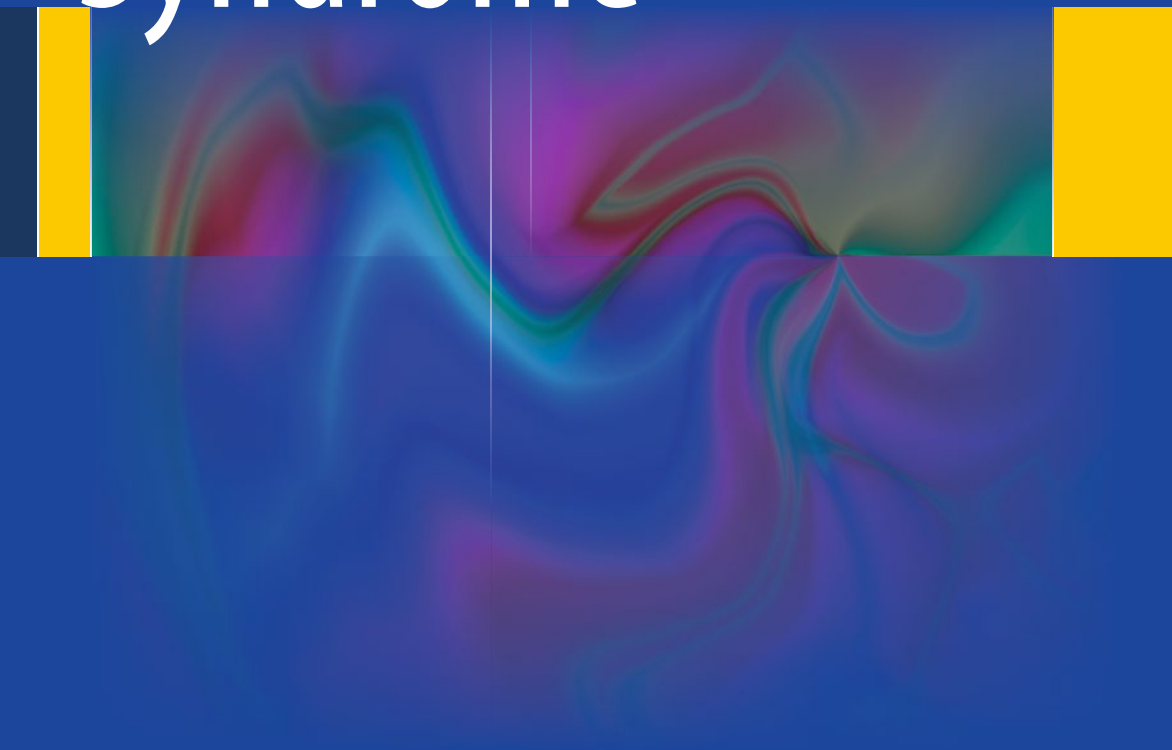
Alexander V. Akleyev

Chronic Radiation Syndrome



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Devoted to my wife

Galina Akleyeva

Foreword

Dear colleagues! It is a distinct honor and privilege to assure you that I will never forget the extensive and in-depth collaborative activities that we were able to conduct in the past and that resulted in a better and sometimes new appreciation of the health impairments that may occur in persons after long-term chronic radiation exposure.

Our joint experience is related to population exposed to ionizing radiation due to their living along the Techa River. It was a real privilege to cooperate with our Chelyabinsk colleagues in this field of clinical research regarding these patients and their health development. This cooperative activity culminated in the establishment of the satellite-supported execution of teleconsultations between the Urals Research Center for Radiation Medicine (Chelyabinsk) and Ulm University. Going back to 30 years ago, that was in 1983, it was the time when all of us would not have been able to imagine the miracle that about 10 years later we would be able to discuss the establishment of a teleconsultation communication link between research and clinical institutions in Germany and Russia. Even more so, looking 50 years back at that time of the Cold War, such a collaborative project would have been unthinkable. Nevertheless, we achieved with the support of the German government and of the German Telecom the establishment of the satellite-anchored communication system between Chelyabinsk and Ulm. And it was wonderful that week after week, we were able to exchange information on patients that had been exposed to ionizing radiation due to a various number of radioactive nuclides. It was a real progress to have in Chelyabinsk as well as in Ulm all the identical equipment ready to analyze information about such patients. We were able to discuss in depth cytological and histological effects using a microscope system of the highest possible quality. These cytological abnormalities are indicators of effects. One can recognize mitotically connected abnormalities that are seen in blood and BM smears. These abnormalities include apoptotic cells, binucleated cells, giant cells, and cells with karyomeres. We were able to develop out of all the findings biomathematical models that make us understand what is happening after sublethal chronic radiation exposure. The efforts conducted between 1994 and 2000 resulted in reports describing the possible pathophysiological mechanisms of chronic radiation injury. Many of the results of these research efforts were discussed in the year 2001 in Ulm and published by the *British Journal of Radiology* as Supplement 26 with the title "Chronic irradiation: tolerance and failure in complex biological systems" edited by T.M. Fliedner, L.E. Feinendegen, and J.W. Hopewell.

What does this all mean? How was it possible to develop such an intensive and realistic and in-depth scientific collaboration between two research cultures that eventually, as we do hope, are on the way to harmonize in order to develop strategic strength for the future. Let us remember that scientific collaboration requires three major elements to be effective. First of all, it is essential that the senior participants in this collaborative effort are competent in their particular field of expertise. A second requirement is that the participants are persons with vision and in particular creativity to look beyond the borders of their sphere of interest and try to combine observations to new hypothesis. I am extremely grateful to confess that these three Cs – competence, creativity, and confidence – evolved indeed in the collaboration between our group in Ulm and the group of Prof. Akleyev in Chelyabinsk. Dear Alexander! I think you agree that the RATEMA project might be used as the doorway to new worldwide activities in the development of means and ways to mitigate health impairments should they occur to members of our communities after ionizing radiation exposure. The next steps should be to develop and use an interactive telemedicine, assistance system, and healthcare delivery and advanced training as a means to:

- Conduct medical teleconferences which would allow patients to benefit of medical consultations on the spot without having to move from the area of the residence.
- Prepare and conduct teleconferences.
- Develop recommendations concerning diagnosis and treatment of patients with rare diseases and victims of accidents.
- Improve existing knowledge and develop new knowledge with respect to health impairments caused by toxic environmental exposure such as radiation and chemicals as a basis for new diagnostic, therapeutic, and rehabilitative approaches.
- Render consultative assistance to the physicians of local health organizations in the Chelyabinsk region.

I would like to take this opportunity to express my sincere thanks to Prof. Akleyev and to the entire team of URCRM for the wonderful years of joint work. In addition my best wishes are with my colleagues in Chelyabinsk in the hope that our medical knowledge will be used to prevent harmful health effects of radiation exposure or to treat in the best possible way if in spite of all the efforts the population was accidentally exposed to ionizing radiation. Thank you.

Taken from the speech of Prof. T.M. Fliedner presented at the International Scientific Conference "Present Day Radiobiology" on 4th September, 2008.

Chelyabinsk, Russia T.M. Fliedner
2008

Abbreviations

α-HBD	Alpha-hydroxybutyrate dehydrogenase
AA	Aplastic anemia
ACE	Angiotensin-converting enzyme
ACTH	Adrenocorticotropic hormone
AFC	Antibody-forming cells
AIDS	Acquired immunodeficiency syndrome
ALA	Aminolevulinic acid
ALE	Average life expectancy
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AML	Acute myeloid leukemia
APC	Antigen-presenting cells
AP-endonuclease	Apurinic/apyrimidinic-endonuclease
APM	Absolute phagocytizing monocytes in 1 l of blood
APN in 1 l of blood	Absolute number of active (phagocytizing) neutrophils in 1 l of blood
APUD-system	Amine precursor uptake and decarboxylation system
AR	Adaptive response
ARS	Acute radiation syndrome
ASMase	Acid sphingomyelinase
AST	Aspartate transaminase
ATM	Ataxia telangiectasia mutated
BBB	Blood–brain barrier
BE	Bystander effect
bFGF	Basic fibroblast growth factor
BM	Bone marrow
BMP-2	Bone morphogenetic protein 2
BSCB	Blood spinal cord barrier
CA	Chromosome aberrations
cAMP	Cyclic adenosine monophosphate
CDCP	Centers for Disease Control and Prevention
CDK	Cyclin-dependent kinase
cGMP	Cyclic guanosine monophosphate
CI	Confidence interval

CIC	Circulating immune complexes
CLL	Chronic lymphocytic leukemia
CNS	Central nervous system
CPK	Creatine phosphokinase
CRF	Chronic renal failure
CRS	Chronic radiation syndrome
CSF	Colony-stimulating factors
CT	Computed tomography
CTGF	Connective tissue growth factor
DIC syndrome	Disseminated intravascular coagulation syndrome
DMF	Dose modification factor
DNA	Deoxyribonucleic acid
DSB	Double-strand breaks
DTH	Delayed-type hypersensitivity
ECG	Electrocardiogram
EDTA	Ethylene diamine tetra-acetic acid
EEG	Electroencephalography
EPO	Erythropoietin
ERK	Extracellular-regulated kinase
ESR	Erythrocyte sedimentation rate
ETP	Early thymocyte progenitors
FGF	Fibroblast growth factor
FISH	Fluorescent in situ hybridizations
FL	Flt-3 ligand
FMBA	Federal Medical-Biological Agency
FSH	Follicle-stimulating hormone
FSUs	Functional subunits
GAS	General adaptation syndrome
GCS	Glucocorticosteroids
G-CSF	Granulocyte colony-stimulating factor
GGT	Gamma-glutamyltransferase
GH	Growth hormone
GIT	Gastrointestinal tract
GLA	Gamma-linolenic acid
GnRH	Gonadotropin-releasing hormone
GSH	Glutathione
GT3	γ-tocotrienol
GVH	Graft-versus-host
H_2O_2	Hydrogen peroxide
HELLP	Syndrome in pregnancy
HGFs	Hematopoietic growth factors
HIV	Human immunodeficiency virus
HLA	Histocompatibility complex
HRT	HRT-mediated inflammation in the bone marrow
HSC	Hematopoietic stem cells

HSF	Heat shock factor
HSP	Heat shock proteins
ICD-9	International Classification of Diseases
ICRP	International Commission on Radiological Protection
IEL	Intestinal epithelial lymphocytes
IGF- 1	Insulin-like growth factor
IGFBP-3	IGF-binding protein 3
IHD	Ischemic heart disease
IL	Interleukin
Ins	Insecticides, particularly DDT
IQ	Intelligence quotient
IR	Ionizing radiation
JNK	c-Jun N-terminal kinase
KL	c-kit ligand
LAK	Lymphokine-activated killer
LAMAS	Lysosomal activity of monocytes
LAN	Lysosomal activity of neutrophils
LBC	Left Bank channel
LD/LDR	Low dose/low dose rate
LDH	Lactate dehydrogenase
LET	Linear energy transfer
LGL	Large granulocytic lymphocytes
LH	Luteotropic hormone
LHGH	Luteinizing hormone-releasing hormone
LRW	Liquid radioactive wastes
LSS	Life Span Study
MAPK	Mitogen-activated protein kinase
Mayak PA	Mayak Production Association
MGDF	Megakaryocyte growth and development factor
MNP	Malignant neoplasms
MPA	Monocyte phagocytosis activity
MPI	Monocyte phagocytosis index
MRI	Magnetic resonance imaging
MSCs	Mesenchymal stem cells
NCAM	Neural cell adhesion molecule
NF-kB	Nuclear factor kappa B
NHEJ	Nonhomologous end joining
NK	Natural killer
NO	Nitric oxide
NPA	Neutrophil phagocytosis activity
NPI	Neutrophil phagocytosis index
NSAIDs	Nonsteroidal anti-inflammatory drugs
NST induced	Induced NST test of neutrophils
NST test	Nitro blue tetrazolium restoration
NSTM ind.	Induced NST test for monocytes

NSTM sp.	Spontaneous NST test for monocytes
NSTN sp.	Spontaneous NST test of neutrophils
PAM	Phagocytic activity of monocytes in 1 l of blood
PAN	Phagocytic activity of neutrophils in 1 l of blood
PAS	Positive material accumulation in interstitial tissues
PCNA	Proliferating cell nuclear antigen
PET	Positron emission tomography
PKC	Protein kinase C
PLC	Phospholipase C
PLPs	Products of lipid peroxidation
PNS	Peripheral nervous system
PPARα	Peroxysomal proliferator-activated receptor
PSC	Posterior subcapsular cataract
RAS	Renin–angiotensin system
RBC	Right bank channel
RBE	Relative biological effectiveness
RBM	Red bone marrow
RES	Reticular-endothelial system
RIGI	Radiation-induced genomic instability
RNA	Ribonucleic acid
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
s.u.	Standard unit
SALM	Summarized activity of lysosomes of monocytes
SALN	Summarized activity of neutrophil lysosomes
SAPKs	Stress-activated protein kinases
SOD	Superoxide dismutase
SSB	Single-strand breaks
STAT	STAT family of proteins
SUBI	South Urals Biophysics Institute
TBI	Total-body irradiation
TCR	T-cell receptor
TEC	Thymic epithelial cells
TGFβ	Tumor growth factor β
Th	T-helper cells
TLR5	Toll-like receptor 5
TNF	Tumor necrosis factor
TR	Tissue reactions
TRC	Techa River Cohort
TRDS	Techa River Dosimetry System
TSH	Thyroid-stimulating hormone
TSLP	Thymic stromal lymphopoietin
UCR	Unified Computer Registry
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
URCRM	Urals Research Center for Radiation Medicine

UV	Ultraviolet
VEGF	Vascular endothelial growth factor
VVD	Vegetative-vascular dystonia
vWF	Von Willebrand factor
WBC	Whole-body counter
ZAGS	Civil Status Registration Office

Contents

Introduction

More than 60 years have passed since the beginning of the Techa River radioactive contamination. However, those far-off events still attract a lot of attention. Health effects remain the main issue that bothers the population of the region and is of great interest for the international scientific community. In the last 20 years late health effects of the chronic radiation exposure in population became the focus of the numerous scientific research which were carried out under the auspices of the intergovernmental Russian–American Agreement, within the framework of Euroatom programs, were reflected in United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and International Commission on Radiological Protection (ICRP) reports, and are widely discussed in scientific literature. Estimating the importance of this kind of research for the improvement of radiation protection system, UNSCEAR in the report to the General Assembly in 2010 pointed out special significance of epidemiological "information concerning health effects of long-term low dose radiation exposure in the population of the Techa River area." As for the early health effects of the Techa River radioactive contamination, it is necessary to note considerable uncertainty of the available data connected both with data inconsistency and with lack of information on this issue. It is important to emphasize that medical examination of the Techa River residents began almost in 1.5 years after the onset of the river contamination, and in the following years, it was carried out regularly. The results of this follow-up were published in the journal "*Bulleten Radiatsionnoy Meditsiny*" and in different annals of scientific papers available only to a narrow circle of experts.

Chronic radiation syndrome (CRS) until now remains a little-known radiation pathology not only for the general public but also for experts in the field of radiobiology and radiation medicine. Several reasons determine the existing state of affairs. First of all, cases of CRS were registered mostly in the Southern Urals region: in Mayak PA personnel and residents of the Techa Riverside villages. Secondly, CRS cases were registered quite a long time ago (generally in 1950s). Thirdly, certain researchers expressed the idea that conditions for long-term radiation exposure of persons to doses sufficient for CRS formation can hardly appear in the future, and therefore, this pathology ceased to be relevant. Particularly encouraging was the thought, expressed in 1960s–1970s when working conditions of the Russian nuclear facilities personnel improved considerably and new CRS cases ceased to be registered that CRS is a disappearing radiation pathology.

Utterly important clinical descriptions of CRS cases were made by A.K. Guskova, G.D. Baysogolov, N.A. Kurshakov, P.M. Kireyev, and other Russian scientists already in 1950s–1960s. However, for a long period of time, international organizations did not recognize CRS as an independent form of radiation pathology.

Only in 2007 in ICRP Publication 103, for the first time, the possibility of CRS formation under chronic radiation exposure of the person was marked, and in the subsequent Publication 118, devoted to the radiation tissue reactions, CRS clinical description and radiobiological conditions of its formation were provided. The problem of CRS regained interest not only in connection with fundamental review of approaches to the assessment of deterministic effects of radiation exposure that currently acquired the name of tissue reactions but also in connection with real possibility of long-term radiation exposure of humans (e.g., of astronauts during long flights to Mars or of population in case of terroristic attacks).

Long-term combined external and internal exposure of the Techa River residents was caused by scheduled and accidental releases of the liquid radioactive wastes of the Mayak PA. The undertaken protective measures were insufficiently effective due to their delayed inadequate character. Population of the riverside villages, especially of those located in the upper reaches of the Techa River, was subjected to long-term radiation exposure.

The first medical examinations of the population began in the summer of 1951. They were carried out by mobile teams of the staff of the Biophysics Institute of the USSR Academy of Medical Sciences and physicians of Mayak PA Hospital. It is important to note that participants of these expeditions have already had experience of CRS diagnosis in Mayak PA personnel. Nevertheless, CRS diagnosis in population in the expeditionary conditions was obviously difficult due to lack of initial data about health status in residents of the Techa Riverside villages and of dosimetry data. First medical examinations of the population, carried out in the village of Metlino, located only 7 km far from the radioactive waste release point, already showed essential deviations in health status of certain individuals that clinically reminded CRS manifestations in Mayak PA personnel. The most expressed and steady changes in health status of Techa River residents were registered in hematopoietic system and were determined not only by considerable impact of internal BM exposure in some part of the population due to ^{90}Sr intake with water and local foodstuffs but also by high radiosensitivity of the hematopoietic cells. Hematopoiesis inhibition was often accompanied by changes in other organs and systems (nervous, immune, cardiovascular, digestive, musculoskeletal systems, etc.). The subsequent medical examinations of Techa River residents, carried out in 1951–1955, confirmed researchers' concerns and that demanded the establishment of a special clinic for carrying out regular medical examination of the exposed population and treatment of affected persons on the basis of the Chelyabinsk Regional Clinical Hospital. It should be noted that since 1955, the follow-up of the Techa Riverside villages population has been performed by the specialists of the clinic of the Urals Research Center for Radiation Medicine (URCRM) of Federal Medical-Biological Agency of Russia.

In the present book, the attempt was taken to analyze and summarize the status of different organs and systems, including such radiosensitive system, as

hematopoietic-immune system with consideration for individual organ doses and dose rate dynamics not only during the period of CRS formation but also during recovery period and late effects. Current radiobiological understanding of the low dose rate exposure effects, tissue radiation reactions, and modifying factors gave the possibility to develop considerably the understanding of CRS pathogenesis and to establish pathogenetic methods of treatment. Issues of diagnosis, including CRS differentiated diagnosis and health evaluation, are also discussed in the monograph.

I would like to express my profound gratitude to my colleagues from URCRM Clinical Department who have been rendering medical care to the residents of the Techa Riverside villages for many years; to Mira Kossenko, who has been organizing the follow-up of the persons with CRS for a long time; to Tatyana Varfolomeyeva, who helped me to analyze hematological data; to Lyudmila Krestinina for the help in carrying out epidemiological analysis of the late effects; and to my son, Andrey Akleyev, for consultations on problems of modern biology and medicine. And I want to express special gratitude to Prof. Theodor Fliedner for long-term cooperation, discussions of the monograph material, consultations of the patients who had CRS, and great support during the whole period of work on the book. I would also like to thank Ekaterina Zhidkova and Nadezhda Kotova for the great job they did translating the book into the English language.

The author hopes that the book will be useful both for the researchers who are interested in problems of radiobiology, radiation medicine, and radiation safety and also to a wide range of physicians and biologists.

1 Definition, Classification, and Clinical Presentation of Chronic Radiation Syndrome (CRS) Associated with Total Exposure to External Radiation

The development of nuclear industry and wide application of radioactive isotopes and ionizing radiation (IR) in the industry, medicine, science, and other fields of man's activity considerably increased the number of people affected by long-term radiation exposure. The operation of nuclear enterprises was performed without proper protection of the personnel. As a result, already in the early 1950s physicians noted the development of a specific clinical syndrome associated with long-term exposure to IR in doses exceeding the threshold for the appearance of tissue reactions. Follow-up of these exposed persons demonstrated that they develop a number of consecutive system changes that gradually form the chronic radiation syndrome (CRS). Russian scientists (Guskova et al. 1954; Kurshakov 1956; Glazunov et al. 1959; Baysogolov 1961; Kireyev 1962, etc.) showed that changes in hematopoietic and nervous systems dominate in clinical CRS picture.

1.1 Definition of Chronic Radiation Syndrome

Traditionally, ICRP and UNSCEAR provide the description of separate organ and system reactions to IR. However, in practice under long-term (months–years) low-dose-rate (less than 0.1 mGy/min) exposure of a person due to external exposure and/or radionuclide intake, not only organs and tissues but also the whole body could be affected. Tissue reactions within a unified organism are not independent from each other; they can superimpose on one another in time and mutually burden the course of each other, forming rather specific clinical syndrome of multiorgan radiation effects.

Although CRS manifestations are not specific, the sequence of their appearance under prolonged radiation exposure and their regress after the termination or considerable decrease in dose rate are characteristics of it, and that allowed Russian scientists AK Guskova, GD Baysogolov, NA Kurshakov, SA Kirillov, et al. to identify chronic radiation syndrome (in Russian literature, this syndrome acquired the name "chronic radiation sickness") as an independent nosological form of radiation pathology.

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NA Kurshakov in one of his first summarizing scientific papers, related to the issues of CRS, defined chronic radiation syndrome as pathological "process gradually developing as a result of repeated exposure to low but accumulating doses of external gamma- or X-rays, or due to repeated intake of radionuclides, and also in case of their single intake if they have a long-term half-life period and low clearance rate, as the influence of alpha- and beta-emitting radionuclides on the organism depends on their decay time and clearance rate" (Kurshakov 1956).

Utterly important characteristics of CRS were provided in the publications of AK Guskova et al. (1954). Authors emphasize that CRS results from long-term repeated exposure to rather low doses and has a long-term intermittent course. On the basis of the persons with CRS follow-up, the authors made an important addition that the disease can manifest not only within the period of protracted exposure but also even some time after its termination. The authors identified certain periods in CRS course that consistently succeed and displace one another under protracted radiation exposure (Guskova et al. 1954). Later on, not only clinical manifestations arising during chronic radiation exposure but also those that appear after its termination were defined as CRS. The late effects period was also distinguished. It was shown that disease development and progression are determined mainly by dose rate dynamics in critical organs (red BM and nervous system). The authors demonstrated that in case of low-dose-rate exposure, CRS clinical manifestations developed after rather a long period of time (the latency period made up to 2–5 years and more), whereas high-dose-rate exposure led to more severe changes in critical systems that appeared after a short latency period or even without it (Kurshakov 1956).

The subsequent follow-up of the nuclear enterprises personnel made it possible to specify the conditions of CRS formation and to note that the disease can appear as a result of long-term contact with sources of external γ-exposure that leads to accumulation of doses exceeding maximum permissible levels or due to intake of radionuclides (mainly through respiratory tract, gastrointestinal tract, injured skin). By this time, the evidence was obtained that in 3–4 years of work under increased external radiation exposure to doses up to 70–100 R and more, an organism develops CRS symptoms (Kurshakov and Kirillov 1967).

Particularly, important conclusions concerning CRS pathogenesis were made already in the 1950s by AK Guskova. It was shown that under chronic exposure at rather low doses, the changes in the nervous system appear early enough and progress in the course of CRS. It was established that early cardiovascular and other internal organs CRS manifestations are mainly determined by the central nervous system regulation changes. Pathological changes in internal organs in later terms of CRS course in their turn have adverse impact on the central nervous system status (Guskova 1960).

It is important to note that the term "chronic radiation syndrome" does not imply the duration of a disease (acute radiation syndrome manifestations can also remain for a long period of time); it only characterizes the result of protracted (chronic) radiation exposure of man.

Earlier it was considered that CRS manifestations might also include the acute radiation syndrome (ARS) consequences. However, as tissue reaction mechanisms at

ARS and CRS differ, then such association was recognized as incorrect (Kurshakov 1956). It is necessary to agree that isolated initial signs of tissue radiation damage cannot be considered CRS manifestation either. However, their diagnosis is of great importance as it provides evidence of early body reactions to IR and possibility of CRS formation in case of radiation exposure continuation.

Thus, in view of current radiobiological understanding, CRS can be defined as a clinical syndrome appearing in a person due to protracted exposure to IR at doses exceeding the threshold values for the development of tissue reactions in critical systems (hematopoietic and nervous systems) which is characterized by a specific set of various organ dysfunctions.

The main criteria of CRS diagnosis are:

- Excess of a threshold dose for the CRS development.
- Existence of latency period, the duration of which is inversely proportional to the exposure dose rate to critical organs.
- Nonspecific symptoms.
- Clinical manifestations in multiple organs (major symptoms are inhibition of hematopoiesis and neurologic dysfunctions).
- Dynamics of syndrome formation and recovery are determined by doses to organs and to a great extent by dose rate.
- Syndrome progresses if exposure proceeds at doses exceeding the threshold for the formation of tissue reactions in critical systems.
- In mild CRS cases at exposure termination or decrease in exposure dose rate below threshold levels for tissue reactions, there can occur spontaneous recovery of hematopoiesis, neurologic dysfunctions, and other organ changes.

Threshold doses sufficient for CRS formation are being actively discussed so far. Threshold values of cumulative and annual dose vary considerably even for the Mayak PA personnel, among whom CRS cases are thoroughly studied (Guskova 2001; Guskova et al. 2002). According to the data of AK Guskova, the last estimates of a threshold dose of relatively uniform total-body γ-exposure sufficient for CRS formation make up 0.7–1.0 Gy/year and cumulative dose 2.0–3.0 Gy for the whole exposure period of 2–3 years (Guskova 2007). The lower limit of a threshold dose for CRS formation due to external γ-exposure in Mayak PA personnel estimated by other researchers makes up 0.7 Gy at dose rate of about $5.8 \cdot 10^{-4}$ mGy/min (Osovets et al. 2011).

Threshold dose values for the CRS formation in population are not estimated so far. It should be noted that ICRP defines a threshold value of annual dose of chronic radiation exposure for the inhibition of hematopoiesis as ≥0.4 Gy (ICRP 2007), which is below a threshold for neurologic changes. Proceeding from the CRS concept as multiorgan pathological process in whose pathogenesis hematopoietic and neurologic disturbances predominate, it is logical to assume that the threshold dose for the CRS formation has to be slightly higher and should approximately correspond to a threshold dose for the formation of postradiation neurologic dysfunctions. In this context, the results of threshold dose estimations for the neurologic dysfunctions in Mayak PA personnel present a great interest although they are ambiguous. According to certain data, the main neurologic manifestations of CRS

(vegetative dysfunction, asthenia, microorganic disorders of the central nervous system (CNS)) developed at an annual dose of γ-exposure >1 Gy (Okladnikova et al. 1992). The other research states that the appearance of vegetative dysfunction and asthenic syndrome was noted at cumulative dose of total-body γ-exposure 2.5–3.0 Gy and dose rate of 1.3–1.5 Gy/year, and organic changes in the nervous system were registered at cumulative doses >4.0 Gy and dose rates >2.0 Gy/year (Sumina and Azizova 1991).

Probably, threshold dose values for the appearance of early CRS manifestations, which are predominantly of functional nature, in population can be lower than in the personnel that consists mainly of young healthy males. It is obvious that the population which is much more heterogeneous in age, initial health status, and other factors that influence radiosensitivity includes a larger group of radiosensitive people than the personnel does and threshold dose values for the CRS formation in the population might be lower.

The time necessary for the syndrome formation (the latency period) as well as severity of CRS are generally determined by dose rate and exposure dose to critical organs and also by individual radiosensitivity. The period of CRS formation in the Mayak PA personnel made up from 1 to 10 years depending on exposure dose and dose rate. The shortest latency period (1–2 years) was noted at annual doses of the total-body γ-exposure >2.0 Gy. The higher the exposure dose to persons with CRS, the shorter was the latency period (Okladnikova 2001). The latency period in persons with CRS residing in the Techa riverside villages was longer and typically made up 5–8 years and that indirectly testifies to much lower exposure doses to population than to the Mayak PA personnel.

CRS is characterized by the impairment of a large number of organs and systems, but most prominent changes occur in hematopoietic, immune, nervous, digestive, cardiovascular, and endocrine systems. The longer duration and intermittent character of the disease course are the other characteristic features of the CRS. The health status of persons with CRS undergoes alternations when improvement and deterioration periods succeed and displace one another. Moreover, their duration and intensity are determined by dose rate and cumulative exposure dose to critical organ systems and also by specific features of an organism. For CRS, the combination of local tissue reactions of critical systems and general (regulatory) functional disturbances which develop earlier than structural tissue changes is rather typical. It is important to note that separate unstable symptoms of chronic radiation exposure which should be considered as independent tissue reactions precede syndrome formation. In case of the exposure termination, the latter quickly regress; hence, CRS does not develop.

Already, the initial stage of CRS is characterized by a set of multiorgan functional changes in hematopoietic, cardiovascular, digestive, and other systems caused by impairment of regulatory systems function (nervous, endocrine, and immune systems). Cytopenia in this period occurs due to functional changes of proliferation and maturation of BM cells (Muksinova and Mushkachyova 1990). Such initial signs of CRS as arterial hypotension, disturbance of motor and secretory functions of the organs of the gastrointestinal tract (GIT), and others are directly connected

with changes in regulatory function of the central nervous and endocrine systems. It essentially distinguishes CRS from ARS, at the basis of which already at the early stages lies the cell death in critical organs (HSC, GT epithelium, etc.).

The main manifestations of CRS are dose-dependent inhibition of hematopoiesis and neurologic dysfunctions. The most typical changes in peripheral blood at whole body uniform exposure are moderate but persistent leukopenia induced by the decrease in the number of neutrophils ($1.3–2.6 \cdot 10^9$/l) and band shift in the leukogram. In certain patients, toxic granulation of neutrophils and single promyelocytes and myelocytes were registered in the peripheral blood. In some cases, absolute lymphopenia was noted. Tendency to monocytosis, moderate thrombocytopenia, and emergence of giant thrombocytes frequently occurred. Typically, erythrocyte count remained within the normal range. Moderate erythrocytosis with tendency to reticulocytopenia was observed less often (to 1 %). Macrocytosis was quite often registered (Sokolova et al. 1963).

In the BM in 30 % of the patients, decrease in quantity of myelokaryocytes (to $30.0–50.0 \cdot 10^9$/l) and increase in reticular and plasma cells and monocytes were noted. The delayed granulocyte maturation at the stage of band neutrophils and younger cells and the accelerated maturation and increase in mitotic activity of erythrokaryocytes frequently occurred. Given that hematopoiesis from the functional point of view is a unified system, hematological changes in CRS should be considered not as isolated impairment of separate hematopoietic lineages but as an outcome of the system radiation response of hematopoiesis. In cases of severe CRS, all hematopoietic lineages are involved in pathological process, including lymphopoiesis and erythropoiesis (Sokolova et al. 1963).

Comparing frequency and intensity of various neurologic syndromes with cumulative exposure dose, three main sequential neurologic syndromes were identified: syndrome of vegetative dysfunction or impairment of neurovisceral regulation, asthenic syndrome, and syndrome of radiation encephalomyelosis-type organic lesion of the CNS (Guskova 1960). The earliest neurologic syndrome of CRS is vegetative dysfunction. Clinical manifestations of this syndrome are multiform and are expressed in neurovascular and neurovisceral regulation impairment; the hypothalamus function (diencephalic syndrome) is less often affected. Generally, vegetative dysfunction is combined with temporary decrease in leukocyte, neutrophil, and thrombocyte content in blood and is characteristic of mild CRS cases. If the exposure proceeds, then a more profound functional impairment of the nervous system, in particular asthenic syndrome, develops which correlates with more expressed and permanent manifestations of hematopoiesis inhibition and changes in internal organs inherent to CRS cases of medium severity. Asthenic syndrome as a manifestation of CNS functional failure is characterized by inhibition of vegetative nervous system activity, bioelectrical brain activity, and changes in the higher nervous activity. It is shown that exactly these two neurologic syndromes determine CRS clinical picture and are early indicators of functional reaction of the nervous system to radiation exposure at doses exceeding threshold values. The syndrome of organic nervous system lesion is late CRS manifestation and occurs only at total-body exposure dose >2.0–3.0 Gy. It is formed gradually as a result of prolonged neurovascular,

metabolic, and trophic disturbances, direct damage of the most sensitive structures of the nervous system, and is expressed in diffused microorganic encephalomyelosis-type symptomatology (Guskova 1960; Glazunov et al. 1959).

Changes in GIT (first of all, in stomach) in CRS cases also develop in a certain sequence. At first, unstable secretory function impairment (acidity decrease or increase can be observed) and delay in evacuation function of the stomach occur. If the exposure proceeds, then the intensity of functional disorders increase, and organic changes characterized by secretory function inhibition with the development of histamine-resistant achlorhydria appear. In severe cases, persons with CRS show both persistent functional and marked organic changes. Inhibition of the stomach secretory function was observed in majority of persons with CRS (Kabasheva and Doshchenko 1971). Patients suffered from regurgitation, nausea, and diarrhea. The above-mentioned digestion disorders usually developed in 2–3 years, and sometimes 4–5 years after the appearance of the first CRS symptoms (Doshchenko 1960).

The progression at all stages of CRS is to a great extent determined by vascular disorders. At the onset of a disease, they are limited to temporary disorders of peripheral blood circulation. Later, there appear more permanent changes in blood circulation in various sites of the vasculature. In case of lethal outcomes, pathological shifts in nervous system are caused by the development of severe cerebrovascular accidents with hemorrhages into brain matter and meninges. In parallel with direct radiation damage, vascular disorders aggravate neurotrophic tissue changes and determine development of the main neurologic syndromes of CRS (Guskova et al. 1954; Guskova 1960).

1.2 Classification of CRS

Follow-up of the persons with CRS allowed to establish both general patterns of pathological process development associated with various types of IR and characteristic features. Peculiarities of clinical picture of certain CRS manifestations (polymorphism of symptoms, depth and predominant level of impairment of different organs and systems function, a combination of various syndromes), and also a different ratio of neurologic, hematological, and visceral disorders, were determined by organ doses, their distribution in time and throughout the organism (Guskova 1960; Baysogolov and Springish 1960, Baysogolov 1961). A variety of clinical forms on the one hand and the established pathogenesis of the CRS on the other presupposed the necessity to develop a classification of the disease.

The first classification of CRS was suggested by GD Baysogolov in 1950, and in the subsequent years, it was modified (Baysogolov 1961; Guskova and Baysogolov 1971). According to the severity of the CRS course, three degrees are usually distinguished (I, II, and III degree). Severity of CRS as a result of total external γ-exposure correlates with the value of cumulative dose and annual exposure dose. In assessment of CRS course severity, one takes into account prevalence of pathological manifestations, their intensity, and also their reversibility in case of exposure termination or under the influence of medical assistance. Thus, severity of a syndrome is determined by:

- Prevalence of pathological process in an organism, i.e., by a number of organs and systems involved
- Character (functional or structural) and intensity of changes
- Extent of the pathological phenomena regress after exposure termination and medical treatment (Guskova et al. 1954; Kurshakov 1956; Glazunov et al. 1959; Baysogolov 1961, etc.)

Sometimes, the IV degree of CRS severity is distinguished, which is characterized by BM aplasia and infectious and septic complications with a hemorrhagic syndrome, and could have lethal outcome. Thus, the assessment of CRS severity is determined on the basis of the analysis of all CRS manifestations with due account for dynamics of organ exposure dose formation.

According to GD Baysogolov, it is hematological changes that influence the degree of CRS severity. It is shown that intensity of changes in the BM markedly correlates with the total CRS severity and depth of changes in peripheral blood cellular composition. Thus, in persons with CRS of mild severity, the amount of myelokaryocytes was within limits of $90.0–120.0 \cdot 10^9$/l; the number of megakaryocytes, leukoerythroblastic ratio, and also neutrophil maturation index usually were within normal range. At the same time in severe CRS cases, absolute number of myelokaryocytes did not exceed $60.0 \cdot 10^9$/l, megakaryocyte content decreased sharply or there were no megakaryocytes at all, and leukoerythroblastic ratios and neutrophil maturation index were going down. Decrease in neutrophil maturation index was caused by sharp reduction in the number of young granulocytes (Baysogolov 1961).

All researchers note low intensity, dynamic character, and reversibility of organ and system changes at initial stage of CRS (mild or I degree). Medium severity CRS cases (the II degree) are characterized more by expressed permanent changes in a number of organs and systems (hematopoietic, nervous, immune, etc.) and by the presence of relationship between objective data and subjective manifestations of a syndrome. Severe or III degree (some authors also distinguish most severe or IV degree) CRS cases are characterized by profound hypo- or aplastic-type inhibition of hematopoiesis with signs of organic disorders of the central nervous system (CNS) and irreversible dystrophic changes in visceral organs.

It is important to note that the division of CRS according to the degree of severity is rather relative as the intensity of different tissue reactions in patients can differ immensely and tissue reactions do not always correlate with each other. Moreover, poorly expressed clinical signs of CRS can have irreversible character and vice versa. It is also necessary to consider exceptional dynamism (progression if the radiation exposure continues, and regress in case of radiation exposure termination and medical treatment) of CRS pathological manifestation. With spreading of the process and intensification of symptoms, the CRS severity increases (Kurshakov 1956).

Long-term follow-up of the persons with CRS made it possible to identify provisionally the following stages: syndrome formation, recovery, and late effects (Guskova and Baysogolov 1971). As a rule, CRS formation period coincides with the accumulation of exposure dose in a person and sometimes includes the nearest time periods (usually up to 1 year) after the exposure termination. In this period, the major CRS manifestations develop and progress depending on dose rate and

cumulative exposure dose to critical organs. If the exposure proceeds, pathological process gradually intensifies and changes in hematopoietic, nervous, and other systems become more profound.

As it was mentioned above, the intensity of clinical manifestations can be mild (I), medium (II), severe (III), or most severe (IV) depending on exposure dose and specific features of an organism. If the exposure continues, then the severity is basically the same as the stage (phase) of uniform pathological process development which succeeds each other during CRS formation period (Guskova and Baysogolov 1971). Clinical manifestations characteristic of each degree of severity in residents of the Techa riverside villages are presented in Chap. 5. After termination of exposure or significant reduction in exposure dose rate, CRS progression can stop at this or that stage of syndrome formation and the period of recovery begins (it is more characteristic of mild and less of medium CRS severity).

The period of tissue damage recovery typically occurs within several months–years after the termination of exposure or significant reduction of dose rate. During this period, compensatory and repair processes start to predominate over tissue damage. It is important to note that CRS develops more favorably in comparison to ARS and quite often the outcome can be a complete recovery of the impaired functions and cure or recovery with defect (more often cancerogenic effects, BM hypoplasia, etc.). Quite often, the recovery process takes a few or even many years. Thus, the recovery of cellular blood composition in Mayak PA personnel took several decades (Pesternikova and Okladnikova 2003). In 35–40 years after the exposure at total doses of 2.0–9.33 Gy (the annual dose comprised >1 Gy) the presence of moderate leukopenia was noted in 20% of cases (Okladnikova 2001), and moderate BM hypoplasia was registered in 7.3% of the cases (Pesternikova and Okladnikova 2004).

The mechanism of late CRS effects development differs from changes occurring during formation period. Quite often, signs of functional failure and structural changes of organs (tissues) during the periods of recovery and late effects are determined by vascular disorders, trophic disorders, immunological changes, and others. Depending on the intensity and completeness of compensatory and adaptive reactions, the CRS recovery period can have the following outcomes: complete recovery (cure), recovery with defect, stabilization of the earlier developed changes, or deterioration of a disease course.

Due to long-term radiation exposure, functional activity of organs and tissues as well as structure can undergo considerable changes (fibrosis, hypoplasia, malignant transformation, etc.). In some cases, both under proceeding exposure and later after its termination, severe irreversible effects (e.g., aplastic anemia or leukemia) can occur. In case of proceeding high-dose-rate exposure and accumulation of total dose, there is a probability of lethal aplastic anemia development due to the death of HSC in RBM. In Mayak PA personnel exposed predominantly to external γ-radiation, BM hypoplasia with inhibition of all hematopoietic lineages and lethal outcome developed at dose rate >4.5 Gy/year and total dose >8 Gy (Okladnikova 2001). Infections are frequent complications of CRS course due to hematopoiesis inhibition. Quite often, they have a dramatic impact on the CRS outcome.

Due to similarity of biological effects induced by different types of IR, AK Guskova and GD Baysogolov distinguish two types of CRS (Guskova and Baysogolov 1971). The first CRS type develops due to total external γ-radiation exposure or intake of uniformly distributed isotopes, whereas the second is caused by primary damage of separate organs and systems under combined internal (due to organotropic radionuclides) and external radiation exposure. CRS formation due to accumulation of long-lived radionuclides leads to long-term internal exposure and appearance of some specific features of tissue reactions. Actually, from the clinical point of view, the second CRS type is rather heterogeneous and depends not only on individual peculiarities of the patient but also on radiation type and physicochemical properties of radionuclide. For instance, peculiar features of CRS induced by compounds and fission products of uranium, thorium, polonium, and others are well known (Guskova 1960; Sokolova et al. 1963).

The clinical picture and course of CRS can be modified by non-radiation factors (concomitant diseases, chemicals, genetic predisposition, etc.). Thus, in CRS cases analysis along with radiation factors, it is necessary to take into account the effect of such adverse production factors as mercury, iodine, acids, ammonia, nitric oxides, various solvents, ether, acetone, and other chemicals which can significantly modify CRS clinical course. The clinical picture can also be modified by concomitant diseases, including those affecting radiosensitivity of an organism (autoimmune diseases, AIDS, etc.) (UNSCEAR 2009).

1.3 CRS Clinical Presentation Associated with Total Exposure to External Gamma-Radiation

CRS progresses gradually under long-term exposure to external most often γ-radiation. As it was mentioned above, CRS is a system pathology of an organism which development is determined first of all by hematopoietic and nervous system response to chronic low-dose-rate (LDR) exposure. Contribution of other systems at the early stages of CRS formation is secondary and is induced by radiation responses of regulatory systems, predominantly hematopoietic and nervous systems. As the radiation exposure proceeds, other, more radioresistant systems (including musculoskeletal, urinary) can be involved into pathological process, but CRS clinical picture even of the most severe CRS cases is still determined by critical systems' status (hematopoietic and nervous systems). In case of exposure termination in medium and severe CRS cases, pathological process progresses due to the development of irreversible structural, vascular, degenerative–dystrophic organ changes.

Initial CRS symptoms are functional and reversible. Due to the fact that these symptoms are not specific, CRS diagnosis at initial stages often presents certain difficulty. At early stages of its development, CRS is characterized, first of all, by neuroregulatory disorders of various systems of an organism. The earliest symptoms are that of vegeto-vascular dysfunction. However, in CRS clinical picture, hematological changes, cardiovascular system disorders, and gastrointestinal tract

disorders may also be observed early enough; changes in the function of liver, kidneys, and endocrine organs and dysmetabolism are less frequently registered. After the exposure termination, CRS symptoms regress, and the patient usually fully recovers. As it has already been mentioned, changes in gastrointestinal tract, heart, kidneys, and endocrine organs appear as a result of vegetative-visceral dysfunction; therefore, they are reversible, and the impaired organs restore completely. At the early stage of CRS formation, moderate unstable changes of peripheral blood cellular composition and initial manifestations of asthenia occur. Usually patients complain of general weakness, increased fatigue, decrease in working capacity, headaches, appetite deterioration, and sleep disorders. Sometimes patients have no complaints, and only changes in blood composition testify to CRS formation (more often it is leukopenia, neutropenia, and thrombocytopenia). Under protracted exposure, the emergence of temporary moderate cytopenia, vegetative-vascular dystonia, and asthenic manifestations in the absence of other etiopathogenetic factors is characteristic of early CRS stage (Guskova and Baysogolov 1971).

If the radiation exposure proceeds, asthenic manifestations progress. Headaches, dizziness, general weakness, sleep disorders, and memory impairment increase. Decrease in sexual ability can be observed in men, and women have menstrual disorders. Objective changes in cardiovascular system are manifested in labile heart rate with tendency to tachycardia, arterial blood pressure with fluctuations from lowered to moderately elevated level, and muffled heart sounds. These changes are often accompanied by persistent dermographism and increased perspiration. Neurasthenia, increase of tendon and periosteal reflexes, tremor of eyelids, and fingers of outstretched arms are also rather typical signs of mild CRS severity (Guskova and Baysogolov 1971).

Quite often, persons with CRS have disorders of gastric mucosa secretory function manifested in heterochylia, i.e., changes in gastric acidity. Sometimes, anacidity but without roentgenologic signs of gastric mucosa damage was observed. However, the majority of persons with CRS had normacid condition of gastric juice. Evacuation function disorders of the stomach were less often noted.

Changes in peripheral blood in mild CRS cases are transient. Increase in the number of reticulocytes, moderate leukocytosis with lymphocytosis, and left neutrophil shifts are observed. Moderate nonpersistent leukopenia (up to $3.5–4.0 \cdot 10^9$/l) may occur. In the context of the proceeding radiation exposure, persistent leukopenia, induced by neutropenia, develops. Toxic granulation, pycnosis, fragmentosis, and hypersegmented forms are observed in neutrophils. Moderate ($150.0–180.0 \cdot 10^9$/l) but persistent thrombocytopenia can be registered (Ivanova 1959). Typically, the number of erythrocytes in blood does not change. Relative monocytosis (up to 14–16 %) and reticulopenia are seldom observed (Kurshakov and Sokolova 1959).

As a rule, BM contains normal amount of cells ($60.0–150.0 \cdot 10^9$/l). However, in single cases, moderate decrease in the number of myelokaryocytes to $30.0 \cdot 10^9$/l can be observed. Signs of granulopoiesis inhibition can appear already at the early stage. In 65 % of mild CRS cases, the decrease in the number of band and segmented neutrophils in BM is registered which is considered as a result of the accelerated release of mature cells from BM into bloodstream or delayed granulocyte maturation at the stages of myelocyte and metamyelocyte. The delayed granulocyte

maturation is manifested in increased myelocyte content in BM, neutropenia, and left shift in peripheral blood (Baysogolov 1961; Sokolova 1963). In mild CRS cases, it is possible to note signs of erythroid lineage stimulation (reticulocytosis, increased amount of erythrocytes) and stimulation of white cells (increase in amount of immature cells of myeloid lineage and also of plasmocytes) in BM. Mitotic activity of BM cells usually continues to persist. Changes in erythroid lineage can be manifested in increased mitotic activity of erythroblasts and sometimes in appearance of single megaloblasts. In certain cases, the increase in reticular and plasma cells (Baysogolov 1961) is observed.

CRS cases of medium severity are characterized by further hematopoiesis inhibition, aggravation of astheno-vegetative disorders, and development of hemorrhagic events. In blood of the patients, persistent and permanent decrease in the number of leukocytes to $2.0–3.0 \cdot 10^9$/l and lower is observed. Left shift predominates in neutrophil count. Leukopenia is accompanied by absolute neutropenia and lymphopenia. Toxic granulation, degenerative neutrophil changes and thrombocytopenia are more expressed than in mild CRS cases. Sometimes in case of sharp decrease in the amount of neutrophils, relative lymphocytosis and monocytosis are registered. Moderate erythrocytopenia, anisocytosis of erythrocytes, and increase in color index of blood occur. Usually, hyperchromatic-type anemia gradually develops. The amount of reticulocytes decreases (1–3 %); sometimes, they completely disappear. In peripheral blood, megaloblasts and megalocytes appear (Baysogolov 1961).

In BM, sharp decrease in blood cell elements to the extent of aplasia is observed. The study of BM shows expressed delay in processes of myeloid elements maturation more often at the stage of young myelocyte (Sokolova 1963). Impairment of thrombocyte formation is noted; thrombocytopenia is accompanied by the appearance of denuded megakaryocyte nuclei, megakaryocyte vacuolization, and pycnosis (Ivanova 1959). In the majority of cases in the red lineage, the right shift and perverted megaloblast-type erythropoiesis occur. Mitotic cell activity is preserved and sometimes increased (Pesternikova and Muksinova 1973). Increase in the amount of reticular cells, plasmocytes, and monocytes in BM appears more frequently in CRS cases of medium severity than in mild ones (Baysogolov 1961). Hematopoietic disorders are also more resistant to treatment in CRS cases of medium severity than in mild CRS cases.

Inhibition of BM hematopoiesis in patients with medium CRS severity leads to the development of the marked secondary immunodeficiency and severe infectious complications, including sepsis.

Persons with CRS of medium severity have gradual progression of asthenia which quite often dominates at this stage, influencing the health status and working capacity of the patients. Headaches and dizziness increase. Memory worsens considerably, and marked sexual disorders (decrease in sexual potency, menstrual disorders) occur (Verbenko et al. 1959, 1963). In the process of CRS diagnosis, all variety of asthenic manifestations and symptoms of vegetative dysfunction at this stage of the disease can be united in an astheno-vegetative syndrome.

Patients at this stage suffer from trophic disorders of skin and cutaneous appendages (xeroderma, decrease in elasticity, dermatitis, hair loss, brittleness, and longitudinal ridges of nails), and initial symptoms of organic CNS disorders in the form of

tendon reflexes change toward their increase as well as decrease; anisoreflexia of tendon, periosteal, and abdominal reflexes; mild ataxia at Romberg's test; optic-vestibular disorders; and lateral nystagmus can emerge. Diencephalic syndrome rarely occurs.

Approximately in 20–25 % cases in patients with medium severity, signs of myocardiodystrophy are noted: systolic noise, extrasystole, voltage decrease of deflections on ECG, expansion of ventricular complex, and flattening of R and T waves. Although decrease in glomerular filtration and renal blood flow is registered, as a rule, renal function is not impaired.

The nature of hemorrhagic events (cutaneous petechia, dermatorrhagia and mucosal hemorrhage, visceral hemorrhage) in CRS is complex. They are the result of both increased vascular permeability and thrombocytopenia and failure of coagulation and formation of prothrombin.

Dyspepsia (heartburn, nausea), loss of appetite, intestinal and epigastric pain, and constipation occur quite frequently in patients with medium severity CRS. They are induced by the development of a histamine-resistant achylia; enzymatic function disorders of the stomach, pancreas, and intestines; and atonic GIT. These changes in the digestive system can lead to considerable eating disorders and weight loss.

In patients, trophic disorders of skin and its appendages in the form of xeroderma, thinning and brittleness of nails, and hair loss persist. Quite often, signs of carbohydrate metabolism disorder (hyperglycemic-type glucose curve), lipid disorder (cholesterol level increases), and protein metabolism disorder (albumin–globulin ratio decreases) are registered.

In medium severity cases, disorders of endocrine glands function can be observed. Decrease in function of adrenal cortex is manifested in persistent arterial hypotension, flaccidity, and adynamy with decrease in 17-oxycorticosteroid concentration and 17-ketosteroid concentration in urine and blood. Decrease in level of active estrogen fractions in urine is noted in women. The majority (about 82 %) of women with CRS have menstrual disorders in the form of rhythm and duration change (more often, it is hypopolymenorrhea and hypooligomenorrhea; hypermenorrhea is less frequent). The most expressed changes of a menstrual cycle up to amenorrhea development occurred in women with external γ-exposure dose exceeding 3 Gy (Verbenko and Chusova 1967).

Quite often, the CRS course of medium severity was complicated by infectious diseases of respiratory and digestive systems. They are characterized by course areactivity, absence or low intensity of inflammatory response, severe intoxication, and marked changes in the nervous system.

Severe CRS is characterized by irreversible changes in an organism: sharp inhibition of hematopoiesis, organic disorders of the nervous system, and degeneration of internal organs. The performance status of patients continues to worsen; sharp weakness, adynamy, and marked and persistent arterial hypotension develop. Manifestations of organic disorders of the nervous system and profound inhibition of hematopoiesis come to the fore in clinical picture of the disease. Changes in the nervous system are generally characterized by symptoms of more severe organic disorders of the CNS. Organic disorders of the nervous system proceed as demyelinating encephalomyelitis. Very seldom diencephalic syndrome occurs.

Severe degree is characterized by the development of BM hypoplasia. In such cases in peripheral blood, the persistent and marked granulocytopenia, profound thrombocytopenia, and moderate anemia occur. In the BM, the marked delay of granulocyte maturation processes and perverted megaloblast-type erythropoiesis are observed. In BM of patients with severe CRS, dramatic changes in cell ratio of granulocyte lineage occur: the promyelocyte content increases considerably with normal amount of myelocytes and young cells and decreased level of band and segmented cells. Mitosis frequency of BM granulocytes is normal or increased (Sokolova 1963).

In case of exposure termination, hematopoiesis recovery in patients is very problematic or even impossible. The process progression acquires irreversible character even after the exposure termination. Frequent complications are hemorrhagic syndrome (cutaneous petechia and ecchymosis, nasal and gingival hemorrhages) and infectious complications.

Disorders of cardiovascular, digestive, and endocrine system functions are more expressed than in less severe cases. Patients suffer from dyspnea, palpitation, and precordialgia. Heart borders are extended, heart tones are muffled, and bradycardia, extrasystole, and arterial hypotension are observed. Usual manifestations of changes in digestive system are dyspeptic disorders. The liver increases in sizes. Patients may suffer from toxic nephritis and endocrine gland disorders. This stage is characterized by marked metabolism disorders (hypoproteinemia, hypocholesterolemia, and hypochloremia), trophic skin disorders, hair loss, and brittleness of nails.

Due to hypotrophic changes in reproductive organs of men, marked sexual weakness is noted; women have menstrual and gestation course disorders (Verbenko et al. 1959, 1963). As a rule, periods are long (10–15 days) and hypopolymenorrhea-type. In some cases, hypomenorrhea or even temporary amenorrhea occurs (Verbenko and Chusova 1967).

The patients' health status in terminal CRS stage (the most severe cases) deteriorates dramatically; general weakness and adynamy dominate clinical picture of the terminal CRS stage. Patients often have infectious complications which can be the cause of death. Marked inhibition of BM hematopoiesis is typical. Considerable inhibition of lymphopoiesis also occurs but to a lesser extent than that of granulopoiesis. The amount of neutrophilic granulocytes is dramatically reduced, and in severe cases down to agranulocytosis. Thrombocytopenia is markedly manifested. Erythrocyte content decreases to $1.5–2.0 \cdot 10^{12}$/l. Coagulation of blood is impaired (Sokolova 1963).

Vascular atony, increased vascular fragility, and permeability disorders are noted in cardiovascular system. Vascular changes, as well as changes of the blood, play the key role in hemorrhagic syndrome formation. Hemorrhages develop on a body surface at insignificant traumas in the form of small petechiae and big ecchymomas. Patients suffer from visceral, mucosal, nasal, and gingival hemorrhages. The examination of the urine samples reveal the presence of the protein and casts. Typically, adrenal gland failure occurs. The most frequent cause of patients' death is sepsis resulting from inhibition of hematopoiesis and immunity.

In the majority of cases at the exposure termination, the life forecast at CRS is favorable. In later terms, CRS can possibly result in blood diseases (partial BM