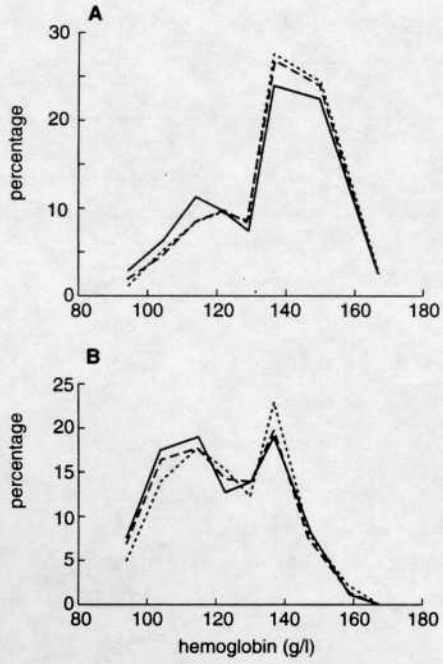

Fig. 7.1. Variance curves for hemoglobin levels: (A) men; (B) women. Doses to RBM: —— 1.0 Gy; ---- 0.5-1.0 Gy; ---- 0.5 Gy.

values cited in references 18, 28, and 29 and with respective findings for persons who had no CRS but were exposed to uranium fission products and were examined in the same time period [30, 31].

The most pronounced blood parameter changes were observed in the group of patients with CRS at the highest radiation dose—more than 1 Gy to RBM—during the period of development of CRS. Thus, the mean content of hemoglobin was estimated to be only 118 g/l for women. The hemoglobin levels that could be interpreted as anemia, below 100 g/l for women and below 126 g/l for men, were recorded in 26% of women and 29.7% of men (fig. 7.1). It should be noted that, in the works published in the fifties [18], hemoglobin levels interpreted as normal for healthy people, 108 g/l for women and 117 g/l for men, were significantly lower than the reference values in later periods, 129.9 g/l for women and 148 g/l for men (table 7.2) [28, 29]. Obviously, the hemoglobin levels during the postwar years were influenced by extremely hard living conditions, characterized by inadequate nutrition, lack of vitamins, and presence of trace elements. These conditions should be kept in mind when considering red blood count findings in patients with CRS.

In comparison to control groups, a considerable decrease in thrombocyte count in patients with CRS was recorded during the period 1951-1955. Thrombocyte distribution is shown in figure 7.2A. The percentage of patients with thrombocyte counts below 199.0 x 10^9/l was 68.7%, while in the comparison groups, such levels were observed in 47.9% of examined individuals. Leukopenia (4.1 x 10^9/l and lower) was recorded with higher frequency during development of CRS and was particularly pronounced in patients with the highest doses (tables 7.3 and 7.4). In some patients, leukocyte counts were in the range of 2.1 x 10^9/l to 3.5 x 10^9/l. Curves of leukocyte distribution during the period of disease development for patients with CRS and comparison groups are shown in figure 7.2B.

Total leukocyte count decreased mainly at the expense of neutrophils. Reduction in numbers of neutrophils was distinctly dose- and time-dependent: the lowest number of neutrophils was recorded in patients with the highest radiation doses from 1951 to 1959. Neutropenia was combined with increased counts of stab neutrophils during that period. The maximum doses of radiation brought about decreases in neutrophil and lymphocyte counts as well. The mean content of lymphocytes was 1.7 x

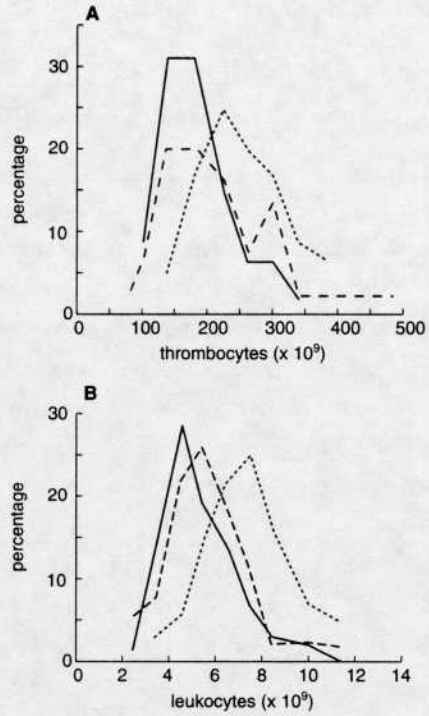

Fig. 7.2. Variance curves, 1951-1955. (A) Thrombocytes; (B) leukocytes. Patients with CRS ——; exposed people ----; controls ----.

Table 7.3. Incidence (%) of blood and bone marrow changes beyond the reference value of $\bar{x} \pm 1.5\sigma$.

	Period of follow-up (years)											
	1951-1955			1956-1959			1960-1969			>1970		
	Dose to RBM (Gy)											
Parameter	<0.5	0.5-1.0	>1.0	<0.5	0.5-1.0	>1.0	<0.5	0.5-1.0	>1.0	<0.5	0.5-1.0	>1.0
Erythrocytes M, $<4.0 \times 10^{12}/l$	6.42	7.68	12.84	5.39	8.74	13.59	6.24	6.84	11.5	4.79	10.02	8.01
Erythrocytes F, $<3.7 \times 10^{12}/l$	8.14	11.61	13.99	8.75	11.07	13.44	8.87	9.7	13.14	10.39	9.17	11.36
Thrombocytes, $<180 \times 10^{9}/l$	10.17	15.55	16.6	8.1	11.89	15.95	7.50	14.22	12.49	6.69	11.06	13.24
Leukocytes, $<4.1 \times 10^{9}/l$	19.72	17.13	23.59	15.86	21.56	22.45	16.08	18.74	22.67	13.05	17.11	21.67
Neutrophils, $<2.0 \times 10^{9}/l$	13.62	15.55	16.39	12.65	12.82	19.65	12.36	12.13	18.95	12.72	12.67	16.86
Neutrophils, $2.0 \times 10^{9}/l$ to $2.5 \times 10^{9}/l$	20.81	21.06	23.7	17.54	21.68	21.12	16.60	19.07	24.21	17.67	17.11	22.44
Stab neutrophils, >6%	44.13	37.99	39.25	40.76	41.84	40.62	41.79	43.22	36.91	42.58	43.48	39.79
Lymphocytes, >40%	18.94	25.2	28.08	24.46	21.68	31.17	25.87	78.39	27.16	25.29	22.12	27.67
Erythrokaryocytes, >26.4%	10.26	28.57	18.75	13.64	18.18	16.67	17.95	9.68	5.13	27.27	6.67	6.25
Neutrophil maturation index, >0.9	71.79	60.71	75.0	72.73	63.64	50.0	43.59	38.71	33.33	18.18	33.33	31.25
Bone marrow plasmocytes, >1.8%	28.21	32.14	37.5	34.09	18.18	25.0	15.38	16.13	5.13	0.0	13.33	18.75
Bone marrow lymphocytes, >13.7%	5.13	17.86	12.5	20.45	0.0	16.67	53.85	45.16	51.28	9.09	46.67	37.5

Table 7.4. Incidence (%) of blood and bone marrow changes beyond the reference value of $\bar{x} \pm 1.5\sigma$. (Cases with diseases affecting the patient's hematologic status were excluded from the study.)

	Period of follow-up (years)			
Parameter	1951-1955	1956-1959	1960-1969	≥1970
Erythrocytes M, $<4.0 \times 10^{12}/l$	26.5	18.0	9.1	5.5
Erythrocytes F, $<3.7 \times 10^{12}/l$	18.4	11.9	7.2	6.6
Thrombocytes, $<180 \times 10^{9}/l$	45.9	12.0	4.0	3.3
Leukocytes, $<4.1 \times 10^{9}/l$	21.3	14.0	12.6	6.7
Neutrophils, $2.0 \times 10^{9}/l$ to $2.5 \times 10^{9}/l$	22.2	23.4	17.0	14.2
Neutrophils, $<2.0 \times 10^{9}/l$	24.5	26.6	19.3	7.0
Stab neutrophils, >6%	57.5	60.0	23.9	10.8
Lymphocytes, >40%	21.6	36.3	32.8	22.5
Erythrokaryocytes, >26.4%	14.6 ± 5.54	18.6 ± 5.95	10.0 ± 3.35	6.45 ± 4.41
Neutrophil maturation index, >0.9	36.6 ± 7.7	60.5 ± 7.45	7.5 ± 2.94	0
Bone marrow plasmocytes, >1.8%	21.9 ± 6.45	16.3 ± 5.63	11.2 ± 3.52	6.45 ± 4.41
Bone marrow lymphocytes, >13.7%	14.6 ± 5.52	11.6 ± 4.88	57.5 ± 5.51	8.3 ± 7.95

10^9/l in the group of patients with doses in excess of 1 Gy during the period of development of CRS. In other groups and different periods of the follow-up, lymphocyte counts did not decrease.

The mean percentage of monocytes in patients with CRS from 1951 through 1969 was somewhat higher than in the exposed population without CRS and was higher than the reference value.

The following conclusions can thus be made on the basis of hematologic data analysis for CRS patients in different periods of the follow-up:

- The most frequent and pronounced decreases in peripheral blood parameters were recorded during the period of CRS development when dose burdens to RBM were more than 1 Gy. Anemia, thrombocytopenia, and leukopenia were recorded with higher frequency in CRS patients than in controls, indicating a somewhat inhibited hematopoiesis function. In addition to a decrease in total neutrophil count, an increased number of stab neutrophils and monocytes were noted.

- On serial examinations/studies, hematologic findings improved with time after exposure. Thrombocyte counts returned to normal. However, the mean counts of leukocytes and neutrophils in patients with CRS persisted in being lower than in controls over the entire follow-up period.

Bone marrow studies. Bone marrow hematopoiesis was studied by puncturing the sternum or iliac bone spine using a Kassirsky needle, aspirating a drop of bone marrow, and studying it according to Arinkin's method. Biopsies were evaluated by counting 500-1,000 cells.

Of the 278 CRS patients whose bone marrow was analyzed, 71 received doses greater than 1 Gy, 80 received doses ranging from 0.5 to 1 Gy, and 127 received doses less than 0.5 Gy. The number of bone marrow biopsies analyzed during development of CRS, stabilization and recovery, and the late period of long-term consequences were 82, 163, and 33, respectively. A number of CRS patients were examined repeatedly. The patients who developed agranulocytosis or leukemia after CRS was diagnosed were not included in the total analysis. Their hematopoietic data should be considered separately.

Mean values of bone marrow parameters at different times of the follow-up and for the three dose groups are listed in tables 7.5 and 7.6; the frequency

Table 7.5. Mean values of RBM parameters ($\bar{x} \pm \sigma$) for patients with diagnosed CRS.

	Period of follow-up (years)					
	1951-1955			1956-1959		
	Dose to RBM (Gy)					
Parameter	<0.5 (38)	0.5-1.0 (28)	>1.0 (16)	<0.5 (44)	0.5-1.0 (11)	>1.0 (12)
Myelokaryocytes, 10^9/l	107.4 ± 80.6	82.3 ± 48.90	75.1 ± 75.06	103.8 ± 60.26	114.00 ± 51.77	105.5 ± 64.13
Megakaryocytes, 10^9/l	-	-	-	36.0 ± 0.00	-	-
Reticulocytes, °/oo	-	23 ± 0.00	-	21.5 ± 2.12	-	27.0 ± 0.00
Total neutrophils, %	61.8 ± 5.76	59.5 ± 7.58	58.7 ± 8.46	59.8 ± 7.75	61.94 ± 8.46	59.4 ± 5.33
Eosinophils (all generations), %	3.2 ± 1.25	3.3 ± 1.61	3.0 ± 1.03	3.2 ± 1.74	3.21 ± 1.99	3.2 ± 2.29
Total granulocytes, %	65.3 ± 6.03	62.9 ± 7.34	62.0 ± 7.99	63.3 ± 7.65	64.45 ± 9.32	63.0 ± 4.50
Neutrophil maturation index	0.9 ± 0.29	0.9 ± 0.41	1.0 ± 0.55	0.9 ± 0.26	1.08 ± 0.31	0.9 ± 0.26
Lymphocytes, %	9.1 ± 3.21	9.5 ± 4.29	8.5 ± 4.41	10.6 ± 3.42	7.8 ± 2.93	11.0 ± 3.86
Monocytes, %	1.5 ± 1.02	1.7 ± 1.07	1.3 ± 1.27	1.8 ± 1.10	1.9 ± 1.03	1.9 ± 1.48
Plasmocytes, %	1.6 ± 0.97	1.4 ± 1.05	1.7 ± 1.17	1.6 ± 0.98	1.3 ± 1.04	1.4 ± 1.36
Total erythrokaryocytes, %	19.0 ± 5.41	21.5 ± 6.84	23.3 ± 5.04	20.0 ± 8.06	19.6 ± 6.36	19.7 ± 4.63
Erythroblast maturation index	0.8 ± 0.07	0.8 ± 0.08	0.8 ± 0.07	0.8 ± 0.09	0.8 ± 0.059	0.8 ± 0.06
LE index	4.3 ± 1.44	5.4 ± 9.31	3.3 ± 1.14	4.2 ± 1.56	4.1 ± 1.61	3.9 ± 1.40

Continued on next page.

Table 7.5. Mean values of RBM parameters ($\bar{x} \pm \sigma$) for patients with diagnosed CRS (continued).

	Period of follow-up (years)					
	1960-1969			≥1970		
	Dose to RBM (Gy)					
Parameter	<0.5 (37)	0.5-1.0 (27)	>1.0 (32)	<0.5 (8)	0.5-1.0 (14)	>1.0 (11)
Myelokaryocytes, 10^9/l	75.7 ± 55.0	102.8 ± 103.58	53.60 ± 33.42	65.91 ± 47.36	47.7 ± 34.41	42.7 ± 25.57
Megakaryocytes, 10^9/l	15.9 ± 12.21	27.5 ± 27.20	12.6 ± 11.80	12.1 ± 9.45	9.7 ± 16.82	10.4 ± 8.62
Reticulocytes, °/oo	21.2 ± 15.88	17.6 ± 12.39	17.0 ± 7.58	20.6 ± 10.86	16.9 ± 8.90	15.8 ± 5.72
Total neutrophils, %	55.9 ± 7.37	59.7 ± 15.65	58.3 ± 7.08	57.2 ± 6.81	55.8 ± 16.75	55.5 ± 8.43
Eosinophils (all generations), %	3.1 ± 1.67	4.0 ± 2.51	2.7 ± 1.12	4.0 ± 1.69	3.4 ± 1.35	3.2 ± 1.01
Total granulocytes, %	59.2 ± 7.25	63.7 ± 16.96	61.2 ± 6.66	61.5 ± 6.69	60.0 ± 16.66	58.8 ± 8.09
Neutrophil maturation index	0.7 ± 0.19	0.7 ± 0.29	0.6 ± 0.19	0.6 ± 0.15	0.5 ± 0.22	0.5 ± 0.16
Lymphocytes, %	16.1 ± 7.42	15.4 ± 11.99	17.1 ± 5.68	10.7 ± 4.50	14.2 ± 8.13	14.7 ± 4.11
Monocytes, %	2.2 ± 1.46	2.0 ± 1.27	2.5 ± 1.57	2.8 ± 1.23	4.9 ± 5.65	3.7 ± 1.68
Plasmocytes, %	1.0 ± 0.89	1.2 ± 1.71	0.9 ± 0.76	0.6 ± 0.38	1.0 ± 1.03	1.1 ± 0.82
Total erythrokaryocytes, %	19.3 ± 7.55	15.7 ± 7.08	16.8 ± 5.47	23.05 ± 5.21	18.4 ± 5.43	19.3 ± 6.62
Erythroblast maturation index	0.8 ± 0.09	0.8 ± 0.07	0.8 ± 0.09	0.82 ± 0.04	0.8 ± 0.06	0.9 ± 0.043
LE index	4.7 ± 2.44	7.9 ± 9.05	5.5 ± 2.63	3.49 ± 1.29	4.6 ± 1.82	5.0 ± 3.81

Note: The number of patients followed-up for each dose is indicated in parentheses.

Table 7.6. Mean values of RBM parameters for patients with CRS and the control group.

	Patients with CRS Period of follow-up (years)				Control group
Parameter	1951-1955 (41)	1956-1959 (43)	1960-1969 (80)	≥1970 (12)	(12)
Myelokaryocytes, 10^9/l	87.3 ± 14.3	122.0 ± 12.9	81.8 ± 11.0	95.7 ± 12.7	118.4 ± 4.9
Erythrokaryocytes, %	21.9 ± 1.19	21.0 ± 1.62	17.7 ± 0.98	19.6 ± 1.48	20.5 ± 0.11
Erythroblast maturation index	0.79 ± 0.08	0.77 ± 0.01	0.86 ± 0.1	0.85 ± 0.02	0.78 ± 0.006
Neutrophil maturation index	1.06 ± 0.13*	1.05 ± 0.06**	0.62 ± 0.01	0.65 ± 0.04	0.68 ± 0.011
Lymphocytes, %	9.5 ± 0.86	9.9 ± 0.85	16.2 ± 1.11**	9.32 ± 0.81	9.0 ± 0.29
Reticulocytes, %	0.69 ± 0.12	0.73 ± 0.1	0.49 ± 0.05	0.57 ± 0.15	0.87 ± 0.045
Monocytes, %	1.4 ± 0.21	1.7 ± 0.21	2.3 ± 0.26	2.49 ± 0.36	1.9 ± 0.075
Plasmocytes, %	1.33 ± 0.17*	1.5 ± 0.17**	0.93 ± 0.12	0.48 ± 0.09	0.93 ± 0.0053
Megakaryocytes, 10^9/l	-	-	0.017 ± 0.003	0.016 ± 0.004	0.020

*P < 0.05
**P < 0.01
Notes: The number of patients followed up is indicated in parentheses.
Cases with diseases affecting blood count findings were excluded from the study.

of changes in values beyond $\bar{x} \pm 1.5\,\sigma$ of the normal values are listed in tables 7.3 and 7.4.

The absolute numbers of myelokaryocytes in bone marrow biopsies from CRS patients varied widely but on average did not differ significantly from reference values [29].

During the period of CRS development, a certain increase in erythrokaryocytes was recorded (table 7.5), and several CRS patients had erythrokaryocyte counts in excess of 26.4% (table 7.6). The relationship between specific stages of development of erythroblasts was normal, and the erythroblast maturation index was within normal limits.

During the same period, "a shift to the left" was noted in granulocytopoiesis, i.e., percentages of myelocytes and metamyelocytes increased in a considerable number of followed-up patients. From 1951 through 1955, a high neutrophil maturation index (over 0.9) was recorded in 60%-75% of CRS patients with exposure doses greater than 1 Gy to RBM.

An increase in the number of plasmacytes, as compared to reference values, was noted from 1951 to 1959. The percentage of patients with plasmacytes in excess of 1.8% was highest in the group with doses greater than 1 Gy over the entire period of CRS development. During the period of stabilization and recovery of CRS, increased lymphocyte and monocyte counts in RBM were recorded. The percentage of patients with lymphocyte counts exceeding 13.7% in 1960-1969 was 45%-53%.

The results of myelographic studies in CRS patients thus identified (a) slight proliferation of erythroblastopoietic cells, evidently associated with reduced levels of hemoglobin and erythrocytes in the peripheral blood at the stage of development of CRS; (b) slow maturation and differentiation of granulocytes at the final stage of cell development recorded in 1951-1959; (c) moderate increase in plasmacyte count at the same time; (d) increase in mean lymphocyte and monocyte counts in late periods after the exposure; and (e) no morphologic granulopoietic and erythropoietic alterations during the period of recovery.

Cytogenetic studies. Cytogenetic studies, specifically those of structural chromosome changes in lymphocytes from peripheral blood cultures, were started in the seventies, and there is therefore a lack of information on cytogenetic findings that relate to the initial period of radiation exposure with significant annual doses of radiation. Cell clones with atypical monocentrics resembling a Ph'-chromosome were revealed in 5 cases in the same study group. The percentage of such cells was from 4.6% to 30%. A similar clone, revealed in one of the patients who was exposed to uranium fission products, had a skeleton content of ^{90}Sr in excess of 500 nCi, but was not a CRS-diagnosed patient. It should be noted that an exact identification of a damaged chromosome presented a certain difficulty because we were unable to apply the method of differential chromosome staining in this study. Such a chromosome was first registered in a CRS patient about 15 years ago in both peripheral blood lymphocytes and in bone marrow where cells with a Ph'-like chromosome made up 60%-70% of the patient's cells. No clinical signs of chronic myeloleukosis were detected in that patient. In the remaining four CRS cases, similar clones were recorded for the first time in 1983 as a result of peripheral blood lymphocyte studies. Clinical signs of leukosis were also absent in these patients. No cells of this type were revealed in controls.

Sixty-nine individuals, aged 40-74 years, with previously diagnosed CRS, were studied by the cytogenic method 33-35 years after they were irradiated. These studies were performed at URCRM by N. A. Petrushova and G. I. Zvereva. The results were compared to findings in nonirradiated persons (table 7.7).

An analysis of 1,968 metaphases from CRS patients and 1,270 metaphases from a comparison group was made. Cells with euploid chromosome set 2n=46 were an overwhelming majority of cells. The percentage of cells with structural chromosome abnormalities in patients with CRS was 0.15% (according to literature findings, the normal limit was up to 1.3% [32], and for our control group, it was 0.79%). Cells with dicentrics and without concomitant fragments were detected in 3 of the 69 CRS patients studied.

Table 7.7. Incidence of structural chromosome changes in lymphocytes from peripheral blood cultures.

Cohort studies	Patients with CRS (69)	Comparison groups: Nonirradiated persons (22)	Comparison groups: Irradiated persons with body content >50 nCi of ^{90}Sr in skeleton (14)
Metaphases	1,968	1,270	553
Cells with chromosome-type aberrations (%)	0.15	0.79	0.0
Chromosome aberrations per 100 cells (%)			
Acentric	0.0	0.79	0.0
Dicentric fragments	0.15	0.0	0.0
Monocentric	0.0	0.0	0.0
Number of persons with clones of aberrant chromosomes (%)	7.25	0.0	7.14

Note: The number of CRS patients and of persons in comparison groups is indicated in parentheses.

Nervous System

The status of the nervous system in persons with CRS was evaluated on the basis of neurologic complaints, objective symptoms, and incidence of neurologic syndromes (vascular regulation disturbances, asthenia, vertebrogenic syndrome, and organic nervous system affection syndrome). In later years, rheoencephalographic (RE) studies were also carried out; the results are provided in this section. The studies were performed in the Clinical Department of URCRM by V. A. Savostin.

About half the patients with CRS complained of headaches, and one third of the patients complained of vertigo. Vasomotor reactions and psychoemotional disturbances were identified on the basis of the patients' own accounts of their symptoms: they were questioned by physicians about the occurrence of chills, sensation of hot flushes, syncopes (for evaluating vasomotor reactions), sleep disturbances, failing memory and attention, and increased excitability (for evaluating psychoemotional status). In relation to the frequency of the above-described complaints as well as that of complaints of extreme unmotivated weakness, no connection with the CRS patients' radiation exposure rates was revealed (table 7.8).

As far as objective neurological symptoms were concerned, patients' increased tendon reflexes and impaired coordination, sometimes manifested by ataxia, were recorded with higher frequency in CRS patients than in the nonexposed population.

The incidence of neurological syndromes is provided in table 7.9. The suggestion about possible effects in the hypothalamic area following ^{90}Sr incorporation into bone structures could not be confirmed. The absence of such manifestations as hypochondria and hysteria, designated as anomalous personality syndromes, was noted. Vertebrogenic syndrome was distinctly dependent on the age of the examined people; evidently, it was age that accounted for the increased prevalence of this syndrome among CRS patients after 1970, the late period of follow-up. The mean age of patients was 56 years in this period.

Dose dependence can be correlated with three neurological syndromes: vascular regulation impairment, asthenia, and organic injury to the nervous

Table 7.8. Incidence (percentage) of neurological complaints and syndromes in different follow-up periods.

	Dose to RBM (Gy) <0.5				0.5-1.0				>1.0			
	Period of follow-up (years)											
Signs and symptoms	1951-1955 (122)	1956-1959 (293)	1960-1969 (225)	≥1970 (241)	1951-1955 (135)	1956-1959 (185)	1960-1969 (174)	≥1970 (221)	1951-1955 (338)	1956-1959 (142)	1960-1969 (161)	≥1970 (278)
Headache	56.6	48.1	42.7	41.9	60.7	51.9	54.6	48.4	58.6	68.3	63.4	43.0
Vertigo	28.7	21.5	20.9	23.2	44.4	32.4	31.0	28.1	35.2	32.4	23.6	23.7
Weakness, fatigue	22.1	23.2	16.0	26.6	28.2	21.1	25.3	22.2	28.1	40.1	33.5	30.9
Vasomotor reaction	2.5	1.7	2.2	2.1	0.0	1.6	3.5	2.7	0.0	0.0	2.5	0.0
Psychoemotional disturbance	13.1	13.6	15.6	22.4	25.9	21.6	21.8	28.0	27.8	22.5	24.8	23.0
Tendon reflexes reduced	0.8	1.0	0.9	2.5	0.0	1.6	1.2	4.1	0.0	0.7	0.0	1.1
Tendon reflexes overactive	31.2	28.7	16.0	21.6	17.8	26.5	25.9	16.7	2.7	23.2	16.2	14.0
Presence of pathologic reflexes	0.0	0.0	2.2	3.3	1.5	0.0	1.2	4.5	0.6	0.0	0.0	6.8
Muscular tension reduced	4.1	3.8	1.3	2.1	4.4	3.2	1.7	0.5	9.5	6.3	3.7	1.1
Muscular tension overactive	0.0	0.3	0.0	0.8	1.5	1.1	1.2	2.7	2.7	0.0	0.0	0.0
Impaired coordination	9.8	15.0	15.0	24.5	19.3	11.9	33.3	32.1	17.5	23.2	34.8	29.1
Impaired coordination with ataxia	2.5	4.1	4.1	6.2	6.7	3.8	6.9	5.4	6.2	8.5	5.6	6.5

Note: The number of patients followed-up is indicated in parentheses.

Table 7.9. Incidence (percentage) of neurological syndromes.

	Dose to RBM (Gy) <0.5				0.5-1.0				>1.0			
	Period of follow-up (years)											
Signs	1951-1955 (122)	1956-1959 (293)	1960-1969 (225)	≥1970 (241)	1951-1955 (135)	1956-1959 (185)	1960-1969 (174)	≥1970 (221	1951-1955 (338)	1956-1959 (142)	1960-> 1969 (161)	≥1970 (278)
Regulation disorders	18.8	24.2	21.3	29.4	17.8	21.1	31.0	33.9	24.3	28.2	26.7	33.1
Asthenia	32.0	31.7	28.4	31.5	47.4	37.8	43.1	37.1	40.2	43.0	49.7	37.1
Organic micro-symptoms	7.4	7.2	7.6	5.8	8.2	11.9	9.8	11.3	13.0	11.3	11.8	11.9
Hypothalamic syndrome	0.0	0.0	0.0	0.0	0.0	0.0	0.6	0.5	0.0	0.0	0.6	0.4
Personality changes	0.0	0.3	0.4	0.4	0.0	0.0	0.6	0.0	0.0	0.0	0.6	0.7
Vertebrogenic syndrome	2.6	3.1	9.8	28.2	0.7	3.8	5.2	26.2	0.3	4.2	11.8	28.4

Note: The number of patients followed up is indicated in parentheses.

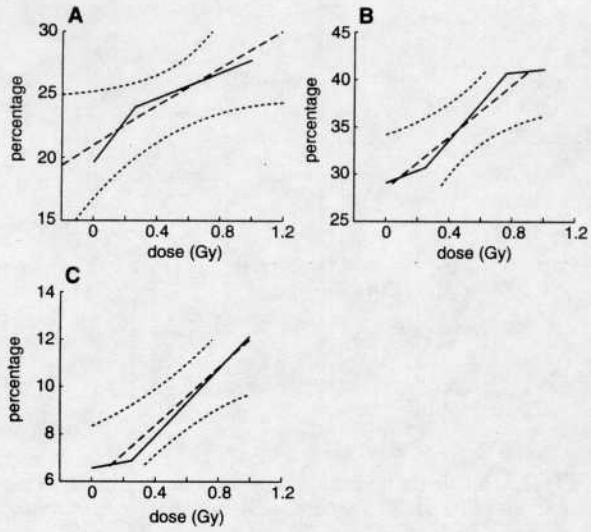

Fig. 7.3. Dose dependence for neurological symptom manifestations. (A) Vascular regulation disturbance; regression 7.596 1.666. (B) Asthenia; regression 13.83 2.14. (C) Organic injury to the nervous system; regression 5.82 0.81. Estimate for CRS patients ——; regression line - - - -; confidence interval - - - - .

system (figure 7.3). Among these syndromes, organic injury to the nervous system deserves closer consideration. The pathological changes underlying clinical microsymptomatic manifestations are represented by diffuse micronecrotic disorders that involve primarily the myelinic membrane of nerve conductors, and are accompanied by scattered glial proliferation and circulatory disturbances. It could be a consequence of both the direct damaging effect of uranium fission products and the indirect effect of exposure-induced vascular disorders [33, 34]. Organic microsymptomatology was manifested mainly by motor reflex disturbances with a fairly satisfactory function compensation.

RE studies were performed for 74 patients with CRS (table 7.10). Judging from long-term RE findings, the intensity of brain vessel blood supply at rest did not differ significantly from respective control group values. Only a tendency towards an increased reaction to nitroglycerine ($p<0.1$) was observed in persons with diagnosed CRS.

Thus, the results of the nervous system appraisal in dynamics show the development in CRS patients of functional and microorganic effects, some of which were dose dependent. The pathological signs were found to be most pronounced at the initial stage of radiation exposure.

Skeletal System

The skeletal system was a critical system in the irradiated population on the Techa because the main contributor to absorbed dose was ^{90}Sr incorporated in bone tissue. Equivalent doses to bone surfaces proved to be 1.4 to 2.4 times higher than doses to RBM and 1.8 to 12.5 times as high as doses accumulated in soft tissue. These doses accounted for the development of the bone injury syndrome in irradiated persons. Judging by the reports prepared in the first years, complaints of pain in the bones were regarded as a symptom of CRS and were caused by exposure to uranium fission products.

To determine the objective signs of bone tissue injury, different methods of study were suggested, several of which proved to be uninformative and inappropriate. For example, an attempt was made in the sixties to estimate the thickness of the cortical layer of the tibia with the use of roentgenography.

Table 7.10. Mean RE readings for CRS patients.

RE characteristics	CRS patients (74)	Control group (163)
RE amplitude (ohm)	0.120 ± 0.007	0.124 ± 0.004
Increment of RE amplitude following nitroglycerine administration (relative units)	1.76 ± 0.007	1.67 ± 0.05

Notes: RE amplitude increment is expressed as a relation of amplitude following nitroglycerine administration to background amplitude.
The number of CRS patients and of persons in the control goup is indicated in parentheses.

Using the films obtained, the shapes of the cortical layer were outlined on standard transparent paper, and the silhouettes were cut out and weighed on an analytical balance. We assumed that exposure to uranium fission products would result in an increase in the thickness of the cortical layer, which could be demonstrated by the above-described method. This method was discarded because of the uncertainty of the results and in view of inadvisable additional radiation burdens to patients.

The status of the skeletal system in CRS patients was described using several parameters: clinical (incidence of ostealgia), morphological (histological evaluation of iliac bone structure specimens obtained by *in vivo* trephine biopsy), functional (studies of sensitivity to vibration on the basis of the mean perception time of a C-128 tuning fork), and laboratory (biochemical studies of calcium concentration level and alkaline phosphotase activity in blood serum).

The ostealgic syndrome was very important in the clinical picture of CRS. Pains in the bones were characterized by the patients as gnawing, throbbing, bursting, often intensive and tormenting. According to patient descriptions, the pain localized in the depth of the bones, became more acute when the patients were warm and immobile, and were particularly severe in bed at night. Most often the pains were localized in the bones of the legs, less frequently in the forearms, spine, and sternum. To relieve the pain, patients tried to press their legs to a cold surface (metallic parts of their beds) or cover them with a wet sheet. When radionuclide intake stopped and with passing of time, pain became less intense, and at the late stage of CRS, a considerably smaller number of patients complained of ostealgia. The incidence of ostealgic complaints for different times (from 1951 through 1970) is shown in figure 7.4. Obviously, pathogenetic mechanisms of the ostealgic syndrome were governed by the involvement of nervous receptors of bone tissue in the pathological process, disturbances of vascular tension, and changes in bone tissue trophicity as a result of ^{90}Sr incorporation.

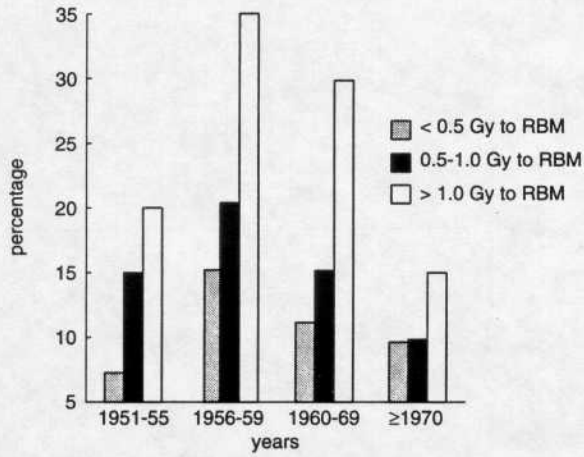

Fig. 7.4. Incidence (percentage) of ostealgic syndrome in persons with CRS at different doses and different times of follow-up.

Physical examinations of patients, e.g., palpation of the periosteum, revealed sharp tenderness, especially over the tibia. The pain increased on percussion of the bone. Hypopallesthesia (reduced perception of vibration) was also observed. The findings of vibration sensitivity studies performed by V. A. Savostin are presented in table 7.11. Vibration sensitivity was found to be somewhat decreased for irradiated persons, particularly in the lower extremities during development of CRS.

Table 7.11. Vibration sensitivity for different periods of follow-up of CRS patients.

Period of follow-up (years)	Number of patients examined	Localization	Sensitivity level (sec)
1952-59	129	Arms	6.5 ± 0.32
		Legs	5.2 ± 0.27
1960-69	114	Arms	9.4 ± 0.32
		Legs	6.7 ± 0.41
1970-85	64	Arms	10.9 ± 0.52
		Legs	8.7 ± 0.72

Table 7.12. Contents of calcium and alkaline phosphatase in blood serum for different periods of follow-up.

Biochemical parameter	CRS patients			Nonirradiated persons
	1960-69	1970-79	1980-85	
Ca (mmol/l)	2.78 ± 0.032 (104)	2.55 ± 0.054 (12)		2.70
Alkaline phosphatase (IU/l)	12.6 ± 0.69 (38)	13.2 ± 0.45 (111)	14.3 ± 0.52 (112)	12.7

Note: The number of patients followed up is indicated in parentheses.

The findings of biochemical analysis (serum calcium, alkaline phosphatase) performed by V. P. Yakovleva, URCRM, are shown in table 7.12. These parameters, which indirectly reflect the skeletal system status, show no differences in comparison to the control group.

The status of bone tissue in 69 individuals with CRS was evaluated using histological findings from iliac bone trephine biopsies performed by N. L. Mutovkina and L. Ye. Kislova, URCRM. From 1968 through 1977, 83 trephine biopsies were performed for these subjects. This procedure was performed under local anesthesia. The weight of the bone tissue specimens obtained ranged from 40 mg to 80 mg. The preparations were decalcified using 5% solution of selectone and were poured into celloidin-paraffin. Sections, 5 *u*m in width, were stained with hematoxylin-eosin according to the van Geison method and with silver nitrate according to Tibor-Papa's method.

Males accounted for 52% and females for 48% of the examined group; most of the women were under 40 years old, and the men were over 40. Doses to bone surfaces ranged from 0.2 Gy to 6.4 Gy. Dose distribution among CRS patients examined was 48.2% with less than 1 Gy, 30.4% with 1 to 2 Gy, and 21.4% with 2 or more Gy.

In nine cases of mainly elderly people, biopsy specimens were crushed, and it was considered impossible to evaluate the bone tissue status. The results of the examinations for a number of morphological characteristics are given in table 7.13. The following specimen description may be considered most typical for nonirradiated cases: "Osteal trabeculae of the spongious bone substance are composed of

Table 7.13. Bone tissue status based on iliac bone trephine biopsies.

Pathologic signs	Dose to bone surfaces (Gy)		
	<1.0 (20)	1.0-2.0 (29)	>2.0 (25)
Thickened and deformed bone beams	10.0 ± 6.71	13.8 ± 6.4	36.0 ± 9.6
Fractured beams	0.0	6.9 ± 4.71	4.0 ± 3.92
Uneven osteocyte distribution	10.0 ± 6.71	20.7 ± 7.52	20.0 ± 8.0
Osteocyte pyknosis and lysis	5.0 ± 4.87	20.7 ± 7.52	12.0 ± 6.5
Increased osteoblast counts in endosteum	25.0 ± 9.68	24.1 ± 7.94	12.0 ± 6.5
Fibroreticular tissue proliferation	0.0	17.2 ± 7.01	12.0 ± 6.5

Note: The number of patients for each dose is indicated in parentheses.

mature laminar tissue of small and medium width, and contain a moderate number of osteocytes. The margins are even and smooth; there are areas of narrow osteoid deposition with a moderate number of osteoblasts."

Signs of bone dysplasia were common in persons with the diagnosis of CRS (table 7.13). The dystrophic process in bone tissue manifested itself by smooth resorption with uneven distribution and loss of osteocytes. There were also signs of restructuring and bone formation disturbances: aggregates of osteoblasts and thickening of bone trabeculae at the expense of newly formed laminae. Obviously, one of the most prognostically unfavourable signs was proliferation of fibroreticular tissue not only around bone trabeculae but also in bone marrow spaces. In a number of cases, endosteal and stromal fibrosis resulted in clinical manifestations of myelosclerosis. The increased incidence of bone dysplasia was, in our opinion, related to incorporation of osteotropic radionuclides.

The findings of histological bone studies for one CRS patient are described below. A trephine biopsy was performed in November 1967 on patient A. (Systemic No. 323), born in 1930 and a resident of the village of Metlino. Dose to patient's bone surfaces was 2.049 Gy.

> "Bone trabeculae consisting of mature laminar bone of different thickness are running in different directions. Some of the trabeculae are thick and deformed, with nonuniform thinning or thickening of different regions, which look inflated. The edges of the trabeculae are partly even and have some small lacunae composed of osteoblasts. In the isthmus areas, aggregations of osteoblasts are noted. There are depositions of osteoid on the edges of the trabeculae. Bone matter is being resorbed in the central parts of the thick trabeculae, resulting in formations of cavities on the edges of which there are depositions of osteoid with multiple osteoblasts. There are up to 100 osteoblasts in the isthmus areas and about 30 in the lacunae. There is a diffusion of a multitude of reticular cells (up to 30-35 within the field of vision) over the entire bone marrow stroma. Focal aggregations of reticular cells can be observed."

Cardiovascular System

To evaluate the status of the cardiovascular system in patients with diagnosed CRS, the following signs and symptoms were taken into consideration: patient's complaints, findings upon auscultation, pulse rate, arterial blood pressure, and from 1980 to 1985 the findings of ECGs taken at rest and during physical exercise on a veloergometer. The results of the examinations carried out by A. N. Zinova (URCRM) are grouped according to the patient's sex and age at the time the diagnosis was made: patients were under 29, 30-49, and 50 and older. An ECG was taken in 12 routine leads, using the apparatus "Elkar-6"; the Minnesota Code was used for evaluating the findings. Veloergometer exercise lasted 5 minutes with powers ranging from 49 to 147 watts, with allowance made for the patient's age and sex. The following signs were assumed as criteria of pathologic ECG responses to physical exercise: (a) downward ST segment displacements—horizontal, oblique-descending, or trough-shaped, 1 mm or lower, and lasting at least 0.08 sec in one or more leads; (b) rhythm disturbances (frequent or multifocal extrasystole, cardiac fibrillation, paroxysmal tachycardia), widening of the QRS complex up to 0.14 sec and more.

An analysis of patients' cardiac complaints showed that, with increasing age, the number of patients without cardiac complaints decreased, and the number of patients complaining of dyspnea, heartache, etc., increased (table 7.14).

The same age-related dependence may also be demonstrated by an analysis of heart auscultation findings (table 7.15). As should be expected, muffled character and dullness of cardiac sounds increased with the patient's age. The incidence of cardiac symptoms was the same as in the nonirradiated population of respective ages [35].

The analysis of the rate of heart contractions in people with diagnosed CRS revealed a trend toward tachycardia, with rates of heartbeat over 80 per minute at the time the diagnosis was established (26.5% of cases diagnosed in 1952-1959) as compared to later periods of follow-up (14.2% of cases in 1980-1985).

The analysis of the incidence of different blood pressure types yielded the following information: at

Table 7.14. Incidence (percentage) of cardiac complaints at different times of follow-up.

	Period of follow-up (years)								
	1952-1959			1960-1969			1980-1985		
	Age of patients (years)								
Complaints	<30 (167)	30-49 (164)	>49 (55)	<30 (69)	30-49 (150)	>49 (82)	<30 (0)	30-49 (82)	>49 (126)
Dyspnea	6.0	16.4	21.8	0.0	2.0	26.8	-	19.5	34.9
Cardiac pains	1.8	11.6	9.1	13.0	14.0	15.8	-	25.6	39.7
Arrhythmia	0.0	1.2	3.7	0.0	0.0	1.2	-	0.0	2.4
Tachycardia	5.4	9.7	7.3	8.7	4.0	9.7	-	4.9	7.9
No complaints	90.4	73.2	67.2	81.1	84.6	59.7	-	59.7	45.2

Note: The number of patients is indicated in parentheses.

all times of the follow-up period, the normotensive type of arterial blood pressure prevailed. However, at the time the diagnosis of CRS was made, the incidence of recorded cases of hypotension (arterial blood pressure of 100/60 mm Hg and lower) was higher than in later periods of follow-up when an increase in the number of cases with hypertensive type of blood pressure was observed (160/95 mm

Table 7.15. Incidence (percentage) of pathological signs revealed on auscultation in different periods of follow-up.

	Follow-up periods (years)								
	1952-1959			1960-1969			1980-1985		
	Age of patients (years)								
Signs	<30 (167)	30-49 (164)	>49 (55)	<30 (69)	30-49 (150)	>49 (82)	<30 (0)	30-49 (82)	>49 (126)
Dullness	11.9	50.0	56.3	14.5	24.7	80.5	-	43.9	70.6
Systolic heart sounds	7.2	21.9	14.5	17.4	22.0	18.3	-	3.7	4.8
Increased S_2 sound above aorta	3.6	5.5	16.4	8.7	6.0	13.4	-	0.0	5.6
Arrhythmia	1.2	1.2	3.6	0.0	0.0	1.2	-	0.0	0.8
Absence of pathological signs	81.4	34.8	9.1	66.7	56.0	12.2	-	54.9	-
Heart rate									
Bradycardia (<60 in 60 sec)	1.9	1.9	5.8	6.3	3.6	1.5	-	16.7	11.8
Normal range (60-80 in 60 sec)	62.7	78.1	75.0	77.8	76.3	75.0	-	78.2	68.0
Tachycardia (>80 in 60 sec)	35.4	20.0	19.2	15.9	20.1	23.5	-	5.1	20.2

Note: The number of patients is indicated in parentheses.

Hg and higher). Studies [35] show that radiation exposure at moderate doses may cause hypotension; however, the established dynamics of measuring blood pressure is most probably associated with the increasing age of examined subjects (fig. 7.5).

The results of ECG changes in patients with the diagnosis of CRS are shown in table 7.16. With increasing age, the number of cases without ECG changes decreased (class I,0 according to the Minnesota Code classes (MCC)), and the number of those with different ECG changes increased. Among the ECG changes, the most frequent were abnormalities of the end portion of the ventricular complex, ST interval (MCC-IV), and T wave (MCC-V), as well as MCC-VII and MCC-VIII, which characterized the disorders of conductivity and cardiac rhythm.

Using different levels of physical exercise on the veloergometer, the incidence of pathologic responses in people with diagnosed CRS was observed in 6.7% of cases and did not exceed the value for controls, which was 8.75%.

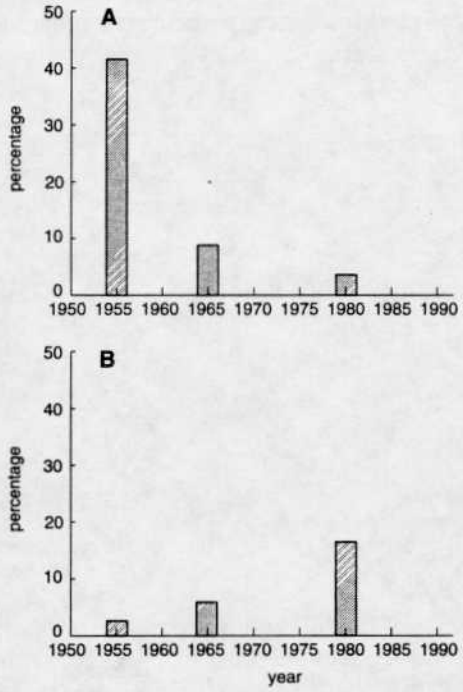

Fig. 7.5. Incidence (percentage) of (A) hypotension and (B) hypertension at different stages of CRS. Mean age was 27 in 1952-1955, 32 in 1960-1969, and 47 in 1980-1984.

Table 7.16. Incidence (percentage) of various ECG changes and pathological reactions to physical exercise in patients with CRS.

		Age (years)			
		30-49		>50	
ECG characteristics		Male (32)	Female (41)	Male (35)	Female (65)
Minnesota Code class	I	0.0	0.0	0.0	3.1
	III	3.1	0.0	2.8	4.6
	IV	15.6	29.3	20.0	61.5
	V	28.5	29.3	34.3	49.2
	VI	0.0	4.9	2.8	3.1
	VII	18.7	7.3	25.7	9.2
	VIII	3.1	7.3	22.8	13.8
	IX,1	12.5	12.2	20.0	6.1
	I,0	28.1	39.0	20.0	10.8
Pathological reaction to physical exercise		7.4 (27)	5.5 (18)	0.0 (5)	0.0 (4)

Note: The number of CRS patients is indicated in parentheses.

Alimentary Tract Status

One of the characteristic features of population exposure on the Techa was that the digestive tract served as a pathway for radionuclide intake, and because of it, the organs of the gastrointestinal tract were exposed to considerable dose burdens. Doses to the large intestine exceeded doses to other inner organs (with the exception of bone and bone marrow). Such manifestations as reduced gastric secretion, tenderness in the liver area, and hepatomegaly were regarded as symptoms of CRS. It was therefore considered very important to analyze the status of digestive organs in patients with diagnosed CRS.

Patient complaints of alimentary tract disturbances were analyzed. The status of the stomach was studied on the basis of its secretory and acid-forming functions. In some patients, morphologic changes of the gastric mucous membranes were evaluated using *in vivo* aspiration biopsy. Moreover, a dynamic study of digestive system morbidity was undertaken for three groups of CRS patients with different radiation burdens.

At the time that CRS was diagnosed, 47% of the patients complained of tenderness in the epigastric and right hypochondriac areas. In 16.5% of cases, dispeptic phenomena were observed. From 1952 through 1958, disturbed peristalsis and changes in mucous membrane relief (thickened or thinned gastric folds) were noted on roentgenologic examination in about one third of the patients.

The functional status of gastric glands was evaluated by studying histamine-induced gastric secretions and by determining the amount of secretion and its content of hydrochloric acid. Histamine was administered subcutaneously at a rate of 0.1 ml of 0.1% solution per 10 kg of body weight. Gastric juice aspirations were performed twice on an empty stomach at a 10-minute interval and, after a histamine injection lasting for an hour, at 5-minute intervals. Each four successive portions were poured together into a flask, and the quantity of gastric juice was measured. After titration using sodium hydroxide, total acidity and the contents of free and bound hydrochloric acid, expressed in titration units, were estimated. Subsequently, the content of hydrochloric acid in 1 millilitre of gastric juice was expressed in milligrams using the coefficient 0.0365; for a more accurate evaluation of the function of the accessory cells that generate hydrochloric acid, the yield of hydrochloric acid per hour was calculated, i.e., the quantity of hydrochloric acid excreted per hour.

During the period of CRS development, the secretory function was inhibited, and acid production decreased in 33.4% of the patients followed up. The results of gastric secretion studies performed during examination of CRS patients in 1983 are presented in table 7.17.

Gastric secretion studies of a small number of followed-up CRS patients indicated a certain inhibition of the acidic function (in nonexposed groups, the incidence of achlorhydria and hypoacidity did not exceed 10% and 25%, respectively). The high incidence of this pattern of secretion in CRS patients

Table 7.17. Gastric secretion characteristics (percentage) of CRS patients, 1983.

	Dose to RBM (Gy) from ingested radionuclides		
Secretion characteristics	<0.5	0.5-1.0	>1.0
Anacidity	23.7 ± 6.9	33.3 ± 15.7	26.3 ± 10.1
Hypoacidity (<6.0 meq/h)	50.0 ± 8.1	33.3 ± 15.7	47.4 ± 11.5
Hyperacidity (>12.0 meq/h)	7.9 ± 4.4	-	10.5 ± 7.0
Mean HCl yield/h (meq)	3.56 ± 0.77	4.83 ± 1.50	3.61 ± 0.97
Mean age (years)	56	54	49

could have been due to their age, which averaged 49-56 years. It was impossible to rule out the inhibiting effects of ionizing radiation on gastric secretions and acidity under the conditions of protracted exposure to uranium fission products. However, the latter assumption is unlikely because of the lack of dose dependence of gastric acid excretion function inhibition and the remoteness of the dates of the beginning of radiation exposure.

Gastric mucosa aspiration biopsy was performed on an empty stomach by means of a probe according to the method suggested by I. J. Wood. With the patient in a sitting position, the probe was inserted to a distance determined from the patient's height. Pieces of gastric mucous membrane obtained by biopsy were treated according to conventional histologic methods with hematoxylin-eosin staining.

In 7 of 11 CRS patients for whom aspiration biopsy was performed by L. K. Metelsky (URCRM) in 1969-1971, dystrophic changes in the main glands of the stomach, manifested by flattening, wrinkling, and intensive staining, were revealed. In five cases, gland cell dedifferentiation (i.e., replacement of the principal and accessory cells by goblet cells) as well as stromal proliferation was noted.

The findings of morphologic studies of the gastric mucous membrane in patient V.I.G-v may serve as an example. A resident of Metlino, born in 1952, V.I.G-v (Systemic No. 3 910) was exposed to radiation *in utero*. The estimated dose to RBM was 1.526 Gy, to the stomach 0.22 Gy, and to the intestine was about 3.3 Gy.

> Specimen description: Deepened and convoluted gastric pits stretching for half the length of the glands, which are located uniformly close to one another. Lumina are wide. Superficial epithelium is flattened, removed in places, with large amounts of mucus. Peeled cells (accessory and principal cells) are visible all over the surface of the epithelium and in the pits. Epithelium of the pits also contains much mucus. Nuclei of different size and shape are basally located, some of them are pyknotic, intensely stained; others are less intensely stained and have clearly visible nucleoli. A marked edema of the subepithelial mucous membrane was noted. The lamina propria of the stomach is thick, richly infiltrated with cellular elements such as plasmatic cells, lymphocytes, eosinophils, and neutrophils. Infiltration, which has a generalized character, is less pronounced in the basal layers of the mucosa. The number of glands is diminished. Principal cells are poorly stained and contain large numbers of granules. Many accessory cells are small and flat and have pyknotic nuclei. Due to edema of the mucous membrane between the glands, the distance between them is larger than normal.
>
> Morphologic diagnosis: Chronic atrophic hyperplastic gastritis.

Because of the small number of follow-ups we cannot state with certainty that such changes could occur in most patients at later stages of CRS. At the same time, the findings obtained give us reasons to suggest that protracted radiation exposure and radionuclide incorporation contribute to dystrophic processes in glandular cells of the stomach.

Results of digestive organ morbidity analysis for CRS patients are presented in table 7.18 and figure 7.6. As can be seen, diseases of the digestive organs were most often registered at later stages of the follow-up, which is obviously a reflection of the age-specific dependence that governs disease causation. A certain dose-dependence of digestive tract morbidity was noted. Gastritis had the highest specific weight in the structure of digestive organ disorders. There is no evidence that the incidence of liver diseases was highest in patients who received the highest doses.

Biochemical Blood Studies

It is assumed that biochemical shifts in chronic exposure to ionizing radiation are not very significant. However, increased loss of cells may cause protein synthesis disorders and dysproteinemia as well as hyperfermentemia. Biochemical shifts that reflect disorders of sympathicoadrenal regulation in irradiation include disturbances of carbohydrate

Table 7.18. Morbidity rate (per 1,000 persons) and structure of diseases of the digestive organs.

	Dose to RBM (Gy)											
	<0.5				0.5-1.0				>1.0			
	Follow-up duration (years)											
Disease index	1951-1955	1956-1959	1960-1969	≥1970	1951-1955	1956-1959	1960-1969	≥1970	1951-1955	1956-1959	1960-1969	≥1970
Morbidity rate/ 1,000 persons	411.1	511.8	543.1	1,533.8	707.1	500.0	1,035.0	1,753.6	947.9	594.4	1,205.9	2,406.5
Structure of digestive organ diseases												
Stomach ulcer and ulcer of the duodenum	6.3	3.9	4.8	2.7	5.7	3.9	5.4	2.9	5.8	5.9	4.9	4.4
Gastritis and duodenitis	56.8	50.4	37.2	28.9	50.0	66.2	37.8	31.4	40.8	61.2	31.7	29.7
Functional disorders of the stomach	5.4	7.8	8.8	4.8	7.1	3.9	11.5	4.1	8.3	4.7	14.6	3.7
Chronic hepatitis	14.4	13.1	8.2	4.1	10.0	7.8	4.7	1.6	3.3	4.7	3.6	1.7
Cholelithiasis and cholecystitis	5.4	11.7	15.9	24.3	8.6	9.1	17.6	23.1	0.8	4.7	14.6	22.0
Diseases of the pancreatic gland	-	-	0.6	0.7	-	1.3	-	1.6	0.8	-	-	1.35
Other diseases of digestive organs	11.7	13.1	24.4	34.6	18.6	7.8	20.9	35.1	40.0	18.8	30.5	37.2

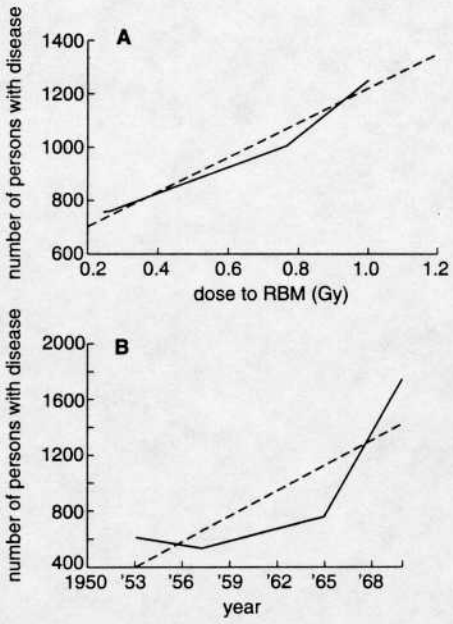

Fig. 7.6. Morbidity for digestive organ diseases: (A) dose dependence; (B) time trend. Morbidity per 1.000 persons with CRS ——; regression line - - - -.

metabolism. Among late-occurring effects of radiation exposure, certain signs of premature involution that lead to changes in lipid metabolism can be distinguished. The above-cited phenomena provided reasons for researching biochemical reactions in our CRS patients.

The choice of the type of biochemical reactions to be studied was determined by the facilities available at our laboratory when examinations of irradiated people were being carried out. From 1955 to 1959, only concentrations of bilirubin, rest nitrogen, and glucose in the blood serum were evaluated. The following findings were obtained for patients with CRS:

Total blood serum bilirubin 9.38 μmol/l
(normal upper bound 20.5 μmol/l)

Mean value of rest nitrogen 6.09 μmol/l

Glucose content 4.94 μmol/l
(normal limits 2.8-5.6 μmol/l)

Early in the sixties, the scope of biochemical studies was extended. Table 7.19 lists biochemical reactions and methods of their evaluation.

Tables 7.20 and 7.21 show the findings of biochemical studies in patients with CRS and in nonexposed individuals (control subjects). A comparison of protein metabolism values in the late period of CRS and those in the control group did not reveal any differences. It should be noted however, that in the course of dynamic follow-up, a trend toward an increase in beta globulins was detected (by about 20% in 1985 versus 1965), which probably accounted for the increased amount of lipids transferred.

As for the quantitative characteristics of lipid metabolism, an increased content of lipids (cholesterol, beta-lipoproteins in particular) in dynamics was observed. It may be explained by a significant advancement in the ages of CRS patients: the mean age of those examined in 1960-1965 was 43 years, and at the end of the follow-up period the mean age was about 53 years. During the last period of the follow-up (1980-1985), cholesterol and triglycerides increased in CRS patients in comparison to control subjects. At the same time, concentrations of atherogenic lipids (alpha-cholesterol) in subjects with diagnosed CRS were level with those in controls.

Among the characteristics of carbohydrate metabolism, only sialic acid level was increased, which was accounted for by exacerbations of concurrent pathologic processes during the follow-up of patients with CRS rather than for radiation injury effects.

Table 7.19. Methods used in biochemical studies.

Biochemical parameter	Method	Reference values [29]
Total protein		65-86 g/l
Protein fractions	Paper electrophoresis	
Alanine-amino-transferase	From 1960 to 1980, Paskin's modification of Umbrite method; later, standard method	16-46 IU/l
Aspartate-amino-transferase	From 1960 to 1980, Paskin's modification of Umbrite method; later, standard method	20-50 IU/l
Glucose	Hagedorn and Yensen	2.8-5.6 mmol/l
Sialic acid	Svennerholm	1.3-2.5 mmol/l
Fucose	Dishe and Shattles	60-90 µg/l
Hexose	Orcynic	70-130 µg %
Cholesterol	Liberman's modification of Ilke	3.5-7.0 mmol/l
Alpha-cholesterol	Ilke, in supernatant	0.9-2.1 mmol/l
Beta-lipoproteins	Burstein and Samaia	3.5-6.0 g/l
Triglycerides	Karlson	0.55-1.65 mmol/l
Phospholipids	Blurr	207-297 mmol/l
Alkaline phosphatase	Bodansky	5.4-27.0 IU/l
Calcium	Permanganatometric	1.2-2.0 mmol/l

Table 7.20. Lipid metabolism characteristics.

Metabolism characteristics	Patients with CRS: Follow-up period (years) 1960-1969	1970-1979	1980-1985	Control subjects
Cholesterol (mmol/l)	5.36 ± 0.082 (164)	5.77 ± 0.07 (111)	5.78 ± 0.061 (185)	5.42 ± 0.031 (1,154)
Triglycerides (mmol/l)	-	0.99 ± 0.058 (48)	0.96 ± 0.033 (128)	0.88 ± 0.021 (671)
Beta-lipoproteins (g/l)	4.43 ± 0.091 (17)	5.03 ± 0.157 (147)	5.35 ± 0.127 (181)	5.08 ± 0.082 (800)
Phospholipids (mmol/l)	235 ± 23.2 (15)	262 ± 18.4 (47)	260 ±19.6 (14)	251 ± 5.2 (453)
Alpha-cholesterol (mmol/l)	-	-	1.5 ± 0.38 (28)	1.52 ± 0.068 (120)

Note: The number of CRS patients and of control subjects followed up is indicated in parentheses.

Table 7.21. Protein and carbohydrate metabolism characteristics.

Characteristics	Patients with CRS, Periods of follow-up (years): 1960-69	1970-79	1980-85	Control subjects	Reference values [29]
Total protein (g/l)	80.1 ± 1.01 (57)	8.12 ±1.15 (43)	81.8 ± 1.34 (29)	79.9 ± 1.23 (15)	65-86
Albumin (g/l)	46.9 ± 1.0	46.0 ± 1.13	45.8 ± 1.06	43.3 ± 1.15	38-55
Globulins					
alpha-1	3.4 ± 0.12	3.1 ± 0.13	3.6 ± 0.18	3.7 ± 0.25	2.2-6.5
alpha-2	7.4 ± 0.33	7.1 ± 0.35	7.8 ± 0.44	6.9 ± 0.4	3.8-9.3
beta	8.6 ± 0.46	9.4 ± 0.44	10.4 ± 0.48	9.1 ± 0.49	5.3-11.5
gamma	13.8 ± 1.12	15.6 ± 1.23	14.0 ± 1.42	16.6 ± 1.37	9.0-16.0
Sublimate (ml)	1.9 ± 0.13 (94)	1.99 ± 0.29 (14)	-	1.94 ± 0.1 (10)	
AST (IU/l)	19.3 ± 1.8 (14)	25.4 ± 2.19 (55)	-	19.8 ± 1.22 (17)	
ALT (IU/l)	17.7 ± 1.52 (16)	15.7 ± 1.05 (67)	-	20.2 ± 2.13 (17)	
AST (μmol)	-	-	0.44 ± 0.013 (47)	0.45 ± 0.011 (10)	
ALT (μmol)	-	-	0.55 ± 0.010 (47)	0.53 ± 0.015 (10)	
Sialic acid (μmol/l)	2,035 ± 38.4 (63)	2,200 ± 29.4 (118)	2,089 ± 47.9 (66)	1,937 ± 49.1 (45)	1,300-2,500
Hexose (g/l)	102 ± 6.7 (16)	109 ± 4.8 (64)	104 ± 6.0 (17)	111 ± 4.7 (36)	70-130
Fucose (μg/l)	98 ± 7.5 (10)	10 ± 6.1 (47)	91 ± 7.1 (18)	105 ± 3.7 (36)	
Glucose (mmol/l)	5.02 ± 0.065 (99)	5.16 ± 0.059 (36)	5.3 ± 0.048 (71)	5.21 ± 0.053 (40)	2.8-5.6

Note: The number of CRS patients and of control subjects followed up is indicated in parentheses.

Immune System

The few reports that discuss the state of health of people exposed to radiation present evidence of the high radiosensitivity of the immune system [36-39]. Even the early investigations, conducted 2-4 years after contamination of the Techa started, led to the discovery of decreased resistance to infections and to signs of autosensitization [40]. With equivalent irradiation dose to the RBM amounting to 30-40 cSv/year and higher, immunity inhibition was recorded by changes in skin microflora status [41]. It was quite natural that immunity changes were recorded as a rule in CRS patients with high doses of radiation.

Comprehensive laboratory studies of immunity in patients with CRS were carried out at the initial stages of the exposure (1954-1961) by a group of researchers headed by O. G. Alexeyeva.

The investigations of the superficial and internal microflora of the skin and oral mucous membrane in CRS patients revealed a significant increase in the incidence of a marked imbalance between the microflora and the human organism, which manifested itself by a sharp decrease in the number of microorganisms, especially those of pathogenic strains, on the skin and mucous membranes [41]. The antimicrobial functions of the skin were evaluated using the method of Klemparskaya and Alexeyeva [42]. The incidence of such immunity changes (figure 7.7) in patients with CRS was almost identical to that observed in people whose average equivalent radiation dose to RBM was 0.85 Sv.

Initial CRS manifestations were accompanied by both quantitative and qualitative immunity changes that mainly involved the deep flora of the skin. Further development of the disease was accompanied by a spread of pathologic changes to the superficial flora. It should also be stressed that even initial CRS manifestations were accompanied by changes in the properties of microorganisms in the depth of the skin (ability to disintegrate mannite more readily, hemolytical properties, and an increase in the numbers of microbial strains resistant to bromthymol blue, a bactericidal agent); however, no increase in the number of microorganisms resistant to bromthymol blue was observed in the deep flora of the skin.

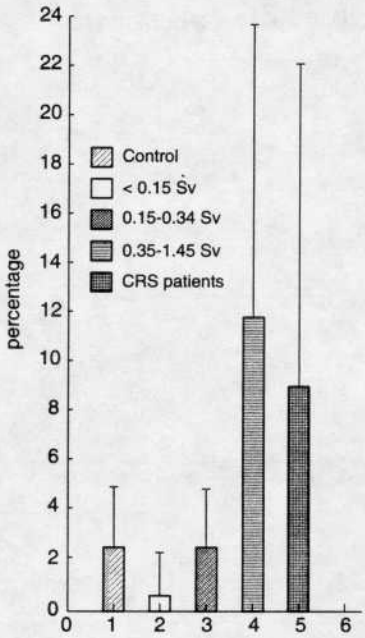

Fig. 7.7. Incidence (percentage) of pronounced immunity inhibition in findings of skin automicroflora tests for different study groups in the follow-up.

To evaluate the status of the flora of the skin and mucosa in CRS patients, special attention was paid to the increase in microorganisms, presence of dysbacteriosis (suppression of normal gastrointestinal microflora and overgrowth of potentially pathogenic microflora), adaptability to the conditions of the host organisms, and resistance to some bactericidal agents [40]. These disorders increased with disease progression.

At the early stages of the disease, the following phenomena were noted in individuals with CRS: inhibition of the phagocytic activity of peripheral blood neutrophils, reduction in lysozyme content in the saliva, and antibody production disturbances following tetravaccine injection. In CRS patients, the appearance of antibodies was delayed to a certain degree, and their detection was possible in smaller titers [40].

The development of CRS was accompanied by a restructuring of the organism's immunosensitivity that manifested itself by nonspecific allergic reactions to brucellin and changes in heterophilic antibody titers. Obvious signs of immunity restructuring were noticed at the early clinical stages of CRS along with hematopoietic and neurological changes.

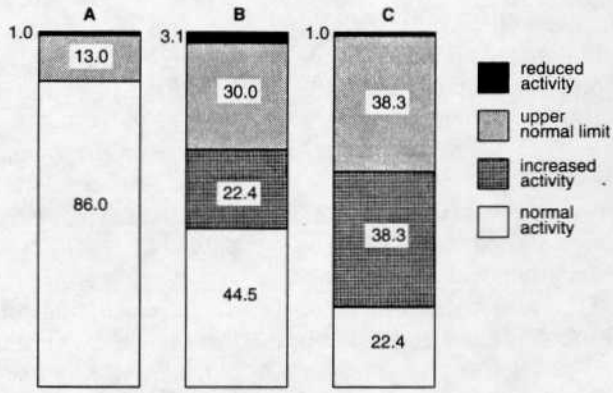

Fig. 7.8. Structure (percentage) of phagocytic activity of neutrophils in irradiated persons 12 years after exposure. Dose ranges and mean equivalent dose to RBM (cSv) for exposed persons (groups B and C): (A) control; (B) 15-34 (20); (C) 35-145 (85). Number of exposed persons is indicated in parentheses in this legend.

It is important to note that the extent of immunity disorders in the majority of cases depended on the gravity of radiation effects and decreased with stabilization and regression of these effects. The course of CRS was largely determined by the irradiation rate, and 3-4 years after the beginning of contamination of the river system, the signs of immunity recovery in conjunction with a sharp decrease in dose rate were observed. However, even as late as 10-15 years after irradiation started, disturbances of symbiotic relations with flora still persisted, and an increased phagocytic activity was observed in individuals who received the highest doses (average cumulative dose to the RBM of 122 cSv [41]. The incidence and degree of phagocytosis depended on the dose of radiation and were particularly pronounced in persons with maximum radiation dose (fig. 7.8).

Long after radiation exposure, no changes in the immunity status were noted in patients with diagnosed CRS. Thirty years after exposure, values of cellular and humoral immunity in such patients were found to be within the normal range of variations of the parameters studied and corresponded to those in irradiated individuals without CRS (table 7.22).

Table 7.22. Immunity parameters (M ± SE) evaluated in CRS patients 30 years after initial exposure to radiation.

Parameter	CRS patients (81)	Irradiated persons without CRS (68)	Normal values
T-lymphocytes (%)	52.96 ± 2.53	49.36 ± 2.30	50-80
B-lymphocytes (%)	18.07 ± 1.76	21.31 ± 1.37	10-30
T-lymphocytes, 10^9/l	0.97 ± 0.26	0.96 ± 0.06	0.70-0.92
B-lymphocytes, 10^9/l	0.39 ± 0.07	0.38 ± 0.08	0.21-0.81
BTR (%)	58.09 ± 1.88	47.85 ± 3.13	18-89
Immunoglobulins			
IgA, IU /ml	118.18 ± 2.09	124.45 ± 2.11	72-268
IgG IU/ml	113.83 ± 2.18	114.20 ± 2.72	57-172
IgM, IU /ml	87.16 ± 2.01	84.22 ± 2.06	58-197

Notes: The number of persons evaluated is indicated in parentheses.

In individuals with diagnosed CRS, only a slight increase in blast-transformation reaction in lymphocytes following incubation with lymphocytic mitogen was observed as compared to nonirradiated persons without CRS.

An evaluation of the immune status in CRS patients 40 years after contamination started is presented in table 7.23. The comparison group was matched for age and sex according to the case-control method. Standard unified tests for immunologic studies were used for the evaluation. The relative and absolute content of peripheral blood T-lymphocytes (E-RFC), theophylline-resistant and theophylline-sensitive E-RFC, E-RFC with few or multiple receptors, B- and O-lymphocytes [43], large granulocytic lymphocytes (LGL), and classes A, G, and M of serum immunoglobulins (Ig) were determined [44]. Blast-transformation reaction to PHA was studied as a functional characteristic of T-lymphocytes [45]. Phagocytic and lysosome activity of monocytes was evaluated in order to characterize the mononuclear phagocyte system [46, 47].

Follow-up studies conducted over many years and analyses of the state of health in patients with CRS have led to the conclusion that a considerable contribution was made by immunity disorders to CRS pathogenesis, which in the long run determined the disease course to a significant degree. In the early years of radiation exposure, immunity changes contributed to the development of infectious complications. It should be noted that concurrent infectious processes contributed to the advancement of the underlying disease [40].

Infectious processes concomitant with the underlying CRS had some specific features. Inhibition of granulopoiesis and infectious reactions often resulted in attenuation of the clinical symptoms of acute pneumonia, respiratory infections, etc. In such cases, a protracted course of tonsillitis and a lasting subfebrile condition following acute respiratory diseases [41] were observed. On the other hand, an increased incidence of destructive processes and hemorrhagic syndrome was also noted [40].

At late stages, disorders of immunity could obviously be one of the causes predisposing to more frequent development of malignant growth in CRS patients.

While discussing the causes of the persistence of these changes in immune status, it should be remembered that the uptake of osteotropic ^{90}Sr does result in many years of radiation exposure of the RBM, one of the central organs of the immune system. Considering the function of the immune system in the organism as a whole, one should stress the immune system's close functional relation to the nervous, endocrine, and hematopoietic systems: any changes in these systems may bring about immunity disorders and vice versa. It should also be stressed in this connection that the changes in these systems played the principal part in the clinical picture of CRS and determined its symptoms.

The results of many years of follow-up examinations of individuals who had CRS provide evidence that changes in immune status play an essential role in the pathogenesis and clinical course of CRS. Failure to detect any changes using routine immunity studies in persons who had CRS in the early years cannot in our opinion be regarded as evidence of the immune system's status as being normal.

Prospective immunological studies in this population group should be aimed at studying factors that determine antitumor immunity, particularly the status of natural killers, the phagocytic link, the interferon system, etc. Detection of long-term antitumor immunity changes and the research into their nature in people who had CRS will provide the basis for applying immunomodulators for long-term prophylaxis.

Table 7.23. Immunity parameters (M ± SE) evaluated for CRS patients 40 years after initial exposure to radiation.

Parameter	CRS patients (22)	Comparison group (22)
E-RFC (%)	75.68 ± 2.09	76.96 ± 2.26
E-RFC, 10^9/l	1.45 ± 0.13	1.56 ± 0.13
ME-RFC (%)	22.86 ± 1.73	22.59 ± 1.96
ME-RFC, 10^9/l	0.44 ± 0.05	0.43 ± 0.05
MN-RFC (%)	52.86 ± 3.31	55.73 ± 3.10
MN-RFC, 10^9/l	1.01 ± 0.10	1.13 ± 0.11
E-RFC_{thr} (%)	61.22 ± 4.25	63.46 ± 3.88
E-RFC_{thr}, 10^9/l	1.18 ± 0.13	1.31 ± 0.13
E-RFC_{ths} (%)	12.68 ± 2.23	13.09 ± 1.53
E-RFC_{ths}, 10^9/l	0.26 ± 0.05	0.33 ± 0.08
AE-ROC (%)	54.68 ± 4.93	60.91 ± 4.63
AE-ROC, 10^9/l	1.05 ± 0.14	1.26 ± 0.14
B-lymphocytes (%)	6.14 ± 0.63	6.64 ± 0.78
B-lymphocytes, 10^9/l	0.13 ± 0.02	0.13 ± 0.02
O-lymphocytes (%)	16.64 ± 1.77	14.86 ± 1.80
O-lymphocytes, 10^9/l	0.33 ± 0.05	0.32 ± 0.05
BTR (%)	65.77 ± 4.10	71.48 ± 2.86
IgA, g/l	1.33 ± 0.11	1.47 ± 0.10
IgG, g/l	7.70 ± 0.44	8.09 ± 0.36
IgM, g/l	0.97 ± 0.07	1.04 ± 0.06
ANAM, 10^9/l	0.065 ± 0.009	0.07 ± 0.005
PAM, IU/l	0.19 ± 0.03	0.25 ± 0.04
PA (%)	24.73 ± 2.81	24.96 ± 2.04
NMLA, IU/l	0.59 ± 0.08	0.85 ± 0.12
LGL (%)	4.30 ± 0.68	4.77 ± 0.91
LGL, 10^9/l	0.23 ± 0.04	0.31 ± 0.06

Note: The number of CRS patients and of the comparison group is indicated in parentheses.

CHAPTER 8

Verification of Diagnosis of Chronic Radiation Sickness

Differential Diagnosis Between Chronic Radiation Sickness and General Somatic Diseases

As described in chapter 7, CRS has no specific symptoms that would not occur in other diseases or that would only be inherent to CRS. Therefore, in order to establish the diagnosis of CRS, at least two requirements must be met: (1) reliable information on the character of the irradiation and the absorbed dose must be available, and (2) a differential diagnosis between radiation effects and general somatic conditions must be established.

Structure of general somatic diseases in exposed population. This chapter focuses on the results of a retrospective analysis of other diseases diagnosed in CRS patients at the time CRS was diagnosed. The analysis is based on the diagnostic information file that contains 9,691 entries of different diseases diagnosed in CRS patients at different times during the total period of follow-up.

Of the total number of diseases occurring in our patients, a considerable portion can be assigned to the type of pathology that requires no differential diagnosis from CRS, e.g., nutritional disturbances manifested by obesity, diseases of solid tissues of the teeth, ocular refraction and accommodation disturbances, hernias, and trachoma, which were widespread in rural localities of the Urals in the fifties.

Other types of diseases included in the analysis were those with signs and symptoms commonly seen in CRS and could be confused with it. It should be pointed out that a fraction of the CRS population (106 people) were lost to follow-up very early because of forced or freely willed migration. Their medical records contained findings on only one or two outpatient examinations, making it impossible to establish a differential diagnosis for CRS. In 238 patients with CRS, no diseases that could be confused with CRS were recorded at the time of diagnosis. The rest of the patients had other diseases at the time of CRS diagnosis or about that time; the most important of them are listed in table 8.1. For each examined individual, only the most serious disease concurrent with CRS is indicated.

Brucellosis. Infectious and parasitogenic diseases were diagnosed most often, with brucellosis the most common among the 149 cases. In fact, brucellosis was a disease endemic to the Chelyabinsk region since the thirties. Due to an epizootic situation in the region at that time, the disease reached epidemic proportions in humans. On the basis of serologic reactions, a large number of infected people with acute or chronic epizootic processes were detected on the farms of the region, with the highest incidence being observed in milkmaids, veterinary workers, and cattle-farm workers [48]. In the villages located along the Techa, flocks of farm animals (cows and sheep) affected by brucellosis had been kept for 30-40 years—since the thirties.

The diagnosis of brucellosis was established in residents of these villages on the basis of clinical signs, positive serologic reactions, and skin tests for allergies. In most cases the condition was diagnosed as a primary-latent (chronic) form of brucellosis,

Table 8.1. General somatic diseases in CRS patients.

Disease class and clinical entity	Number of cases
Infectious and parasitic diseases	199
Tuberculosis	20
Brucellosis	149
Malaria	9
Syphilis	1
Gonorrhea	1
Helminthiasis	19
Neoplasms	5
Cancer of the stomach	3
Connective tissue cancer	1
Chronic lympholeukosis	1
Diseases of endocrine organs	16
Thyrotoxicosis	15
Myxedema	1
Psychiatric disorders	22
Alcoholism	2
Mental retardation	2
Neurosis	14
Other mental diseases	4
Diseases of the nervous system and sense organs	21
Residual phenomena of neuroinfection	13
Chronic otitis	8
Diseases of blood circulation system	85
Rheumatism and rheumatic diseases	26
Heart diseases of pulmonary origin	25
Ischemic heart disease	10
Cerebrovascular diseases	12
Atherosclerosis	12
Blood diseases	25
Iron-deficiency anemia and anemia of unknown etiology	25
Diseases of respiratory organs	57
Influenza	5
Pneumonia	13
Chronic bronchitis	12
Chronic focal infection (sinusitis, tonsilitis)	27
Diseases of digestive organs	87
Duodenal ulcer	13
Appendicitis	4
Colitis	6
Chronic cholecystitis	17
Hepatitis	47
Diseases of urogenital organs	36
Chronic inflammation of ovaries and adnexa	36
Complications of pregnancy and labor	12
Pregnancy	12
Skin diseases	4
Dermatitis	2
Furunculosis	2
Diseases of osteomuscular system	4
Osteomyelitis	4
Trauma	23
Consequences of intracranial trauma	23

manifested by ostealgia, arthralgia, or asthenia, and in a number of cases, by liver enlargement as well as by changes in peripheral blood: a more or less pronounced leukopenia, neutropenia, thrombocytopenia, moderate anemia, and an increased percentage of eosinophils and plasmatic cells.

The serologic titers exceeded diagnostic levels but were not very high. Similar to other researchers [49, 50], we experienced difficulties in a number of cases in finding an answer to the following question: Should a patient be regarded as an individual infected with a causative agent of brucellosis, i.e., showing a positive reaction to the brucellosis antigen, or as an individual affected by the primary-latent (chronic) form of brucellosis with an obscured clinical picture. The situation was also complicated by the fact that cattle-farm workers were vaccinated for prophylactic purposes with an antibrucellosis vaccine, which accounted for positive serologic reaction titers persisting for a long time. Unfortunately, the names of the people vaccinated with the antibrucellosis vaccine were not available to us when a differential diagnosis was determined.

Questions about a differential diagnosis between brucellosis and radiation pathology were constantly considered during medical examinations of the exposed population: time of occurrence of clinical symptoms and their development were thoroughly analyzed, and immunological diagnostic methods and skin tests with brucellosis vaccine were applied [51, 52]. The method of discriminant analysis was also used, the results of which are listed in this chapter.

Chronic and focal infections. Other chronic infectious diseases (tuberculosis, malaria) were registered with lesser frequency in comparison to brucellosis, but as a rule were accompanied by asthenia, leukopenia, and neutropenia, which is typical of this kind of pathology and can imitate CRS [53].

In some CRS patients, focal infections were also recorded: chronic otitis, tonsillitis, sinusitis, adnexitis, cholecystitis, etc. These diseases could present difficulties for a differential diagnosis only in cases when outpatient examinations were conducted by visiting medical teams. When patients were examined at an inpatient department, a differential diagnosis between CRS and infectious diseases did not present any difficulties.

Neoplasms. Three patients developed neoplastic processes with fatal outcomes shortly after CRS was diagnosed (within several weeks to a year). In one case, the patient was administered radiation therapy for a uterine fibrosarcoma a year before CRS was diagnosed. The role of the treatment in development of leukopenia and asthenia syndromes in this patient was evidently more significant than the radiation she was exposed to on the Techa.

Sequelae of Intracranial Trauma. This pathologic condition which manifested itself just like residual phenomena of neuroinfection—by asthenia, disturbances of vascular regulation, presence of asymmetric and abnormal reflexes—could be confused with radiation effects because of the similarity of symptoms, especially if the patient's past history was taken without sufficient care. However, on dynamic follow-up, especially if done at an inpatient department, the causes of the symptoms would have been identified. As a rule, the diagnosis of CRS was not based on neurological symptoms only; the clinical picture included some other manifestations of radiation pathology.

Other Diseases and Symptoms. We experienced considerable difficulty in evaluating diseases such as anemia, hepatitis, and disturbances of thyroid gland function, most commonly thyrotoxicosis, when they were diagnosed simultaneously with CRS. In 25 cases, the diagnosis of anemia was made at about the time the diagnosis of CRS was established. In a number of cases, it was iron deficiency anemia due to hypoacidity of gastric secretions. Three patients had posthemorrhagic anemia caused by hemorrhoidal bleeding or abortion. However, in the majority of cases, the pathogenesis of anemia remained obscure.

It should be pointed out that the cases of anemia are those that were recorded in 1952-1954. During those postwar years, food rations of the population were characterized by trace elements and a lack of vitamins. According to published data [18], the hemoglobin level in 95% of the population was 117 g/l for males and 108 g/l for females. Such values were considered normal. Taking into account such low values (which were considered normal at that time), the still lower levels of hemoglobin and erythrocytes recorded for irradiated patients could be regarded as manifestations of either radiation effects or other pathologic conditions often caused by nutritional deficiencies. At the same time, erythropoiesis impairment is not considered characteristic of the effect produced by the doses recorded for the population irradiated on the Techa.

Liver diseases designated as chronic hepatitis were diagnosed in 47 patients. Analysis of medical records shows that the diagnosis was most often established on the basis of the patient's complaints of discomfort and hepatomegaly revealed by palpation, not on the basis of the findings of liver function tests. In 55.3% of these cases, the findings of duodenal intubation were found to be normal, and in 32% of the cases, giardiasis was revealed. Bilirubin concentration ranged from 2.22 to 10.94 mol/l (0.13-0.64 mg %), but in no case did it exceed normal limits. Liver size normalization took place as a rule during the course of hospital treatment (2-3 weeks). Thus, an independent diagnosis of chronic hepatitis was not sufficiently substantiated.

As for diseases of the thyroid gland, the entire follow-up did not give us sufficient reason for associating this pathology with radiation exposure. We were assured by specialists of the Mayak Production Association that only "old" uranium fission products were discharged into the Techa, i.e., iodine-free wastes, and that the population of the riverside villages was not exposed to other man-made radiation sources.

In August 1993, some oral reports appeared about off-site population exposures occurring over the past 40 years. They were said to occur not only due to nuclear accidents but also to releases of radioactive matter during the so-called "normal" operation of the facility. The principal contributors to the doses were radioactive iodine and plutonium. The

territories exposed to contamination from these releases have not yet been clearly defined, and the doses received by the population have not been estimated. After reliable information on the character and levels of exposure is made available, it will be necessary to resume thyroid pathology analysis for this population. Thus, data cited in this section show that, by the time radiation effects had been diagnosed, most of the population were suffering from general somatic conditions that imitated CRS clinically, which made the establishment of a differential diagnosis absolutely necessary.

Use of discriminant analysis for differential diagnosis. It is well known that some latent chronic processes such as brucellosis cause leukopenia and neutropenia as well as asthenia, which impedes a differential diagnosis for CRS. The task of diagnosing cases of brucellosis is even more complicated because characteristic tests for brucellosis sometimes become nonspecific in cases of radiation exposure [52]. It was therefore decided to classify patients with diagnosed CRS and brucellosis on the basis of sets of quantitative parameters using the method of discriminant analysis [54]. The work was carried out in three stages. At the first stage, a "training sample" was made that included cases of the most reliable diagnoses of CRS and brucellosis. A set of quantitative parameters applicable in the differential diagnosis of these diseases was identified, and the mean values, dispersions, Student's criterion, and linear discriminant function coefficients were obtained on the basis of these parameters.

In our case, classification was complicated because the data used, which had been obtained 20-30 years ago, did not conform to unified requirements, and only a limited number of patients had a complete set of relevant data. The second stage, therefore, dealt with selection of different variants from a complete set of parameters on the basis of which classification was still feasible. The proper classification was made at the third stage.

The training sample included CRS cases that were diagnosed on blood counts, bone marrow, reactions of Wright, Haddleson, and Burney, complaints of ostealgia and arthralgia, and microsymptoms of nervous system effects. All individuals who were examined at an inpatient department had a complete set of parameters that enabled us to consider their diagnoses as fairly reliable. The following quantitative characteristics were selected for discriminant analysis: 10 peripheral blood count parameters, 9 bone marrow parameters, and titers of Wright and Haddleson reactions.

The training sample was composed of 13 cases with diagnosed CRS and complete sets of the parameters indicated above and of 11 cases with brucellosis. The parameters of the training sample are presented in table 8.2; the difference in mean values is only significant for three parameters (Wright and Haddleson reactions and plasma cells of the bone marrow) and is close to the critical threshold for two parameters (neutrophils and myelokaryocytes).

Figure 8.1 shows the results of the classification of training sample subjects with different sets of parameters. Classes are easily differentiated if they have complete sets of parameters. Classification is also feasible on the basis of such combinations as blood and bone marrow or blood and reactions of Wright and Haddleson; however, the combination of blood and bone marrow results in the formation of an uncertain zone in which classes partially overlap. When only blood parameters are available, there is a significant overlap of classes, and classification is not feasible.

At the third stage, the so-called "checking sample" was made. It included 39 cases, of which 23 were previously diagnosed as brucellosis and 13 as CRS, but no suitably reliable verification of diagnosis was carried out. In three cases, the diagnosis was doubtful. Figure 8.2 shows the results of the checking sample classification on the basis of blood counts and of Wright and Haddleson reactions. The diagnosis was confirmed for all 13 CRS cases; of the 23 cases tentatively diagnosed as brucellosis, 5 had to be assigned to CRS case numbers 19-23, which required another analysis of existing medical records and examination findings. As a result, we had to admit that in some cases the symptoms of CRS occurred against the background of brucellosis, with a latent course or positive reaction to brucellosis antigen. Of the three questionable cases, one was assigned to brucellosis (case number 37) and the other two to CRS (case numbers 38 and 39). Thus, discriminant analysis can differentiate CRS from brucellosis on the basis of the following sets of indicators: (1) blood, bone marrow, and reactions of Wright and Haddleson; (2) blood and Wright and Haddleson reactions; and (3) blood and bone marrow.

Table 8.2. Statistical characteristics of the "training sample".

Blood parameters	CRS Mean	CRS Sigma	Brucellosis Mean	Brucellosis Sigma	Student's criterion	CLDF
Peripheral blood						
1. Erythrocytes, 10^{12}/l	4.11	0.37	4.4	0.46	1.65	1.61×10^{-2}
2. Thrombocytes, 10^{9}/l	234.2	35.8	264.4	56.3	1.59	-1.41×10^{-2}
3. Leukocytes, 10^{9}/l	4.3	1.1	4.7	1.01	0.78	-2.99×10^{-4}
4. Stab neutrophils*	7.54	3.04	8.09	5.21	0.32	-3.18×10^{-2}
5. Neutrophils*	32.6	6.5	37.0	9.9	1.30	-6.49×10^{-2}
6. Neutrophils, 10^{9}/l	1.69	0.43	2.02	0.37	2.01	-2.03
7. Lymphocytes*	44.3	7.5	40.5	9.6	1.09	5.26×10^{-2}
8. Lymphocytes, 10^{9}/l	1.90	0.62	1.96	0.77	0.22	-0.13
9. Monocytes*	8.65	2.91	9.55	2.76	0.77	-0.11
10. Eosinophils*	4.77	5.04	3.46	2.04	0.81	8.36×10^{-2}
Bone marrow						
11. Myelokaryocytes, 10^{9}/l	135.5	67.35	87.4	56.85	1.87	1.22×10^{-5}
12. Reticular cells*	0.72	0.69	0.56	0.66	0.56	0.34
13. Lymphocytes*	6.97	2.53	9.52	4.77	1.67	-0.18
14. Plasma cells*	1.22	0.73	2.23	0.83	3.19	-1.69
15. Monocytes*	4.28	8.97	2.38	1.38	0.69	4.24×10^{-2}
16. Eosinophils*	3.64	2.21	2.56	1.09	1.47	0.33
17. Granulocytes*	65.5	4.9	61.9	6.8	1.50	0.11
18. LE index	3.04	1.32	3.67	1.52	1.09	-0.32
19. Neutrophil maturation index	1.05	0.32	0.89	0.25	1.35	1.89
20. Wright's reaction titer	0.15	0.55	2.09	2.98	2.31	-0.46
21. Haddleson's reaction titer	0.70	1.25	3.64	0.81	6.70	-2.56

*Percentage
CLDF, coefficients of linear discriminant function.
LE index, leukocyte-erythrocyte index

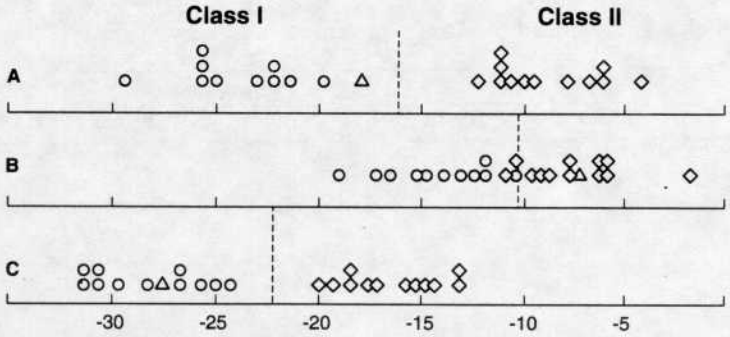

Fig. 8.1. Training sample classification findings for the different sets of indicators: (A) blood count findings + bone marrow study findings + Wright reaction + Haddleson reaction; (B) blood count findings + bone marrow study findings; (C) blood count findings + Wright reaction + Haddleson reaction. Class I, brucellosis; Class II, CRS. Preliminary diagnoses: o, brucellosis; ◊, CRS; Δ, brucellosis and CRS.

In the event that these two conditions occur simultaneously, a case may be assigned to one of the classes when the symptoms of one or the other of the diseases are distinct.

Radiation-induced pathology aggravated by general somatic diseases. In cases of accidental radiation exposure of large groups of a population it is unreasonable to assume that only radiation effects or only general somatic diseases will occur. As shown by the results of the analysis presented in this chapter, most of the population suffered from other diseases before being exposed to radiation. Presence of these diseases did not by any means impede the development of clinical manifestation of radiation effects; it actually stimulated development of radiation-induced pathology. According to our observations, the likelihood of CRS development was higher in those patients who already had diseases such as endocrine disorders, chronic infections, avitaminosis, reduced hematopoietic reserve, etc. These intercurrent conditions weakened the organism's reserve powers and to a considerable degree contributed to increased radiosensitivity.

The use of discriminant analysis to differentiate between brucellosis and CRS revealed some uncertainty in assigning a case to a particular classification even if adequate criteria for diagnosing the disease had been used. The most logical explanation for this phenomenon is the simultaneous presence of two diseases: brucellosis and CRS.

The presence of both a radiation disease and a general somatic condition was most common for two age groups of the irradiated population: children and middle-aged or elderly people. Our clinical experts have researched the reactions of a child's organism to irradiation [55]. The significant sensitivity of a child's organism to radiation (especially when irradiated *in utero*) has been demonstrated. At the same time, the higher flexibility and the well-manifested compensatory-adaptive reactions of a child provided for fairly prompt restoration processes after exposure stopped.

Restoring the functions disturbed by irradiation depended to a great degree on any general somatic diseases accompanying radiation effects. When

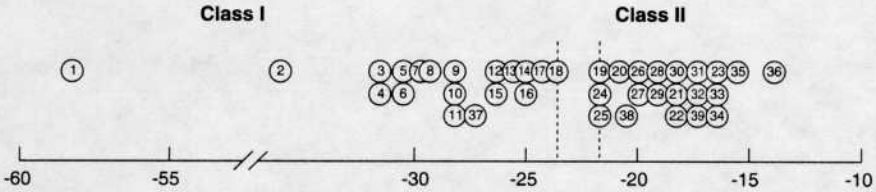

Fig. 8.2. Checking sample classification findings for sets of indicators: blood count findings + Wright reaction + Haddleson reaction. Class I, brucellosis; Class II, CRS. Preliminary diagnoses: numbers 1-23, brucellosis; numbers 24-36, CRS; numbers 37-39, diagnosis uncertain.

such diseases were present, restoration proceeded more slowly, as witnessed by findings of the dynamic follow-up of CRS patients.

Assessment of Annual Dose Rate Threshold for CRS in the Urals Population

As shown in preceding chapters, by the time the diagnosis of CRS was established, doses to bone marrow amounted to 1 Gy in only 17.9% of the people with diagnosed CRS. In only 1 case out of the 940 cases did the dose rate exceed 1 Gy/year. Therefore, the diagnosis of CRS was established for persons who did not attain the dose level assumed to be the threshold for deterministic radiation effect manifestations. The dose threshold value for CRS was estimated as 1.0-1.5 Gy/year in publications [20, 29, 56] on the basis of an analysis of radiation effects in nuclear workers. In ICRP Publication 41 [11], the dose of 0.4-1.0 Gy/year is assumed as the threshold dose for hematologic effects.

The following reasons may account for the inconsistency between radiation dose and establishing the diagnosis of CRS: (1) errors in individual dose estimates (addressed in chapter 3, section entitled Dose Estimation Evolution: Significance of Individual Dose Uncertainty); (2) mistakes in diagnosing CRS (possible mistakes are discussed at the beginning of this chapter); and (3) incorrectly estimated threshold dose for effect manifestations in a specific cohort of irradiated people.

In discussing the incorrectly estimated threshold dose, one should remember that, in cases of irradiation of different age groups with basic health impairment prior to exposure, the threshold dose for radiation effect manifestations may be lower than in occupational groups who have to go through a strict medical selection process before they are hired. In fact, such pathologic processes as autoimmune and endocrine disorders, chronic infections, avitaminosis, and kidney and liver diseases can reduce the hematopoietic reserve, thereby making it possible to develop CRS at lower dose levels than dose levels in healthy individuals. Analyzing one patient's disease history, we considered the diagnosis of CRS made in the early fities as fairly substantiated although her calculated individual dose to RBM was estimated as 0.31 Gy and her body content of ^{90}Sr was 271 nCi in 1975.

This patient (P-na), born in 1913, lived with her parents until 1936 in the village of Brodokalmak, located in the middle reaches of the river Techa. She then married and left for Ukraine. She gave birth to two children. In 1941, during World War II, she was forcibly sent to Germany and kept in a concentration camp from 1941 through 1945. She suffered from adnexitis, hemorrhoids, and frequent respiratory diseases for which she received no adequate treatment.

In 1945, when the war was over, she returned to her parents' home in the village of Brodokalmak because she had lost her family. Her house in Brodokalmak was located within 200 m of the edge of the river water. She felt badly and believed her health had been damaged during the war. Like all residents of riverside villages, she knew nothing about the contamination of the river and used its water for all needs: drinking, cooking, and watering vegetables in her kitchen garden. The first medical examinations revealed peripheral blood leukopenia. As a result of dynamic medical follow-up, a progression of symptoms was noted, and in 1958, CRS was diagnosed on the basis of radioactive element excretion in the urine and feces, persistent leukopenia and neutropenia in the peripheral blood, disturbed maturation of white bone marrow cells, and microsymptoms of organic damage of the nervous system.

Another reason for assuming a dose lower than 1 Gy/year as a threshold for CRS is that the condition was diagnosed in persons exposed in early childhood or *in utero*. In some of these individuals, CRS was diagnosed during the pubertal period, when the most important hormonal changes occur. A child's organism is particularly sensitive to radiation exposure. The view that children are the most vulnerable part of the population is reflected in ICRP Publication 13 [57], which states that the dose limit for schoolchildren must be one-tenth of the dose limit for the older population. Findings of the medical follow-up of A-bomb survivors in Japan showed a particularly high radiosensitivity of the fetus at certain stages of organogenesis [58, 59].

It can be suggested therefore that in some irradiated children the radiation syndrome is likely to develop at dose rates half as low as 1-1.5 Gy/year.

Social Aspects of Diagnosis Reassessment

Over the 40-year period of follow-up of patients with diagnosed CRS the conception of the conditions governing radiation effect manifestations has essentially changed, and a clear enough differentiation between deterministic and stochastic radiation effects has been developed, with threshold doses being defined for various deterministic effects. The perception of radiation hazards by both nuclear workers and an off-site population was changing over the years, methods of diagnosing radiation effects were improving, and estimates of exposure doses in a given situation were verified. A question was then raised about revising the CRS diagnosis established in the past. In the process, two aspects—scientific and social—unexpectedly acquired a special significance.

From the scientific point of view, retrospective analysis of CRS cases based on current scientific knowledge has shown that in a number of cases the diagnoses were mistaken: the dose of radiation was below the threshold limit that could have caused a deterministic effect, and the symptoms recorded in examined individuals resulted not from radiation exposure but from general somatic diseases. Taking into account the social aspect of the problem and the fact that people whose health was damaged by radiation exposure were entitled to certain benefits, none of the previous diagnoses of CRS was invalidated.

Other researchers were also faced with a contradiction between the scientific and social (legal) aspects of radiation effects. A document was issued for military personnel and civilian workers who were seeking compensation for health damage that presumably resulted from radiation exposure [60]. The document contained epidemiologic tables for calculating the "causative probability," i.e., assessing the probability of cancer development due to radiation doses in patients who had been exposed to certain radiation doses prior to cancer development. Thus, the document attempted to overcome the contradiction between the scientific and social aspects of the problem by, for example, the following reasoning: if ten petitioners claiming their rights state that excess radiation exposure received by them earlier had induced cancer development in them, and the tables show that a causative effect of radiation could account for only 10% of the cases, none of the petitioners are entitled to any compensation for health damage, whereas arbitrators maintain that all ten petitioners should receive compensation for 10% of their health damage.

In the present day situation, when newly adopted legislation [61] guarantees more benefits to people who had CRS than to those who were irradiated but did not develop CRS, it is considered impossible to raise the question of cancelling any CRS diagnoses. This decision is motivated by the uncertainty of individual doses in our situation—when the actual dose of external radiation may be proven to be higher than the dose reconstructed as the average dose for a given age group and community.

CHAPTER 9

Clinical Picture of Verified Cases of Chronic Radiation Sickness

"Image" of Chronic Radiation Sickness

Retrospective assessment of the reliability of CRS diagnoses has revealed a number of erroneous diagnoses and, at the same time, has reaffirmed the cases in which deterministic radiation effects were substantiated. Results of the medical follow-up for patients whose CRS diagnoses were verified with sufficient accuracy are provided in this chapter.

The diagnosis of CRS was considered to be substantiated if the following conditions were met.

- Exposure to ionizing radiation sources: long-term residence in a Techa riverside settlement for at least 3 years, starting from 1950; use of river water regularly for drinking, cooking, and other domestic needs; individual measurements of radioactive strontium body burden made with a whole-body counter or by the method of beta-counting in teeth; and a dose of at least 1 Gy to RBM.
- Full-scale medical follow-up, including examinations at inpatient departments at about the time the diagnosis was established as well as dynamic observation in subsequent years.
- Absence of diseases with symptoms closely resembling those of CRS at the time of diagnosis.
- Clinical manifestations of CRS in accordance with the description of radiation pathology and CRS classification provided in reference 20 were used as criteria for CRS diagnosis.

These criteria were met by 66 patients in whom the diagnosis of CRS was considered as substantiated. Of the 66 cases, 21 were residents of the upper reaches of the Techa in the village of Metlino, 44 resided in other upper Techa villages, and 1 patient was a resident of the village of Brodokalmak located in the middle reaches of the river. The percentage of males was 51.5% (34 patients) and that of females was 48.5% (32 patients). The age distribution was remarkable because of the number of individuals irradiated in childhood and adolescence. Among the 66 patients with CRS there were 46 patients (69.7%) who were 0-19 years old at the time exposure started, 18 (27.3%) patients were 20-39 years old, and only 2 patients (3%) were over 40. It should be noted that in patients irradiated in childhood, the symptoms of radiation exposure were recorded during puberty, i.e., 10-15 years after the beginning of exposure.

The clinical symptoms of CRS and their dynamics are shown in table 9.1 and figure 9.1. The patients with confirmed CRS diagnoses had the same clinical manifestations that were described in the preced-

Table 9.1. Clinical symptoms of CRS and their dynamics.

	Stage of CRS course (years)			
	Development	Recovery		Long-term effects (outcomes and sequelae)
Symptoms and syndromes	1951-1955	1956-1959	1960-1969	≥1970
Peripheral blood disorders				
Anemia				
Mean count of erythrocytes, 10^{12}/l, M	4.1	4.4	4.5	4.5
Mean count of erythrocytes, 10^{12}/l, F	3.8	4.2	4.2	4.2
Leukopenia				
Mean count of leukocytes, 10^9/l	4.7	5.4	5.5	5.7
Neutropenia				
Mean count of neutrophils, 10^9/l	2.6	2.5	2.8	3.3
Thrombocytopenia				
Mean count of thrombocytes, 10^9/l	181	240	264	262
Disturbances of bone marrow hematopoiesis				
Hypoplasia				
Percentage of persons with myelokaryocyte count <41.6 x 10^9/l	37.5	11.1	17.1	15.4
Increased proliferation of erythroblastopoietic tissue				
Percentage of persons with erythroblast count >26.4	36.3	16.7	9.3	5.6
Slow maturation and differentiation of granulocytes				
Mean value of neutrophil maturation index	0.9	1.0	0.6	0.5
Occurrence of clones of pathological cells with Ph'-like chromosome				
Number of cases out of 11 followed-up	0	0	0	5
Leukosis				
Number of cases	1	0	1	2
Impairment of vascular regulation				
Percentage of persons with hypotension (BP <100/60 mm Hg)	44.4	37.5	11.4	3.2
Impaired neurological status				
Percentage of persons with microsymptoms of organic injury	32.0	36.1	19.1	17.3
Percentage of persons with ostealgia	24.0	55.6	51.0	22.2
Percentage of persons with vertebrogenic symptoms	16.0	19.4	21.3	64.2

M = male; F = female.

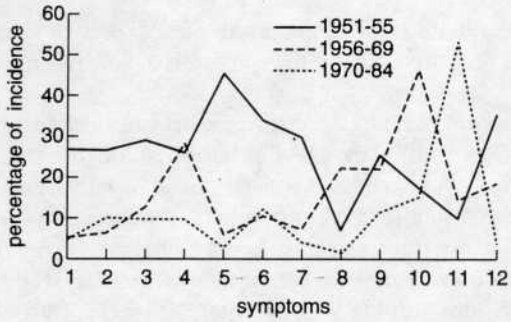

Fig. 9.1. Incidence of various symptoms of CRS at different stages of follow-up. 1951-1955 —; 1956-1969 ----; 1970-1984 - - - -.

(1) Anemia, male; erythrocytes <4.0 x 10^{12}/l
(2) Anemia, female; erythrocytes <3.7 x 10^{12}/l
(3) Leukopenia: leukocytes <4.1 x 10^{9}/l
(4) Neutropenia: neutrophils <2.0 x 10^{9}/l
(5) Thrombocytopenia: thrombocytes <180.0 x 10^{9}/l
(6) Bone marrow hypoplasia: myelokaryocytes <41.6 x 10^{9}/l
(7) Erythroblastopoietic tissue proliferation: erythroblasts >26.4%
(8) Granulocyte maturation disorders (neutrophil maturation index >0.9)
(9) Microsymptoms of organic nervous system injuries (%)
(10) Ostealgia (%)
(11) Vertebrogenic syndrome (%)
(12) Hypotension (%)

ing chapters; however, all pathological changes were more pronounced, were characterized by combinations of symptoms, and persisted for a long time.

The most significant abnormalities were observed in the blood-forming system. The dynamics of the functional state of different organs and systems have demonstrated that pathological manifestations often depended on the rate of radiation exposure, and the most pronounced changes were observed during the years when the rate was highest—the period of CRS development. At that time a certain inhibition of hematopoiesis was noted, which manifested itself by leukopenia (mainly at the expense of neutrophils), moderate anemia, and thrombocytopenia. It may be suggested that changes in peripheral blood composition are due to a certain focal bone marrow hypoplasia, which may be demonstrated by an increased number of cases of a relatively low content of myelokaryocytes. A relatively high neutrophil maturation rate may be evidence of impaired differentiation of granulocytic-type cells, but it may also be regarded, with sufficient grounds, as an activation of regenerative potential in response to the loss of some cells.

During the same period, almost half of these patients had disturbances of vascular regulation, manifested by neurovascular dystonia of hypotonic character. In a third of the patients, the symptoms of organic effects, mainly locomotor/reflex disorders, were determined in the nervous system. Regenerative processes in hematopoiesis were observed with significantly decreased irradiation rates and a slowing down of total dose absorption rates. At that time, increased leukocyte and thrombocyte counts characteristic of the restorative stage, disappearance of anemia, and normalization of total bone marrow cellularity were noted. Of the hematopoietic symptoms, neutropenia persisted. However, it should be noted that hematopoiesis was recovering at a faster rate than nervous system normalization because the number of patients with microsymp-toms of nervous system effects and ostealgia was still significant at that time.

The late stage of CRS, as confirmed by the data cited in table 9.1 and figure 9.1, was characterized by rehabilitation and essential recovery of the patients. Thirty-five years after the exposure started and 30 years (on average) after establishment of the diagnosis, no clinical manifestations were recorded in any cases. The blood count readings and bone marrow studies were approaching normal limits, and the incidence of nervous system disorders was similar to that observed in the nonexposed population.

At the same time, in the late period of CRS due to exposures to uranium fission products, a significant number of individuals with vertebrogenic syndrome were observed. At that stage, in 5 of 11 patients, clones of cells with atypical monocentrics (from 4.6% to 30%) resembling Ph chromosomes were revealed in cytogenetic studies. However, no signs of leukosis were revealed.

During the entire follow-up period, 4 of the 66 CRS patients died from leukemia. Five years after the exposure started, patient Zh.N.D. died at the age of 18; her case history is given in chapter 6. In two other cases, focal hypoplasia of the blood marrow during development of CRS and chronic myeloid leukemia in the late stage of CRS were recorded. These two cases of CRS were confirmed at the clinic of the Institute of Biophysics. A total of six CRS patients died of malignant neoplasms from 1952 through 1985. Alhough we are aware that estimating a mortality rate based on such a small group is unreliable, we used the obtained ratio of 315.8, computed for 100,000, and compared it with the

value 132.9, computed for the total irradiated population. Increased tumor morbidity, therefore, is obviously a long-term outcome of CRS.

Is Chronic Radiation Sickness a Specific "Strontium Disease" of the Population Exposed on the Techa?

Because internal radiation played an important role in the exposure on the Techa and the principal dose-forming factor was ^{90}Sr, it seems reasonable to suggest that the diagnosed radiation disease was "strontium disease."

It was expected that marked symptoms of bone system disorders would be observed. Actually, persistent and pronounced ostealgia, later followed by vertebrogenic syndrome, was frequently noted in CRS patients. Histologic examinations of trephine biopsies revealed the presence of osteodysplastic processes and endosteal and stromal fibrosis in a number of cases. However, it should be noted that, even in those cases of CRS that were caused by uniform external radiation or external radiation combined with ^{239}Pu incorporation, ostealgic and dysplastic changes were also revealed in bone tissue [20]. No increase in the incidence of osteosarcomas was recorded during the 35 years of follow-up.

In comparison to the dynamics of the symptoms of CRS caused by external radiation, exposure to uranium fission products was characterized by a certain "delay" in the development of the hematopoietic process of normalization and by a long-term persistence of neurologic symptoms when the stage of CRS development was over. It was obviously caused by a constant increase in the absorbed dose due to long-lived radionuclide incorporation.

No other characteristic signs of CRS caused by exposure to uranium fission products were noted. Clinical manifestations that were recorded in followed-up patients, in fact, did not differ much from the signs and symptoms of CRS caused by external radiation and described in a number of publications [20, 23]. It is not surprising that the most significant contribution to the total dose to RBM, the organ critical for the development of CRS, was made by external radiation. In the overwhelming majority of cases, CRS diagnoses were confirmed in persons exposed in the villages located in the upper reaches of the river, where the contribution of external radiation to the total dose to the RBM was at least twice as much as that from internal radiation.

CHAPTER 10

Uncertainties in Prevalence Studies of Chronic Radiation Sickness for the Techa River Population

The consequences of radiation accidents that result in environmental contamination may be assessed on the basis of the damage done to the health of the population residing in the area and, more specifically, on the basis of stochastic and deterministic effects. One of the most essential, integral, and deterministic effects is radiation sickness.

There were 66 confirmed cases of CRS among the 28,000 people irradiated on the Techa river. The areas where this population resided are shown in table 10.1. CRS diagnoses were confirmed and recorded in about 1% of the patients residing in the upper reaches of the river, whereas no cases of CRS diagnosis were confirmed in the lower reaches of the river.

The estimates of CRS prevalence should be considered as tentative and minimal. They are tentative because it was not possible to retrospectively estimate the percentage of irradiated individuals with CRS who had not been examined in the early years of exposure. Medical checkups did not include the whole population, and the examined cohorts were not representative of the whole irradiated population in radiation level, age, and basic health status. The estimates are minimal because, as an example, one patient was diagnosed with both radiation effects and somatic disorders. In the 66 cases of CRS there were no general somatic diseases that could be confused with CRS. The necessity to characterize clinical manifestations of CRS as precisely as possible justified the strict approach in confirming the diagnosis of CRS. However, this approach did not correspond to real disease prevalence because combinations of CRS and general somatic diseases were often observed. According to our estimates, the maximum CRS prevalence values are not likely to exceed the minimum values by more than threefold to fivefold and can be confirmed by population radiation burden distribution.

Table 10.1. Techa river areas where CRS patients lived.

Riverside areas	Number of patients	Percentage of total irradiated population
Site of release	21	1.79
Upper reaches	44	0.61
Middle reaches	1	0.01
Lower reaches	0	0.0

CHAPTER 11

Proposals for Further Research Into Chronic Radiation Sickness

This report summarizes the principal scientific results of the analysis of the clinical cases of CRS in the Southern Urals as a result of the disposal of radioactive waste into the river Techa and the long-term exposure of the population to significant doses of radiation. CRS was diagnosed in 940 cases. The methods used for assessing radiation levels are described, and the data on calculated individual doses are given. This report contains detailed descriptions of the status of different organs and of the hematopoietic, skeletal, nervous, cardiovascular, digestive, and immune systems, which were evaluated by clinical and laboratory methods used in medical follow-up. Abstracts from a number of case histories of CRS patients are also provided.

In the course of preparing this report, the initially formulated task (to give a description of cases of CRS in persons exposed to uranium fission products in the Southern Urals) was extended to include an analysis of the certainty of the CRS diagnoses. As a result, we concluded that the diagnoses were not correct. In some cases the dose of radiation did not attain the limit accepted as the threshold for CRS development, and the symptoms observed were manifestations of general somatic diseases and not a result of exposure to radiation.

The causes of erroneous diagnoses have been analyzed. One of the principal causes was the lack of adequate information on individual exposure burdens in the irradiated population. According to the regulatory guide "Norms of Radiation Safety," no individual dose assessment for irradiated persons is required. It was considered permissible to assess radiation doses to the population on the basis of mean individual equivalent doses for a critical population group. However, the concept of a critical group has not as yet been clearly defined. The experience gained in dealing with accidental radiation situations shows that the specialists engaged in rendering medical assistance to the exposed population on the basis of clinical symptoms failed to identify the critical group of persons whose radiation burdens and radiation effects were highest.

As a result of a revision of the criteria for diagnosing CRS, 66 cases that met those criteria were selected for this current analysis. These cases enabled us to describe the clinical symptoms of CRS caused by exposure to uranium fission products. Impaired hematopoiesis was found to be the most crucial symptom. In addition, the effects of exposure to uranium fission products were manifested by vascular regulation disorders, asthenia, ostealgia, inhibited secretion of the gastric glands, and disturbances of the immune function. At radiation doses above 1 Gy to RBM, more severe types of chronic radiation injuries were observed—micronecrotic alterations in the myelinic membrane of nervous conductors and, in a number of cases, fibrous tissue proliferation in the bone marrow stroma.

A number of questions that could contribute to the in-depth conception of the pathogenetic mechanisms of CRS are beyond the scope of this present work. Thus, this report does not contain data on radiosensitive systems such as the lens and the reproductive system. At the time when CRS diagnoses were made, many of the patients were adolescents, and others were adults at the reproductive age. The computer-based data bank of the Urals

Research Center for Radiation Medicine in Chelyabinsk contains both a registry of the exposed population and a registry of their offspring. The latter allows analysis of birth rate data for the exposed population who suffered CRS in the past and comparison to the respective parameters for matched cohorts of the nonirradiated population.

From our point of view, an analysis of the outcomes of CRS is of great importance also. In the majority of our cases, a recovery was recorded, but over the 40-year period that has elapsed since the CRS diagnosis was established, a large number of patients have died. By the time this report was prepared, 217 CRS patients had died. An analysis of death causes and life spans for this population in comparison with control cohorts could provide valuable information on long-term effects of chronic radiation at doses accounting for deterministic effects. Such an analysis ought to comply with the principles applied to epidemiologic studies.

There is finally one more question, that of effective methods for treating CRS. Our clinic used methods and preparations that stimulated hematopoiesis and regenerative processes, symptomatic treatment, and a number of radioprotectors. At present, the restrictions concerning publications covering these issues have been lifted. Until the effectiveness of the measures aimed at reducing radiation levels and abating radiation effects has been thoroughly analyzed, we have no reason to consider that all lessons have been learned from the Urals radiation accidents and that all experience has been taken into account.

The study of CRS should be continued, and the outcome should be the development of an algorithm for automated radiation injury diagnosis and optimum treatment choices.

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ABBREVIATIONS

AE-ROC - active rosette-forming cells (active T-lymphocytes)

AFRRI - Armed Forces Radiobiology Research Institute

ALT - alanine aminotransferase

ANAM - absolute number of active monocytes

AST - aspartate aminotransferase

BTR - blast-transformation reaction

CLDF - coefficients of linear discriminant function

CRS - chronic radiation sickness

E-RFC - rosette-forming cells with sheep erythrocytes (T-lymphocytes)

E-RFC$_{thr}$ - theophylline-resistant T-lymphocytes

E-RFC$_{ths}$ - theophylline-sensitive T-lymphocytes

ICD - International Classification of Diseases

ICRP - International Commission on Radiological Protection

Ig - immunoglobulins

LE - leukocyte-erythrocyte

LGL - large granulocytic lymphocytes

LLI - lower large intestine

MC - Minnesota Code

ME-RFC - few-receptor rosette-forming cells

MN-RFC - multireceptor rosette-forming cells

NIS - Newly Independent States

NMI - neutrophil maturation index

NMLA - net monocyte lysosome activity

PA - phagocytic activity

PAM - phagocytic activity of monocytes

PHA - phytohemagglutinin

RBM - red bone marrow

RE - rheoencephalography

ULI - upper large intestine

URCRM - Urals Research Center for Radiation Medicine

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