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Follow-up of delayed health consequences of acute accidental radiation exposure

Lessons to be learned from their medical management

Co-sponsored by the International Atomic Energy Agency and the World Health Organization

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FOREWORD

While the use of radioactive materials around the world offers a wide range of benefits in medicine, industry and research, safety precautions are essential to limit the exposure of persons to harmful radiation. When the quantity of radioactive material employed is substantial, as when radioactive sources are used for radiotherapy in medicine or for industrial radiography, extreme care is necessary to prevent accidents that may lead to severe health consequences for the individuals involved. Despite the fact that the precautions to be taken are clearly established, accidents with radiation sources continue to occur, albeit infrequently. The IAEA, as part of its 'Safety of Radiation Sources' and 'Emergency Response' subprogrammes, follows up severe accidents of this kind. In so doing, the IAEA attempts to document both the circumstances leading to the accident and the subsequent medical treatment in order to define the lessons to be learned from these events. The overall objective is to provide information that will be of benefit to organizations with responsibilities for radiation protection, the safety of radiation sources and the medical management of radiation accidents.

The International Atomic Energy Agency has issued a number of publications on radiation accidents which have occurred in the past 15 years, reporting on the causes, radiation safety aspects and medical management of those affected particularly in the acute phase following an accident. These reports cover the accidents in Chernobyl, Ukraine (the Republic of the former Soviet Union) and Goiânia (Brazil), and those in El Salvador, Vietnam, Belarus, Israel, Estonia, Costa Rica, Georgia, Russian Federation, Turkey, Peru and Panama. In 1998 the IAEA published three Safety Reports, co-sponsored by the World Health Organization, aimed at disseminating medical information on the recognition and treatment of radiation injuries, planning the medical response to radiation accidents and occupational health surveillance in the event of accidental overexposure.

As part of the co-operative arrangements between the IAEA and WHO, a joint IAEA–WHO technical meeting (TM) was held on 1–3 October 2001 at WHO Headquarters. Ten radiation medicine experts, who had been responsible for providing medical assistance to victims of radiation accidents, and four members of the Joint IAEA–WHO Secretariat, attended the meeting. The objectives of the TM were to review the delayed health consequences of acute exposure to radiation consecutive to a number of recent radiation accidents and to analyse lessons to be learned in their diagnosis and treatment. Eight papers were presented and discussed. These form the basis of this joint IAEA–WHO publication.

Accounting for the conclusions and lessons learned from the medical management and follow up of recent severe radiation accidents, a Joint IAEA–WHO Consultancy Services Meeting (CSM) was held on 8–9 November 2001 at the WHO Collaborating Centre for Radiation Accident Management, at the University of Ulm, Germany, where recommendations were developed by the team of medical experts for the Joint Secretariat on updating the strategy for the treatment of local radiation injuries and of acute radiation sickness. These are to be discussed in an upcoming joint publication together with recent follow-up findings.

The contribution of all participants to the drafting and review of this publication is acknowledged. The Chernobyl chapters have benefited greatly from the technical review of G. Souchkevitch, the Scientific Co-Secretary from the WHO.

The IAEA officer responsible for the preparation of this report was I. Turai of the Division of Radiation and Waste Safety.

EDITORIAL NOTE

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CONTENTS

SUMMARY

The purposes of this publication are: (i) to review the medical follow-up of the delayed health consequences of acute exposure to radiation which occurred following a number of accidents — Chernobyl, Ukraine, 1986; Lilo, Georgia, 1997; Istanbul, Turkey, 1998; Tokaimura, Japan, 1999; Yanango, Peru, 1999 and Samut Prakarn, Thailand, 2000; and (ii) to analyse the lessons to be learned from the long term medical management of the victims. By disseminating this publication, which the IAEA and the WHO have jointly prepared, to health authorities and medical institutions, the two organizations aim to provide information on the most up to date methods for the effective medical management of radiation accident victims.

At the joint IAEA–WHO technical meeting on Follow-up of Delayed Health Consequences of Acute Accidental Radiation Exposure: Lessons to be Learned, held on 1–3 October 2001 at WHO headquarters in Geneva, the primary authors of the chapters of this publication presented eight papers, which were discussed in detail. These papers form the basis of this publication. Subsequently, on 8–9 November 2001, a joint IAEA–WHO meeting was held at the WHO Collaborating Centre for Radiation Emergency Medical Preparedness and Assistance Network (REMPAN) at the University of Ulm, Germany, where recommendations were drawn up for updating the strategy for the diagnosis and treatment of local radiation injuries (LRI) and acute radiation sickness (ARS).

Lessons drawn from the medical management of radiation accident victims

The lessons drawn from the medical management of the accident victims involved in each of the radiation accidents are discussed in turn.

(a) The Chernobyl nuclear accident (Ukraine, 1986)

The medical follow-up of persons who were highly exposed as a consequence of this accident has shown that for the effective management of victims of radiation accidents there is a need for:

(1) Regular monitoring of the state of health of individuals to reveal any stochastic or non-stochastic radiation effects or psychological disorders induced by an accident

(2) Application of the latest diagnostic methods in the examination of overexposed persons, in order to facilitate the early detection of a malignant tumour;

(3) Prevention of progression and the treatment of somatic and psychological diseases of overexposed individuals;

(4) Neuropsychiatric and neuropsycho-physiological investigations to clarify the existence, causes, treatment and prevention of progressive structural–functional brain damage.

(b) The Lilo accident (Georgia, 1997)

In the medical management of those affected by this accident, the following points were noted:

(1) Skin lesions which spontaneously healed and initially appeared stable can, after a long period of time (months, years), deteriorate, leading to secondary reopening;

(2) Satisfactory initial surgery did not prevent in all cases some secondary (often localized) radionecrotic ulcerations that needed to be followed up for a number of years. Late effects of cutaneous radiation syndrome include dermal and subcutaneous fibrosis, a dynamic process that can lead to ulcers even several years after the accident;

(3) A number of sequelae were responsible for a severe impairment in the quality of life of the patients: functional sequelae (e.g. finger amputations) in some cases; cosmetic sequelae in almost all cases; oligospermia or azoospermia in all cases; and various psychosomatic symptoms and nervous breakdowns. Hence, it was felt that regular monitoring of the general health status of patients, involving immunological and psychological methods, could be reasonably undertaken over a period of several years following the accident
(4) These patients were presumed to have a higher risk of developing secondary malignancies (leukaemias, developing from myelodysplasias, and solid tumours). Annual medical examinations, extending over at least 15–20 years after the accident, were therefore felt to be necessary for all 11 victims.

(c) The Yanango accident (Peru, 1999)

The following points arose out of the medical management of the patient involved in this accident:

(1) Hemipelvectomy was considered three weeks post-exposure and before the perianal region became involved, but the decision was postponed. Instead, the lesion was grafted over in an attempt to save the irradiated limb. The graft failed and the limb was amputated a few months later;
(2) There are always uncertainties associated with physical dose estimates based on the observed biological effects. These uncertainties could have been diminished if histopathological and electron spin resonance studies had been carried out on the tissues from the amputated leg. Unfortunately, the amputated tissue had been discarded and was therefore not available for study.

(d) Istanbul (Turkey, 1998)

The following conclusions were drawn in connection with the accident in Istanbul:

(1) The use of cytokines assisted the haematopoietic recovery even one month after the radiation exposure (which involved doses of up to 3–4 Gy to the whole body), and is therefore to be regarded as a useful means of treatment in such cases as it shortened the period of neutropaenia, and thus prevented the development of systemic infections (sepsis) that may lead to fatality. Adverse effects of granulocyte–colony stimulating factor (G-CSF) on platelet recovery were not observed.
(2) The clinical evolution observed in this accident confirms that even with a rather severe haematopoietic syndrome due to whole body irradiation of a few grays (about the $LD_{50/60}$), the use of allogeneic bone marrow transplantation is contra-indicated, owing to the probability of graft complications.
(3) At the late phase of local radiation injury, skin lesions are susceptible to reopening owing to progressive vasculitis. A vascular necrosis and a reopening of lesions were observed 11 and 14 months, respectively, after the local radiation exposure. Local antiseptic solutions and skin hydration were effective in their treatment.

(e) Tokaimura (Japan, 1999)

The following points arose from the medical management of the individuals affected by this accident:

(1) Prompt and radical prophylaxis of infection by Selective Digestive tract Decontamination (SDD), systemic administration of broad spectrum antibiotics and G-CSF can modify the clinical outcome of ARS. It is noteworthy that no clinical infection occurred when the

white blood cell counts were less than 500. Moreover, acute GI syndrome was completely suppressed.

(2) Stem cell transplantation from peripheral blood or cord blood was performed for two patients without testing for graft versus host disease (GVHD). It is essential to analyse the human leucocyte antigene (HLA) types of patients and their family members as soon as possible. The degree of HLA matching is critical to the prevention of GVHD. HLA typing for A, B, C, and DRb loci is recommended. Moreover, DNA typing can further characterize the fine specificity of HLA type. Since DNA typing can be done for any tissues, it is appropriate for lymphopenic patients.

(3) In this accident, the operator, whowas one of the victims, was subjected to accusations of being the proximate cause of its occurrence, even though the cause of the accident might have been attributable to other factors. The psychological stress on the victim brought on by such accusations needs to be recognized and dealt with as early as possible with the help of appropriate specialists.

Recommendations

The following recommendations — made by the team of radiation medicine experts listed at the end of this publication — for the medical management of radiation injuries are based on the lessons drawn from the medical follow-up of the accident victims discussed in this publication. These are structured according to the main types of health consequences resulting from accidental radiation exposure.

(A) Diagnosis and treatment of ARS

(1) Annual medical examinations, involving specialized physicians, ought to be carried out over a period of at least 15–20 years in the case of those persons who have received high exposure to a large part of their bodies, in order to provide early diagnosis and treatment of any radiation induced cancer. These medical examinations would be carried out involving the participation of a clinical team consisting of therapeutic specialists, haematologists, immunologists, oncologists, endocrinologists, ophthalmologists, cardiologists, pulmonologists, neuropathologists and psychologists.

(2) Ultrasound examinations of the abdominal cavity, prostate or ovaries, and thyroid gland ought to be included in the annual health surveillance of ARS patients.

(3) Complete blood counts (CBC) with blood smear analysis; studies of immunogram, liver specific (γ-GT, AP) and non-specific (AST, ALT) enzyme levels in serum; infrared spectroscopy of pyrophosphates in urine sediment and analysis of lipid peroxidation activity need to be performed.

(4) Bone marrow samples (by aspiration or biopsy) need to be analysed and cultured blood samples investigated, if clear changes in peripheral blood cells are observed.

(5) Cytokines can reasonably be used in the treatment of radiation induced severe bone marrow aplasia — even several weeks after the radiation exposure — when extensive bone marrow examination has shown that spontaneous haematopoietic recovery has not yet started.

(6) Electrocardiography (ECG) needs to be performed when the heart is in the irradiated field (and whenever clinically indicated).

(7) SDD using antibiotics *per os* in insoluble non-absorbable form to eliminate aerobic bacteria in colon and systemic administration of antibiotics ought to be undertaken as soon as possible in cases of very severe ARS.

(B) Diagnosis and treatment of LRI

(1) Sonography and thermography ought to be used to investigate dermal vasculitis following LRI; magnetic resonance imaging (MRI) should be performed if muscular vasculitis is also suspected (i.e. in areas with blisters and/or ulcers induced by local radiation exposure).

(2) Antioxidants, including vitamins A, C and E, and vasoactive drugs should be used in the treatment of various diseases suffered by irradiated persons.

(3) Muscular vasculitis benefits from treatment with steroids (0.5–1.0 mg/kg body weight prednisolone equivalent) for one week following exposure; the steroid dose over a longer time period should be substantially lower.

(4) Acute or subacute radiation ulcers require surgical treatment only after completion of steroid therapy or after exclusion of muscular vasculitis. Treatment should consist of excision of the ulcer and the damaged surroundings, wound closure with plastic procedures or split skin grafts after wound conditioning with hydrocolloid dressings or autologous thrombocytic growth factors. Tissue replacement by autologous or allogeneic grafting is an additional option. Small surgical procedures (wound debridement) are performed not later than 10 days after the accident, and major surgical procedures not earlier than 60 days after the accident.

(5) Radiation keratoses that may precede the development of skin cancer need to be treated systemically with retinoids (Acitretin 0.2 mg/kg body weight) until the lesions disappear. If the lesions persist for more than three months (in spite of the use of Acitretin), they should be treated locally either by excision, cryosurgery, laser surgery or topical retinoids.

(6) Radiation fibrosis ought to be treated with interferon using subcutaneous injections (100 μg three times a week for six months, then once a week for another six months). Lifelong administration might be necessary. Another possibility to be considered is the use of a combination of pentoxiphylline (3 × 400 mg per day given orally) with vitamin E (α-tocopherole, 400 mg once per day also given orally) for half a year, at least.

(C) Other aspects of diagnosis and treatment of accidental radiation exposures

(1) Attempts ought to be made to reconcile the estimates of dose using physical and biological dosimetry. Experts with appropriate knowledge of, and experience in, the treatment of ARS and LRI should be consulted.

(2) Human tissue samples (including samples taken from amputated body parts) taken from persons that have encountered high levels of exposure should be preserved for use in the assessment of radiation dose, which may help in the subsequent treatment of the patient, and should only be discarded when it is clear that they are no longer required.

(3) The psychological support of a patient's family needs to be facilitated, for example, by allowing the patient to return home as soon as possible. This has been shown to aid substantially the effectiveness of treatment, even in very severe cases where the prognosis is bad.

(4) Medical students need to be educated and doctors widely trained to recognize radiation injuries and to provide appropriate first aid.

Chapter 1

HEALTH CONSEQUENCES IN THE CHERNOBYL EMERGENCY WORKERS SURVIVING AFTER CONFIRMED ACUTE RADIATION SICKNESS

V. Bebeshko, D. Belyi, A. Kovalenko, O. Gergel

1.1. Short description of the Chernobyl accident

1.1.1. Place, date, circumstances

On April 26, 1986 (1:24 a.m.) the accident at the Unit 4 of the Chernobyl Nuclear Power Plant (ChNPP) took place during the planned test of one of the safety systems [1]. According to the International Nuclear Event Scale (INES of the IAEA) the Chernobyl accident is classified as the only event by today at the 7^{th} (most severe) level [2].

1.1.2. Radioactive source

Approximately 300 MCi ($11 \cdot 10^{18}$ Bq) of radioactive materials exploded into the environment from the destroyed reactor [3]. During the first days and weeks after the accident the radiation situation was determined with nuclear decay of short lived radionuclides, mainly of iodine isotopes — ^{131}I, ^{132}I, ^{133}I and ^{135}I. Further radiation doses were formed mainly with long lived radionuclides, particularly, ^{90}Sr and ^{137}Cs, as well as together with transuranium elements in the Chernobyl exclusion zone [4].

1.1.3. Number of affected persons, estimated individual doses

The accident caused the deaths within a few days or weeks of 30 ChNPP employees and firemen (including 28 deaths that were due to radiation exposure), brought about the evacuation of about 116 000 people from areas surrounding the reactor during 1986, and the relocation, after 1986, of about 220 000 people from Belarus, the Russian Federation, and Ukraine. About 240 000 clean up workers ("liquidators") were called upon in 1986 and 1987 to take part in major mitigation activities at the reactor and within the 30-km zone surrounding the reactor; residual mitigation activities continued until 1990. Altogether, some 600 000 persons received the special status of "liquidator" [5].

The highest doses were received by the approximately 600 emergency workers who were on the site of the Chernobyl power plant during the night of the accident. The most important exposures were due to external irradiation, as the intake of radionuclides through inhalation was relatively small in most cases. Acute radiation sickness (ARS) was confirmed for 134 of those emergency workers. Forty-one of these patients received whole-body doses from external irradiation of less than 2.1 Gy. Ninety-three patients received higher doses and had more severe ARS: 50 persons with doses between 2.2 and 4.1 Gy, 22 between 4.2 and 6.4 Gy, and 21 between 6.5 and 16 Gy [5, 6].

The total number of hospitalized patients with suspected diagnosis of ARS due to the Chernobyl accident included 499 persons [7]. Of these, diagnosis was confirmed clinically in 237 cases. After subsequent re-estimation of clinical and haematological data, diagnosis was confirmed for 134 of these individuals [8–11]. Two patients died at the place of the accident.

Between Day 7 and Day 96 after the accident, 28 overexposed and injured patients died. In the subsequent years 14 patients died due to different causes [12].

1.1.4. Degree and type of initial injuries

All four degrees of severity of ARS were observed in overexposed workers. In addition to the typical haematological, cutaneous and/or gastrointestinal syndromes all patients developed neurological and psychological disorders. Autonomic [vegetative] vascular dystonia (VVD) and neurotic disorders were observed in the clinical picture of *mild* and *moderate degree ARS,* i.e. ARS of the 1st and 2nd degree severity with estimated whole body doses of 1–2 Gy and 2–4 Gy, respectively. *Severe degree ARS* (or ARS of the 3rd severity degree from 4–6 Gy) was accompanied with acute radiation and radiation-toxic encephalopathy, acute psychosis with visual and acoustical hallucinations and brain oedema. *Very severe ARS* (or ARS of the 4th severity degree at >6 Gy) led to acute irradiation and radiation-toxic encephalopathy, acute brain oedema and subarachnoidal-parenchimatous haemorrhage [13, 14].

1.2. Medical actions in the early period after the accident

The Governments of the former USSR and the Ukrainian Republic were informed by managers of the Chernobyl NPP about the fact of the accident immediately after the vapour explosion. Preliminary assessment of results of the reactor explosion given by the specialists of the NPP showed already serious character of consequences for ecology of the country and population health due to the release to the surrounding areas of the radioactive content of the reactor. Besides, radiation situation around the damaged reactor was threatening the life of people. Organization of medical aid to victims was begun without further delay at night on 26 April 1986.

The most important medical measures in elimination of consequences of the ChNPP accident are represented in chronological order:

- In the minutes and hours after the accident first aid is given in premises of the Medical and Sanitarian Unit No 126 on the territory of the ChNPP to wounded people and individuals with the first symptoms of acute radiation syndrome.
- Group of physicians from the Institute of Biophysics, Moscow, headed by Prof. A.K. Guskova arrived to the ChNPP in the morning, on 26, April 1986. Specialists from the Kiev Research Institute for Haematology and Blood Transfusion, the Kiev Institute for Postgraduate Medical Training, Ministry of Health of Ukraine, physicians-haematologists from Kiev hospitals were also involved. On 26 and 27 April more than 350 victims were examined by joint efforts who were sent to the 6th Clinical Hospital, Biophysics Institute, in Moscow. In total, 500 people came to that hospital with a suspicion of acute radiation sickness which was diagnosed in 118 patients.
- In the morning of 26 April 1986 the Governmental Commission was established by order of the Council of Ministers of the USSR for interrogation of causes of the ChNPP accident. A Vice Minister of Health of the USSR was included into the Commission. Decision making on organization of medical aid to individuals participating in elimination of the accident consequences, implementation of radiation injuries prophylaxis and evacuation of civil population from the zone around the Chernobyl NPP was within the competence of the Commission.
- Accounting for the continued release of radioactive isotopes for a week, iodine prophylaxis was conducted for 5 million persons including 1.6 millions children of Russia,

Belarus and Ukraine together. In Ukraine the iodine prophylaxis was extended to all Chernigov, Zhitomir and Kiev residents [4].

- In late April early May 1986, medical examination of overexposed persons working on elimination of consequences of the accident was conducted in different hospitals of Kiev and Moscow. Patients in the Kiev hospitals were repeatedly consulted by radiation medicine experts arriving from the Institute of Biophysics, Moscow and the Military Medical Academy, St. Petersburg. Diagnosis of ARS was preliminary made for 237 persons admitted to hospitals in Kiev and Moscow. This diagnosis was later confirmed for 134 patients.
- At the end of April and during May 1986 measures were taken for medical examination and medical aid for evacuees and people residing in areas with enhanced content of radiation. For this purpose 2000 physicians, 4000 medical workers and more than 1200 senior students of Ukrainian medical institutes were engaged, 230 laboratory and dosimetric mobile brigades and more than 400 brigades of physicians were established.

1.3. Follow-up of ARS survivors in the Scientific Center for Radiation Medicine, Kiev, Ukraine

The All-Union Scientific Centre for Radiation Medicine (SCRM), Academy of Medical Sciences of the USSR, with clinics for 300 beds for adult patients and 120 beds for children was opened in Kiev on 1 October 1986. The Centre was to play a role of a head scientific medical establishment (in Ukraine, first of all) dealing with problems of radiation medicine.

The decision was made in 1987 about the establishment of the All-Union Registry of the Chernobyl Catastrophe Survivors. In parallel, the National Registry was established in Ukraine as a part of the All-Union Registry. It should be pointed out that after USSR disintegration and establishment of the Ukrainian state the National Registry became a real instrument allowing to provide medical-prophylactic and social aid to all the Chernobyl catastrophe survivors residing in Ukraine.

The Council of Experts was established in the SCRM in 1988 for connection of diseases appeared at people after cleanup works at the ChNPP with harmful factors of the Chernobyl accident. Data accumulated in the Council of Experts were used for the scientific analysis of stochastic and non-stochastic radiation effects on survivors.

A Commission on verification of diagnosis of ARS made in 1986 was established in 1989. This Commission was headed by Professor A.K. Guskova. Criteria used for verification of ARS are given in Table 1.1 [8].

Analysis of medical documents showed that for only 134 individuals from a total of 237 (Table 1.2) there were haematological symptoms of ARS of different degrees of severity. The basic cause of diagnostic errors was the fear of physicians to “fail” such serious disease under condition of mass arrival of irradiated people to clinics. That is why ARS is often diagnosed by a fact of stay in the zone of the ChNPP and presence of primary reaction in the outlook of nausea, vomiting, headache etc. If in the course of subsequent observation changes of haematological indices were absent, specialists had not always courage to cancel preliminary diagnosis.

TABLE 1.1. ARS DIAGNOSIS, ARS SEVERITY AND TIME DELAY FOR CLINICAL MANIFESTATIONS

Indexes	Grade of ARS severity and the associated absorbed dose to the whole body (Gy)			
	I. (1-2)	II. (2-4)	III. (4-6)	IV. (> 6)
Manifestation starts	On 30th day or later	15–26th day	8–17th day	In less than 7 days
Clinical manifestation	Asthenia	Infections, bleeding, epilation	Infections, bleeding, epilation	General intoxication, fever, intestinal syndrome, hypotension
Peripheral blood leucocytes (10^9/L)	3.0–1.5	1.5–0.5	0.5–0.1	Below 0.5 or have no time for decrease
Peripheral blood thrombocytes (10^9/L)	100.0–60.0	60.0–30.0	Less than 30.0	Less than 20.0 or have no time for decrease
Granulocytopenia starts on	30th day or later, or absent	20–30th day	8–20th day	6–8th day
Thrombocytopenia starts on	25–28th day, or absent	17–24th day	10–16th day	Before 10th day
ESR, mm/h	10–25	25–40	40–80	60–80

TABLE 1.2. HOSPITALS WHERE ARS WAS DIAGNOSED AND VERIFIED

ARS	MOSCOW	KIEV	KHARKOV
Diagnosed in 1986	118	118	1
Confirmed in 1989	108	25	1

From 1986 till 1991 many of these 237 individuals were examined in the hospital of the Institute of Biophysics in Moscow. From 1991 (since the disintegration of the USSR) till today the SCRM is the only medical establishment in Ukraine where full-scale monitoring of ARS patients is being implemented.

1.3.1. Patients and methods of study

From October 1, 1986 to April 26, 2001, 96 patients with confirmed ARS were being investigated in the SCRM hospital: 39 of them had suffered from ARS 1st degree, 45 – 2nd degree and 12 – 3rd degree of severity. Average age of ARS survivors was 34.0±8.9[1] (max. – 79, min – 18) years. As the group for comparison, 94 persons (age 36.4±10.4 years) were being monitored too. In 1986, ARS 1 degree was diagnosed in all of them but was not confirmed in 1989 (ARS NC[2]). However, their "radiation anamnesis", evidence of primary reaction and light changes in peripheral blood content of granulocytes and thrombocytes let to consider an exposure to irradiation in doses quite closed to 1 Sv.

[1] The sign ± is to be understood as standard deviation throughout this section.
[2] ARS non-confirmed.

Each patient visited the hospital on average 8.8 times during 15-years period after the Chernobyl accident (or about 3 times each 5 years). The clinical examination programme included both obligatory actions and special procedures (carried out in accordance with the indications) (Table 1.3).

TABLE 1.3. LABORATORY ACTIONS AND TREATMENT PROCEDURES PERFORMED AT THE SCRM IN THE YEARS FOLLOWING THE ACCIDENT

OBLIGATORY	SPECIAL
• Periphery blood test • Biochemical blood test • Glucose blood test • Immunological blood test • Urine test, urine test for glucose • Ultrasound examination (USE) of abdominal cavity organs • Thyroid gland USE • Electrocardiogram (ECG) • Digestion tract endoscopy • Consultation of therapeutist, pulmonologist, gastroenterologist, cardiologist, endocrinologist, haematologist, dermatologist, neuropathologist, psychiatrist	• Bone marrow investigation, HLA-typing, cultural investigations • Definition of CD34+ content and circulating immune complexes, phenotyping of lymphocytes • Cytogenetic investigations • Blood serum lipids test • Definition of thyroid and other hormones in serum • Definition of lipid peroxide oxidation activity and antioxidation defence response • Densitometry of bone tissue • IR[3]-spectroscopy of bone tissue and urine sediment • Bacteriological investigation of biological media • Electroencephalogram (EEG) • X ray investigation methods • Investigation of functional capability of lungs and heart • Thermography

1.4. Follow-up in the delayed period: non-stochastic and stochastic consequences in acute radiation syndrome survivors

From total number of 96 examined ARS survivors, 79 persons are living now in Ukraine, except two who live in Russia and Belarus. All 94 patients with NOARS (non-confirmed) were residents of Ukraine. Between 1986 and 2001, 14 ARS survivors and 7 patients with NOARS died for different reasons (Table 1.4). Among reasons for their death, the highest ratio belongs to sudden coronary death (7 cases), oncohaematological causes (4 cases) and oncological pathology (2 cases), which exceed somatic diseases and traumas by a factor of almost two.

1.4.1. Oncological and oncohaematological pathology

In addition to two lethal outcomes from myelodysplastic syndrome (MDS) and by one death from hypoplasia of haematopoiesis and acute myelomonoblastic leukaemia (Table 1.4) one

[3] IR – infrared

more MDS was revealed in an ARS 1 degree survivor in 1996. His disease was manifested with progressive refractory anaemia and bone marrow fibrosis. The patient gets symptomatic therapy and concentrated thrombocytes transfusions. As a pathogenetic treatment a stimulator of erythropoiesis Eprex (epoetin alpha), immune modulator Cepharanthin and vitamin D_3 were given to the patient. He demonstrated intolerance to Neupogen and Leukomax.

TABLE 1.4. CAUSE OF DEATH OF PERSONS WHO DIED FROM 1986 TO 2001 AFTER ACUTE IRRADIATION

No	INITIALS	DEGREE OF ARS SEVERITY	YEAR OF DEATH	AGE AT DEATH	CAUSE OF DEATH
1	P.V.A.	1	1993	42	Sudden coronary death
2	V.O.E.	1	1995	51	Lung tuberculosis
3	K.A.P.	1	1995	53	Adipose embolism due to trauma
4	S.M.A.	1	1995	27	Sudden coronary death
5	V.V.Ya.	2	1987	80	Gangrene of lung
6	K.Ya.F.	2	1990	68	Sudden coronary death
7	B.V.I.	2	1995	46	Liver cirrhosis
8	G.M.U.	2	1998	45	Liver cirrhosis
9	S.V.K.	2	1998	50	Acute myelomonoblastic leukaemia
10	B.V.M.	2	1998	80	Sudden coronary death
11	V.M.P.	3	1992	67	Sudden coronary death
12	B.G.V.	3	1993	52	Myelodysplastic syndrome
13	D.A.S.	3	1995	64	Myelodysplastic syndrome
14	B.I.Z.	3	2001	88	Sudden coronary death
15	N.G.F.	NOARS	1986	48	Accident
16	G.R.A.	NOARS	1987	48	Hypoplasia of haematopoiesis
17	E.V.A.	NOARS	1988	31	Encephalitis and encephalomyelitis
18	K.M.F.	NOARS	1993	35	Sarcoma of thigh
19	T.V.V.	NOARS	1994	57	Sudden coronary death
20	F.V.P.	NOARS	1995	64	Accident
21	U.V.A.	NOARS	2001	60	Laryngeal carcinoma

Malignant neoplasms were found in 9 patients (age 50.9±13.4 years). Of them, 3 cases were diagnosed in ARS survivors and 6 cases in NOARS patients. Among ARS 2nd degree survivors there were two persons who developed thyroid cancer (operated in 2000) and one ARS 1st degree survivor who manifested sigmoid colon cancer in situ. He was operated in 1997. The six NOARS patients developed the following malignant neoplasms: 1. sarcoma of thigh (died in 1993), 2. laryngeal carcinoma (died in 2001), 3. leiomyosarcoma of skin treated with radiation therapy in 1998 (total local dose 52 Gy). In 1999, this same patient developed a sigmoid colon carcinoma and was operated on in 1998. Cancer of a kidney was diagnosed in the 4th NOARS patient at the end of 2000. The patient was successfully operated. In 2001 a bronchogenic lung cancer was diagnosed in the 5th NOARS patient, who suffered from

chronic obstructive bronchitis for a long time. Cancer of the prostate was revealed in the 6th patient from the same group during ultrasound examination (USE) of the urinary tract in 2001.

All malignant tumours had minor symptomatology and were revealed due to periodical examinations. The geographical distribution of the malignant tumours suggests that the diagnostic procedures during the obligatory annual follow up examinations should include (1) endoscopy of the digestive tract, (2) USE of thyroid gland, abdominal cavity and minor pelvis, (3) X ray examination of lungs and (4) bronchoscopy if chronic bronchopulmonal diseases take place.

1.4.2. Haematopoiesis

The state of haematopoiesis was estimated in the entire post-accident period in 70 patients with NOARS and in 62 ARS survivors, including 29 patients with ARS to the 1st degree, 26 from ARS to the 2nd degree and 7 from ARS to the 3d degree. A bone marrow biopsy or aspiration was conducted when a patient had stable disorders in the haematopoietic system. Haematopoietic progenitor cells were investigated by gel diffusion chambers (GDC) in vivo [15].

As earlier indicated [16, 17], practically all the ARS survivors had qualitative changes to their blood elements and bone marrow at the optical and ultra-structural levels in the follow-up period. There were hypersegmentation, nuclear fragmentation, toxic granularity, outgrowths and basophilia of lymphocyte cytoplasm, vacuolization of cytoplasm and nuclei. The bone marrow hypoplasia with signs of substitution with fat and phenomenon of fibrosis were observed. However, in due course the frequency of the revealed changes gradually decreased.

The investigations of bone marrow haematopoietic cells in the ARS convalescents at different terms after the Chernobyl accident [18] showed that at first days after irradiation colonies of haematopoiesis (CFUdc) in the culture were characterized by primary increase of immature forms of granulocytes, eosinophilic set of differentiation and cells destruction. The reliable reduction of number of early colony forming units of bone marrow was observed, which was more expressed in patients with ARS of 2^{nd}3d degree.

The oppression of colony forming haematopoietic progenitor-cells took place long before the developing of agranulocytosis that usually was realized at 20^{th}–24^{th} days among patients with ARS of 1–2 degree and was characterized by deep leucopenia and granulocytopenia. Among patients with ARS of the 3d degree this phenomenon developed in shorter terms. This fact corresponds to the idea that the events on the level of progenitor-cells of bone marrow go ahead changes in peripheral blood indices.

Under productive recovery in the post-radiation period among persons with ARS haematopoietic potential of progenitor cells restored (Fig. 1.1). Together with normal colony formation in the culture in vivo we observed increase of cloning efficiency of granulomonocytes and eosinophilic progenitor-cells with preferable growth of hypersegment forms of neutrophilic leukocytes. Activation of erythron was expressed by increase of cloning efficiency of early erythroid progenitor cells, which formed bursts from young proliferating erythroid cells instead of maturing and mature ones, as it could be seen in practically healthy people. These investigations were done in 1986 by N. Bilko in the Kiev Research Institute of Haematology and Blood Transfusion, in 1996 by the SCRM [15].

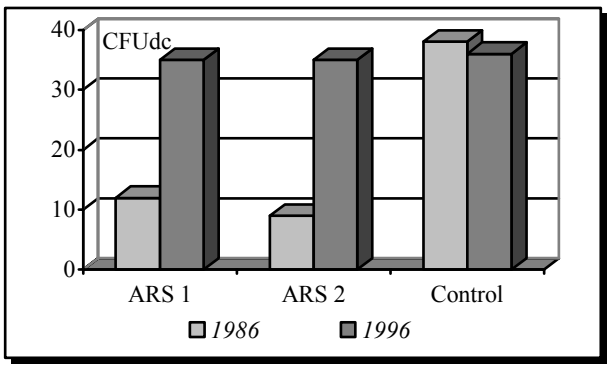
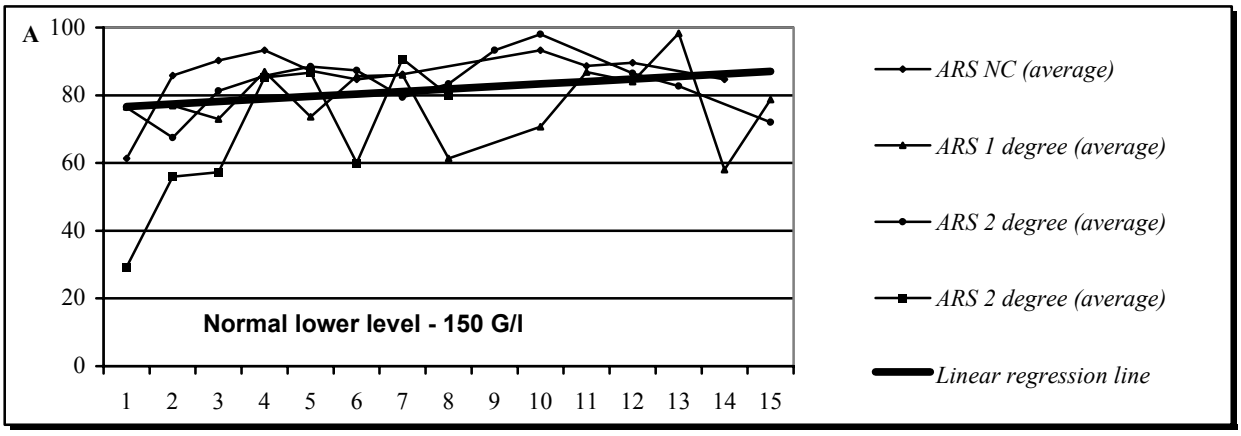


FIG. 1.1. Results of progenitor-cells cultivation at different periods following the Chernobyl accident. (The ordinate axis is the number of colonies multiplied by 10^5).

In cases of deep oppression of colony forming activity in ARS convalescents in the late period after the Chernobyl accident a phenomenon was found in GDC that was not peculiar to bone marrow of healthy donors. Bone marrow of irradiated persons during cultivation showed growth of colonies again after 3–4 weeks that testified about reparation of stem haematopoietic elements. Meanwhile bone marrow of healthy donors showed its colony forming capacity only in term of first weeks of cultivation with subsequent maturation of the cells and their diffusion into a medium.

After acute exposure to radiation in 1986, the recovery to normal content of peripheral blood cells was observed in the most of victims. However, during the first post-accidental year the 16.4% of NOARS persons, 36.4% — ARS 1 degree, 52.1% — ARS 2 degree and 33.3% — ARS 3 degree survivors demonstrated thrombocytopenia, granulocytopenia and leucocytopenia. On the 15th year of study, the number of patients with cytopenia dropped by a factor of 5 to 6 in comparison with the first two years after the irradiation. During the entire post-accidental period, lymphocytopenia, thrombocytopenia and granulocytopenia was revealed in 96.1%, 79.3% and 65.4% of ARS survivors, respectively. These haematological findings were less prevalent in NOARS patients: 42.9%, 30% и 28.6%, respectively. These high cytopenia values in NOARS patients, however, prove that they were also exposed to a whole body dose of about 0.5 Gy. The cytopenia has remained below the lower limit of the normal range throughout the 15 year follow-up period (Fig. 2.2, parts A, B & C).



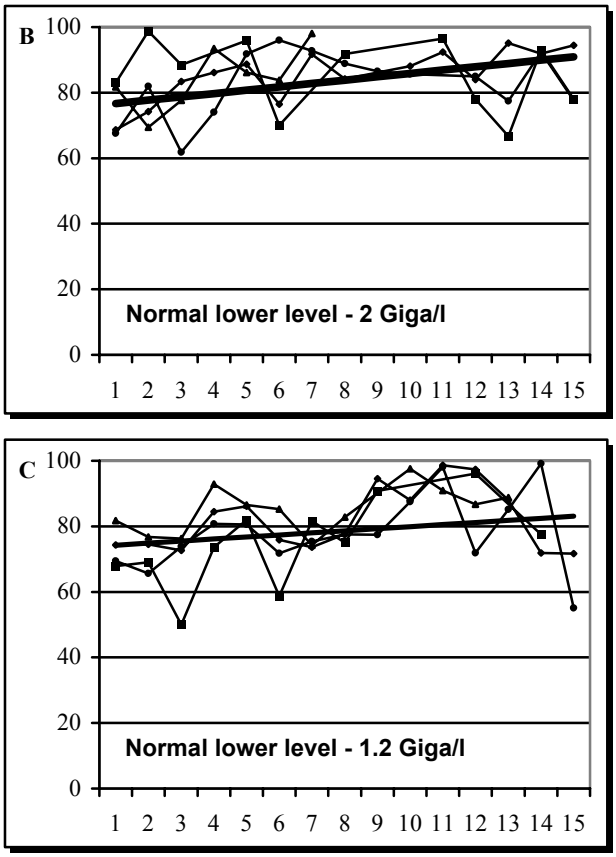


FIG. 1.2. The depth of thrombocytopenia (A), granulocytopenia (B) and lymphocytopenia (C) as a percentage of cell content from the normal lower level (axis of ordinates) in ARS survivors and patients with NOARS (or ARS NC) in the 15 years subsequent to the accidental irradiation.

1.4.3. Immune system

From 1987 to 1990 88 NOARS patients were examined along with 107 patients with confirmed ARS. From 1991 to 1995, immune analysis was done on 66 NOARS and 90 confirmed ARS patients from the initial cohort. From 1996 to 2001, immune analysis was conducted on 49 NOARS patients and 79 patients with confirmed ARS. Before 1989, cellular immunity study was performed by indirect immunofluorescent test with monoclonal antibodies to main differentiation and activation antigens and from 1989, in direct two-colour assay by flow cytometry with *Leu* panel of monoclonal antibodies (MoAbs) (Becton Dickinson, USA). The number of variant T-lymphocytes was estimated in T-cell receptor mutations assay for the enumeration of $CD4^+$ lymphocytes lacking T-cell receptor. PHA/Con A stimulation tests were performed by the estimation of S- and G2+M phases entry of PI stained lymphocytes, surface HLA-DR, RIL-2 and Transferrin receptor expression compared to spontaneous levels. Levels of serum immunoglobulins IgA, IgG, IgM were estimated by radial immunodiffusion, concentration of small and large dispersion circulating immune complexes (CIC) was measured by precipitation in polyethyleneglycol. HLA typing was performed by microlymphocytotoxic test with a panel of specific antisera to A, B, C loci (Leningrad Institute of Haematology and Blood Transfusion, Russia) and DR, DQ (Beringer, Germany). Erythrocyte antigens were estimated by haemagglutination with corresponding antisera; haptoglobin phenotypes were studied by horizontal electrophoresis (LKB, Sweden).

1.4.3.1. Early period of recovery

The immune function of patients suffering from ARS of a severity of degrees 1, 2 and 3 was estimated 3 months after the irradiation as a radiation-induced combined acquired immunodeficiency with depression of cellular, humoral immunity and non-specific resistance mechanisms. A decrease of E-RFC count was registered in 73 % and combined with an increase of E-receptor resistance to theophyllin, functional instability of T- lymphocyte receptors. Follow-up investigations at 12–24, 25–36, 36–48 months after the accident showed satisfactory rate of recovery of cellular and humoral immunity, nevertheless the period of development of radiation injury compensation was protracted between 3 and 5 years. This was accompanied by the decreased surface antigen expression connected to helper-inducer function, mitogen response and wavy oscillations of pan-B and B-immunoblast antigens expression.

1.4.3.2. Remote period of recovery

Remote effects of Chernobyl catastrophe on the immune system were manifested mainly in thymus-dependent compartment between 5 and 10 years after the exposure. The T-lymphocyte count was significantly decreased (Table 1.5). This was especially seen in HLA-DR negative $CD3^+$ lymphocytes of radiation workers with NOARS and the ARS degree 2 and 3 convalescents.

The count of $CD3^+DR^+$ activated lymphocytes reached maximal values between 9 and 10 years after irradiation; the mean values were even higher than the upper normal level. The levels of $CD3^+DR^+$ cells in NOARS convalescents were observed at the same level as in the control group. During the last years, hyperactivation of T-system changed to significant decrease of activated T-cell count. ARS degree 2 and 3 convalescents had significantly increased mean values of B-lymphocytes count of activated HLA-DR-positive B-cells during from 1993 to 1999. Serum immunoglobulins varied widely in all examined persons.

TABLE 1.5. IMMUNE SYSTEM PARAMETERS CHANGES IN EXPOSED PERSONS 10 YEARS AFTER ACCIDENT

INVESTIGATED PARAMETERS	PERCENTAGE OF DEVIATION		
	ARS 1–3 DEGREE	NOARS	CONTROL, UNEXPOSED
CD3+ T-cell count, %	Decrease in 45.6%	Decrease in 26.5%	Decrease in 23.6%
CD4+ helper-inducer cell count, %	Decrease in 48.6%	Decrease in 36.8%	Decrease in 26.1%
CD8+ suppressor/ cytotoxic cell count, %	Decrease in 15.8%	Decrease in 13.9%	Decrease in 5.6%
CD4+/CD8+ ratio	Decrease in 31%	Decrease in 25.6%	Decrease in 24.6%.
	Increase in 5%	Increase in 19.7%	Increase in 5.2%
CD19+ B-cell count, %	Decrease in 15.5 %	Increase in 32%	Increase in 28.8%
Serum Ig concentration	Decrease of IgA concentration	Individual variations	Individual variations

Correlations between variant $TCR^{-}CD4^{+}$ lymphocytes counts at the remote period after exposure to radiation and the level of radiation doses were found. Correlations between above mentioned parameters in 1993–1994 and 1995–1996 were correspondingly r=0.61 (n=21, $p<0.05$) and r=0.37 (n=72, $p<0.05$). Later, between 1998 and 2000, a significant dose-effect dependency was seen only in persons with absorbed doses above 1 Gy.

1.4.3.3. Immunogenetic study

Study of genetic systems of blood revealed different input of each of them into the genetically determined sensitivity to ionizing radiation. Their fading influence could be ranged as follow HLA (DR, B, A, Cw), Hp, MN, ABO, Rh-Hr. ARS degree 1, 2 and 3 survivors had some histocompatibility antigens at a significantly higher ratio than persons of NOARS: HLA-Bw38 (12.4% against 2.4%), HLA-DR3 (28.9% against 15.2%), HLA-Bw16 (20.2% against 9.8%), HLA-Bw35 (14.6% against 4.9%), HLA-DR4 (6.7% against 1.4%). On the other hand, concentrations of antigens HLA-B15 (2.2% against 11%) and HLA-DR2 (8.9% against 22.2%) were significantly lower, and coefficients of association with ARS proved the protective function of these alleles.

Index of relative risk (RR) was increased significantly in people, who were carriers of certain haplotypes (A/B; A/DR; B/DR), containing antigens associated with high radiosensitivity. Redistribution of RR values depending on antigenic compositions suggested the complicated relations between separate alleles (from antagonism to synergism) both under the limits of one locus and between loci of major histocompatibility complex (Fig. 1.3).

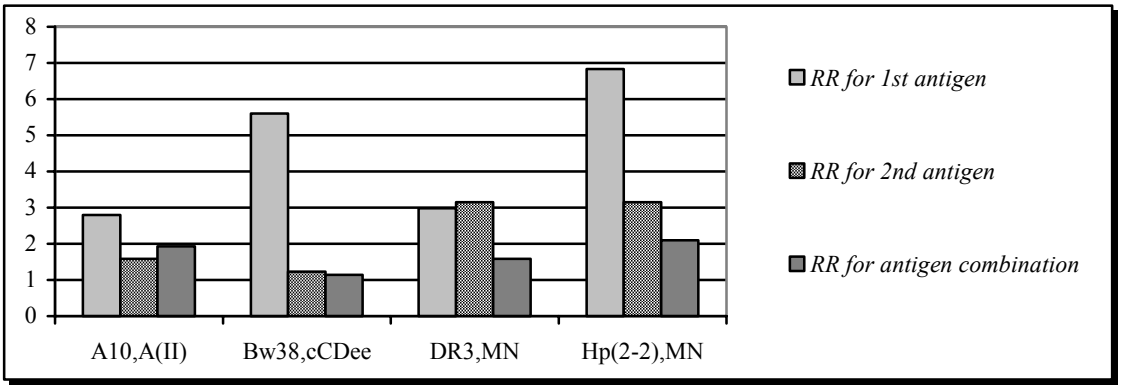


FIG. 3. Relative risks of immunogenetic radiosensitivity for combination of hla and erythrocyte antigen.

1.4.4. Cytogenetic analysis

Cytogenetic analysis was performed in 1987 on 32 NOARS patients and 23 ARS survivors. By 1993 the number of examined NOARS patients had dropped to 12 persons whereas the group of people with confirmed ARS rose to 38.

As the main biomarker in cytogenetic analysis the rate of stable (symmetric chromosomal translocations and inversions) and unstable (acentric, dicentric, ring chromosomes) aberrations of chromosomal type was determined in phytohaemagglutinin stimulated peripheral blood lymphocytes. Not less than 500 cells in metaphase were analysed for each patient.

The time trend of cytogenetic analysis shows a reduction in examined patients of aberrant metaphases, dicentrics and unstable aberrations. In ARS 1 degree survivors a number of dicentrics and rings had a tendency to decrease while in ARS 2 and 3 degree survivors it was at a level observed in 1987.

In all patients stable chromosomal aberrations were registered. There was an increase of the absolute and relative number of abnormal monocentrics, formed on account of symmetric translocations and inversions.

1.4.5. Follow-up of the nervous system

The state of central and autonomic (vegetative) nervous system was estimated in follow-up period starting from 1986 in 84 ARS survivors and 92 NOARS patients. The methods used included routine EEG (device ERA 14-21, O.T.E. Biomedica, Italy), computerized EEG (19-channel brain biopotentials analyser "Brain Surveyor", Saico, Italy) and ultrasound Doppler sonography of carotid and vertebral arteries (Vazoflo-3 device, Sonikaid, England). Test with deep breath, breath delay, isometric physical effort and orthostatic test were applied to estimate cardiovascular system vegetative regulation.

The nervous system morbidity rate was the highest and stable from the first days after the accident (Fig. 1.4). During the time the structure of diseases was changing. The so-called "functional" neurovegetative disorders, as vegetative dystonia and neurovascular dystonia, asthenoneurotic and cerebrasthenic syndromes, transformed in different clinical forms of organic nervous system pathology. It was expressed in diagnoses such as "cerebral atherosclerosis", "dyscirculatory encephalopathy", "organic injury of the brain", "psycho-organic syndrome".

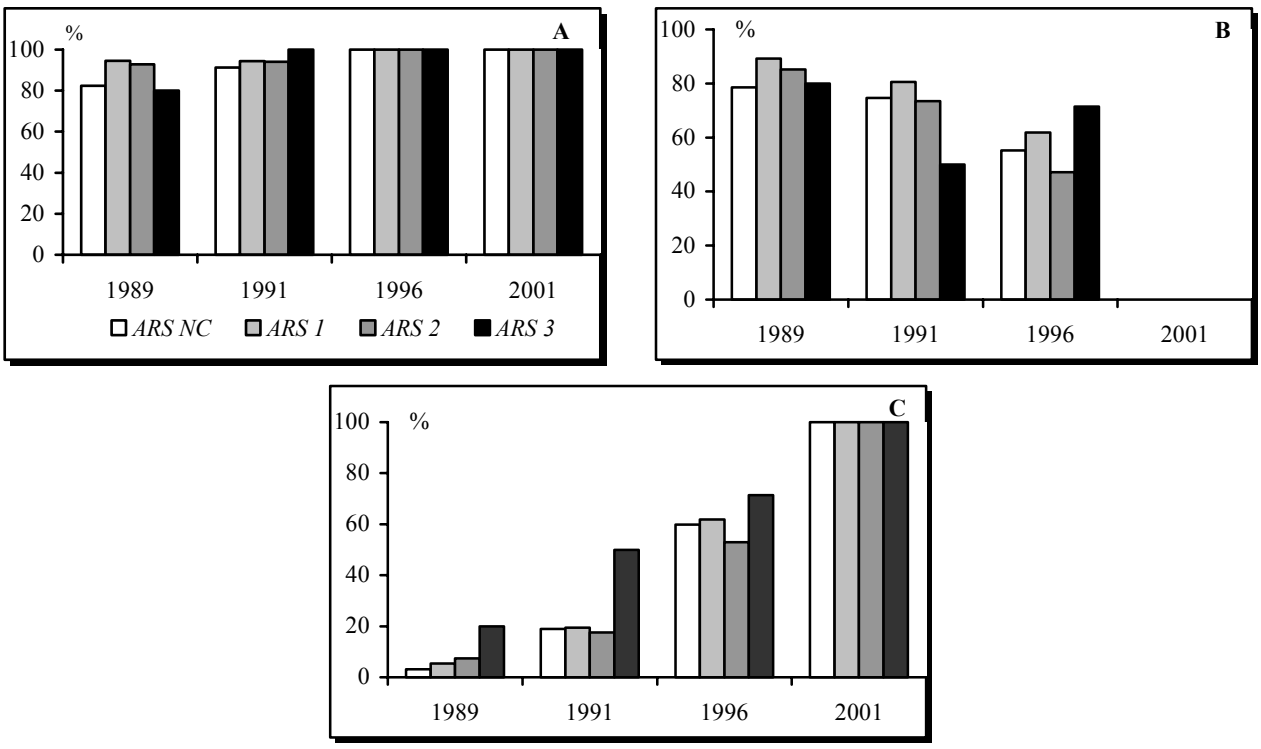


FIG. 1.4. Frequency rate of nervous system disorders in ARS survivors and NOARS patients in the years following the accidental (A= total morbidity, B = "functional" disorders, C = organic diseases).

Organic changes of nervous system were manifest in the results of special investigations. For example, an EEG spectral analysis had showed that in the remote period after ARS there was an essential diffuse amplification of spectral power of δ, β ranges revealed in definite brain zones that reflected the disorders of their activity.

Progressive functional and structural changes in brain are considered post-radiation encephalopathy. Its pathophysiological basis is a damage to the diencephalons-limbic-reticular system and associative frontal and parietal zones, especially to the dominant left hemisphere with essential disturbance of central afferentation mechanisms. In the remote period, a clinical picture included different manifestations of neuropsychical disorders. By 2001 no dose dependence of the severity of the total morbidity and organic diseases from magnitude of absorbed radiation doses were found (Fig. 1.4. parts A and C).

Vasoactive, nootropic, antidepressive remedies — selective inhibitors of serotonin reverse capture, typical antipsychotic drugs and medications effecting the tissue metabolism were used for treatment of the patients.

1.4.6. Endocrine system

From 1986 onwards the endocrine system was analysed in 39 ARS Degree 1 survivors, 45 ARS Degree 2 survivors, 12 ARS Degree 3 survivors and 92 NOARS patients. Thyroid hormones were analysed by radioimmune methods. The following devices were used for this purpose: gamma counters LB 2104 (Berthold, Austria) and Wizard 1470 (Wallac, Finland) with such kits as CIS (France), Amersham (England) and Hoechst AG (Germany). USE (ultrasound examination) of thyroid gland was performed with the Aloka 630 machine (Japan) with probes from 5 to 12 MHz.

In 1986, “laboratory hypothyroidism” (detected on the basis of changes in thyroid hormone levels, only, without clinical symptoms) was found in 15 patients. Years later three persons from this group developed clinical evidence of thyroid gland hypofunction. A risk group was established consisting of 13 patients, who had clear decrease of thyroxin concentration in blood in combination with a normal level of thyrotrophin. In 1986, strumectomy was carried out in one NOARS patient due to initial progressive thyrotoxicosis.

Five years after the accident nodular goitre was diagnosed in three ARS survivors and two NOARS patients by USE. Ten years later, in 2001, these numbers have increased to 18 and 4, respectively. All persons with a diagnosis of “nodular goitre” belong to the high risk group for the development of thyroid cancer. Thus, they are under regular medical control. Partial resection of the thyroid gland due to nodular goitre of the 3rd degree was performed on one ARS Degree 2 survivor in 2000. A stronger ultrasound signal was found in 13.3% of patients and considered to be a consequence of a former thyroiditis. Morphological changes of the thyroid gland were not reflected in the level of thyroid hormones in the blood.

Two ARS Degree 3 survivors and one NOARS patient suffered from diabetes mellitus, Type 2. It was diagnosed during the first years of the follow-up and had an uncomplicated course. Fifteen years after the accident, diabetes mellitus was found in 15 ARS survivors and 6 NOARS patients. However, only 3 patients have used hypoglycaemic agents; the others reached subcompensation through their diet. The hypophysis-cortical-adrenal system was characterized by steady hypercortisonaemia accompanied at the beginning by an increased level of corticotrophin, which later became depressed (1991–1992).

In 38 ARS survivors examined during first 5–6 post-accidental years, hypogonadotropic hypogonadism, hyperprolactinaemia with quantitative-qualitative spermatogenesis disorders and different clinical forms of sexual dysfunction were found. Hereafter the tendency to normalization of these changes in the majority of patients was registered. However, this study has not been completed for a number of reasons.

Concluding this section it is necessary to outline that the patients exposed to radiation due to the Chernobyl accident need regular (annual) examination of thyroid gland function by endocrinologists using ultrasound scanning and laboratory techniques.

1.4.7. Other organs and systems

The functional state of internal organs was studied in 73 NOARS patients and 78 ARS survivors, among them 35 ARS Degree 1, 34 ARS Degree 2 and 9 ARS Degree 3 survivors. For this purpose the following methods were used: ECG (Mingograph 720, Siemens-Elema, Sweden), echocardiogram and UE of internal organs (Aloka 630, Japan and HDI-5000, ATL-Philips, USA), exercise-ECG (cycle ergometer KE-12, Medicor, Hungary), fibrogastroscopy, fibrocolonoscopy and bronchoscopy (family of Olympus endoscopes, Japan), X ray examination of chest, lung functional test (spirograph Flowscreen Pro, Jaeger, Germany), pathomorphological investigation of biopsy material.

During post-accidental years a monitoring of the function of internal organs was done [3, 17]. Slow growth of cardiovascular pathology was found [19], mainly due to hypertonic disease (HD) of Degrees 1 and 2 and ischaemic heart disease (IHD) (Fig. 1.5). A negative correlation between HD and patient's age at the moment of accidental radiation was revealed ($r = -0.413$, $p<0.05$). A combination of the following factors influenced the development of IHD: excess body weight, hypertriglyceridaemia and arterial hypertension ($F=5.144$, $p=0.026$).

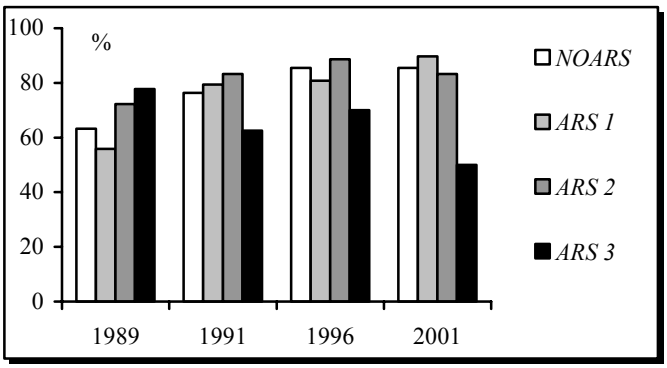


FIG. 1.5. Frequency of cardiovascular pathology in ARS survivors and NOARS patients in the years following the accident.

Selective β-adrenergic receptor blocking agents, angiotensin-converting enzyme inhibitors, calcium channel blockers, diuretics, retarded form of nitrates, low-calorie and salt-free diet were used for treatment of patients with cardiovascular pathology.

The morbidity pattern of digestive system in the examined patients is predominantly characterized by inflammatory and erosive-ulcerous pathological processes of stomach and duodenum. Their frequency has gradually increased over the years (Fig. 1.6).

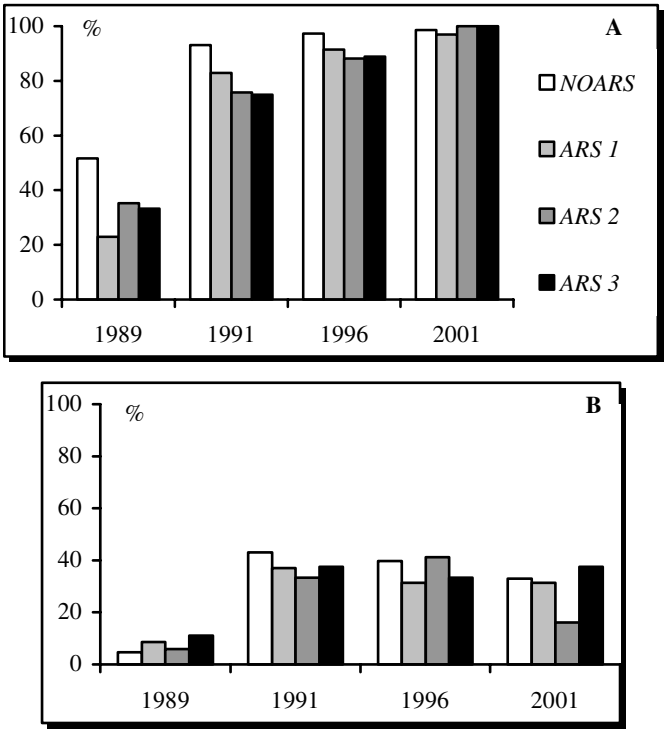


FIG. 1.6. Frequency of digestive tract pathology in ARS survivors and NOARS patients in the years following the accident (A=inflammatory diseases, B=ulcers and erosions of the stomach and duodenum).

To treat digestive tract diseases an appropriate diet, H2-receptor antagonists, acid-pump inhibitors, antimicrobial (against H. pylori) and bismuth remedies and antacids were applied. Frequent exacerbation of liver-bile system diseases took place. Chronic cholecystitis was revealed in 62.5–97% of patients 15 years after irradiation. Starting from 1986–1987 a gradual increase in the number of people suffering from chronic persistent hepatitis was found. Up to 2000–2001, this disease occurred in more than 60% of examined patients, mainly in ARS 2–3 degree survivors. In ARS 1 degree survivors and NOARS patients, a steady remission of the disease was revealed and only light occasional clinical manifestation as pain in the right subcostal region took place. The treatment of these patients with liver-bile pathology included hepatoprotectors, vitamins and cholagogues.

Gradual growth of bronchopulmonal pathology has been observed from 1987. In 2001 it was found in more than 1/3 of the NOARS and ARS Degree 1 patients examined and in half of the ARS Degree 2 and 3 survivors. Chronic obstructive bronchitis with mucous membrane atrophy and disorders of ventilation was the predominant pathology (Fig. 1.7). Treatment of these patients included use of bronchodilatators for inhalation (selective β-sympathomimetics, M-cholinolytics, corticosteroids), theophyllin like drugs, antibacterial drugs (synthetic penicillins, cephalosporines, fluorinoquinolines), mucolytics with mucokinetic and antioxidant activity, remedies with antiviral activity.

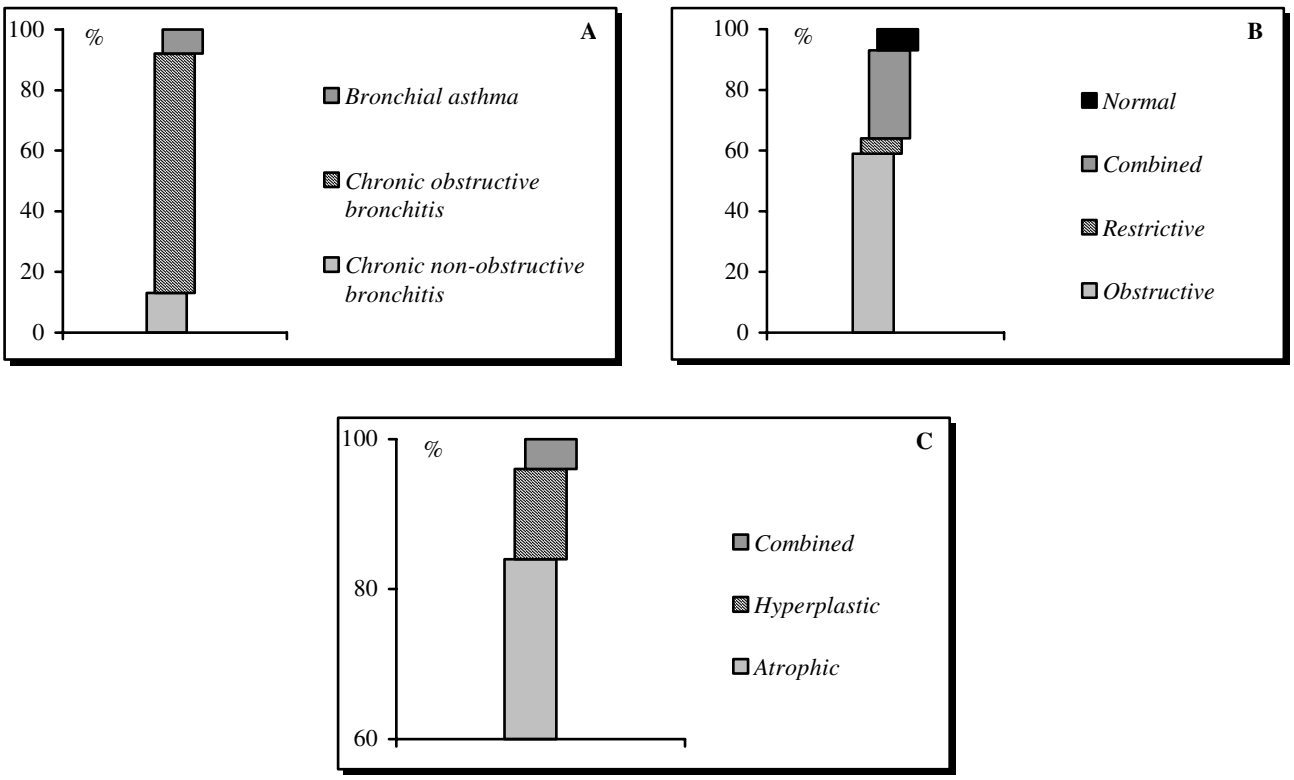


FIG. 1.7. Pathological changes to bronchopulmonal system in ARS survivors and NOARS patients (A =nosological forms, B=type of ventilation disorders, C=forms of endobronchitis).

1.4.8. Metabolic processes

Indices of lipid peroxidation and antioxidant activity were determined in 20 NOARS patients and 27 ARS persons. For this purpose an electron-paramagnetic resonance spectrometer E-109 (Varian, USA) was used. A content of polyamines and cell lysosomal enzymes had been estimated by DU-65 spectrophotometer (Beckman, Austria) and pyrophosphates in the bone tissue and urine sediment by IR spectrometer IRS-31 (LOMO, Russia).

During the period of examination all patients — regardless of the degree of ARS severity — demonstrated an increased content of primary products of lipid peroxide oxidation, such as diene-conjugates, hydroperoxides, ketodienes and trienes, along with a decreased activity of anti-oxidative enzymes (superoxidismutaze and catalase). These observations overlapped with a reduced level of the antioxidative vitamins A and E, and retinol binding protein.

Investigations with magnetic resonance imaging (MRI) revealed structural and functional changes in metal proteins, such as Fe^{3+}-transferrine, Cu^{2+}-ceruroplasmine and methemoglobin. These proteins are necessary for normal haematopoiesis, iron transportation and anti-oxidative protection. Thus, a decreased level of Fe^{3+}-transferrine, substantial deviations of Cu^{2+}-ceruroplasmine and the absence of any change in methemoglobin paramagnetic signals were revealed. Reduction of Fe^{3+}-transferrine level was revealed also in the bone marrow, reflecting a diminished haematopoietic function.

In several ARS survivors hemichromes (products of haemoglobin destruction) were found. A decrease in erythrocyte membrane resistance and an accumulation of erythrocytes with low haemolytic endurance were also revealed in ARS survivors. These changes could be explained by the action of aggressive free radical intermediators developing oxidative destruction of

erythrocytes. Six years after exposure, activation of kinin system in blood with high level of total antiproteolytic activity was revealed in ARS survivors.

At different times there was a substantial increase in some biological agents, e.g. lyzosomal enzymes, such as β-galactozidase and β-glycosidase which bear upon subcellular structures; polyamines (spermidine and putrescine), which take part in the regulation of polyamines connected proteinkinase reactions throughout the phosphorilation processes in cells. In ARS survivors changes to the mineral component of bone tissue hydroxiapatite took place. An increase in the concentration of pyrophosphates in bone tissue and urine sediments was noted. Similar changes were revealed in individuals among the cleanup staff of the Chernobyl accident. This suggests the necessity of using these methods in monitoring the health status of the exposed persons. To improve metabolic processes in these persons, natural antioxidant remedies, vitamins A, C and E, microelements, indispensable amino acids, melanoids and glucosamines were administered.

1.4.9. Follow-up of skin injuries

Skin was examined visually and by taking colour photographs using an Olympus C2020 Zoom digital camera (Japan). The individuals examined were 8 ARS Degree 1 survivors, 15 ARS Degree 2 survivors, 9 ARS Degree 3 survivors and 5 NOARS persons. Mild acute radiation burns were diagnosed in 22 patients, moderate burns in 6 and severe burns in 1 person. The remaining 8 persons presented combinations of burns of different degrees of severity. An example of severe late skin lesions that were found in the follow-up period after local acute radiation exposure is shown in Fig. 1.8.

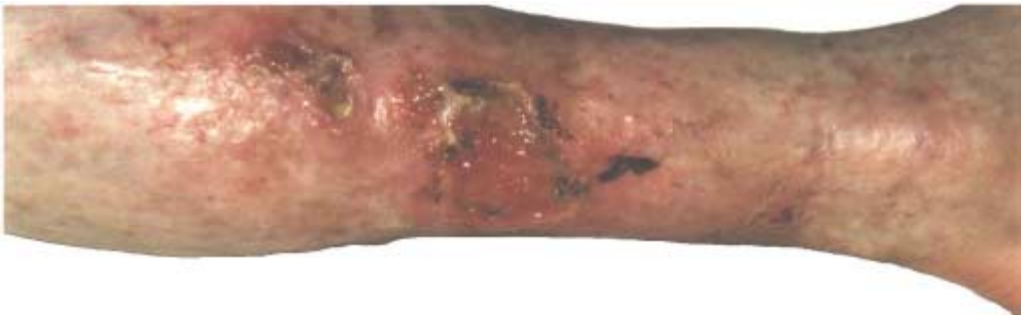


FIG. 1.8. Late radiation ulcers complicated by microbial infection leading to amputation of this leg in 1987.

Early and late radiation ulcers were trophic ulcers and appeared due to progressive fibrosis in derma and destruction of capillary net in the damaged areas. In general, all late ulcers showed minimal subjective symptoms, absence of bacterial infection and healing under conservative therapy only. One ARS survivor with severe radiation damage of the skin was an exclusion. Due to extremely irregular treatment and lack of hygiene, the chronic ulcer of the skin was complicated by secondary bacterial infection.

The conservative treatment of late radiation skin lesions was performed in accordance as follows: (1) cleaning of erosive-ulcerous defect, (2) taking actions against bacterial infection, (3) preventing inflammatory and autoimmune reactions, (4) healing of skin defects by

acceleration of epithelium recovery, improvement of microcirculation and blood rheological features, (5) saving epidermis integrity and (6) improving non-specific organism resistance.

1.4.10. Eyes

In the years consecutive to the accident 30 ARS Degree 1, 33 ARS Degree 2, 11 ARS Degree 3 survivors and 66 NOARS patients were examined. Starting in 1987, eye examinations were performed following a protocol that was quite similar to the procedure described in Ref. [20]. The eye examinations consisted of visual acuity determination, biomicroscopia with split lamp, ophthalmoscopia, perimetria, refractometria, and elastotonometria. Cataract stages were estimated using Vishnevskyi's classification [21].

The number of typical radiation cataracts (posterior subcapsular) directly correlates with ARS severity and was significantly higher in ($P<0.001$) in ARS 3 degree survivors. The latent period for radiation cataract was shorter for the higher ARS degree of severity ($r= –0.393$, $p=0.032$). Within 15 years radiation cataracts were revealed in 81.8% of the ARS Degree 3 survivors (9 cases), in 24.2% of the ARS 2 Degree survivors (8 cases), in 10% of the ARS 1 Degree survivors (3 cases) and in 4.5% persons with NOARS (3 cases) (Fig. 1.9).

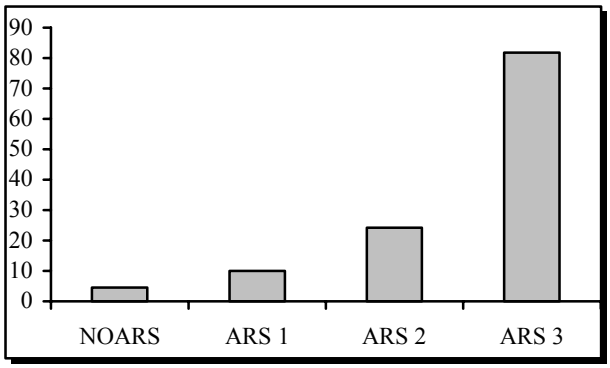


FIG. 1.9. Frequency of typical radiation cataracts in ARS survivors and NOARS patients 15 years after the Chernobyl accident.

Over a period of 15 years, a progressive course of radiation cataract developed in 6 patients. The radiation cataract was treated by extraction of damaged lens with subsequent implantation of artificial lenses in one ARS 3 degree patient in 1991. Other ARS 2 degree patient demonstrated the progressive worsening of visuality due to a cataract that appeared 14 years after the irradiation and hardend within 9 months. The rest three ARS 3 degree survivors and one NOARS patient showed insignificant cataract growth that has not led to vision impairment. Other types of cataracts (nuclear, coronary, flaky, presenile and senile) do not depend on ARS severity. The eye vessel pathology and macular dystrophy (Fig. 1.10) had followed lens changes. This lead to the development of an additional diagnostic criterion of somatic diseases and severity, primarily in the vascular system. Treatment for these patients included eye drops containing vitamins, amino acids and substances that enhanced metabolic processes.

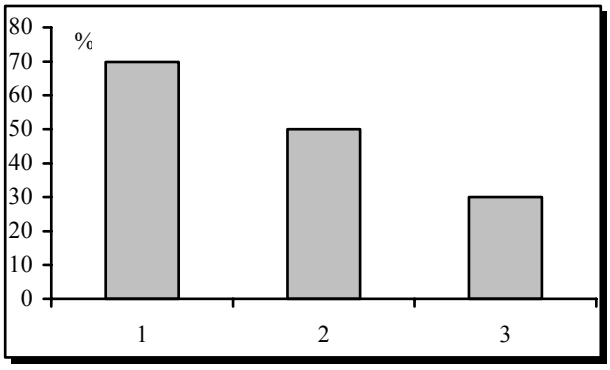


FIG. 1.10. Frequency for ARS Degree 1–3 survivors of (1) different cataracts and combinations, (2) eye bottom vascular pathology and (3) macular dystrophy.

1.4.11. Capacity for work and disability

The level of health deterioration in ARS survivors depends on the degree of severity of the disease. Structural and functional defects of organs and systems are compensated eventually in ARS 1 degree survivors and their health condition is estimated as stable. However, different stochastic and deterministic radiation effects have developed in most of these 78 ARS survivors, including ARS Degree 1 patients, as described above. As a result, all ARS survivors and 96.8% of NOARS patients have partially lost their capacity to work. A few of the ARS patients were classified by the Medical Labour Expert Commission of Ukraine as disabled persons of Grade 3 (the most severe degree of disability). Due to a combination of pathological changes and ageing, a gradual worsening of health has been observed among ARS survivors.

1.5. Conclusions

In 1986–1987 237 emergency workers were diagnosed with ARS. Later, this disease was confirmed in 134 patients, of which 108 were treated in Russia and 26 in Ukraine. Of these confirmed 134 patients, 28 died in the acute period (first 3 months) after the accident due to extremely severe radiation induced bone marrow and skin damages. Between 1987 and 2001, a further 14 ARS patients and 7 NOARS patients died. The main causes of their death were sudden coronary death (7 cases), oncohaematological pathology (3 cases), liver cirrhosis (2 cases) and infectious lung diseases (2 cases).

In Ukraine stochastic health effects (malignant neoplasms) have been observed in 14 ARS survivors and 5 NOARS patients. Among ARS survivors oncohaematological diseases developed in 5 cases, cancer in 7 cases and sarcoma in 2 cases.

Both stochastic and deterministic effects that might be associated with irradiation were revealed in ARS survivors. They can be linked to the high levels of somatic mutations observed, steady pathological changes in membranes, subcellular structures, biomolecules and metabolic disorders. Changes in the haematopoietic and immune system indices may be considered as a pre-pathological condition for a high risk of development of stochastic effects.

At an early recovery period after ARS, the immune system of the patients studied was characterized by a combined acquired radiation-induced immune deficiency with depression of T- and B-lymphocyte compartments. In addition, a failure of the non-specific resistance

mechanisms was observed. Recovery from the radiation induced immunological damage lasted between 3 and 5 years. Post-irradiation recovery was dependent on the absorbed dose and genetic predisposition (individual radiosensitivity). In the remote period, a significant imbalance was detected in the antigen-recognizing and effectory (response) compartments. The high prevalence of hepatitis-C virus and cytomegalovirus carriers suggested non-stable compensation of the radiation injury of the immune system in the remote post-accident period.

The follow-up of patients who survived high levels of exposure to radiation ought to be directed to detecting late health effects, especially leukaemia and myelodysplasia, and secondary immune deficiencies. Special attention needs to be paid to the study of proto-oncogene expression and genomic instability. The treatment strategy requires therapy of possible causes of immunodepression (chronic somatic and psychosomatic pathology, viral carriage). Usage of immunostimulating agents ought to be re-evaluated accounting for the possible induction of oncohaematological and autoimmune disorders.

Vascular disorders of the eye bottom predominated in the eye pathologies observed. Typical radiation cataracts (posterior subcapsular) were revealed in 20 ARS survivors and 3 patients with NOARS. The latent period of radiation cataracts was related to the severity of the ARS. Radiation induced late skin damage poses a clinical problem for many years after irradiation. It demands constant attention in order to prevent further progression of trophic skin lesions. Late radiation ulcers were detected in 8 ARS survivors. The increased rate of chronic somatic diseases, radiation related eye and skin pathology resulted in a high level of disability in ARS survivors. This reached 100% in 78 ARS survivors in 1998.

1.6. Lessons learned

Following overexposure, the main directions of medical management for persons under care are:
(1) to monitor the health status of patients in order to diagnose early the stochastic and deterministic radiation effects and prevent the appearance and progression of other possible diseases;
(2) to treat somatic and neuropsychological diseases in exposed patients which can facilitate the development of oncological and oncohaematological diseases;
(3) to apply new diagnostic methods for diagnosis of malignant tumours.

To achieve these objectives it is necessary:

1. To examine patients in compliance with standard protocols, e.g. based on a questionnaire developed by experts from Germany, Russia, and Ukraine [22] with obligatory participation of internists, cardiologists, pulmonologists, endocrinologists, ophthalmologists, neuropathologists, haematologists and immunologists.
2. To examine annually (or more frequently, as necessary) the ARS survivors using ultrasound techniques for the study of the abdominal area, prostate (for males), adnexa (for females) and thyroid gland; endoscopy of stomach and lower part of the colon; peripheral blood count and blood smear analysis; immunoanalysis; investigation of liver specific (γ-GT, AP) and non-specific (AST, ALT) enzymes in serum; IR-spectroscopy of pyrophosphates in urine sediment; lipid peroxidation activity analysis; ECG.
3. To analyse bone marrow (aspiration or biopsy) and to investigate bone marrow culture.
4. To perform X ray examinations of the chest and bronchoscopy if chronic inflammatory diseases of the bronchopulmonary system have been detected.

5. To analyse thyroid morphology and thyroid hormones following an accidental exposure to radioiodines.
6. To include antioxidants, vasoactive drugs, nootropes, hepatoprotectors, vitamins A, C and E in treatment of different diseases developing in irradiated persons.

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Chapter 2

PSYCHOLOGICAL CONSEQUENCES OF NUCLEAR AND RADIOLOGICAL ACCIDENTS: DELAYED NEUROPSYCHIATRIC EFFECTS OF THE ACUTE RADIATION SICKNESS FOLLOWING CHERNOBYL

A.I. Nyagu, K.N. Loganovsky, K.L. Yuryev

2.1. The accident

A short description of the accident is provided in Section 1.1.

2.2. Follow-up in the delayed period

2.2.1. Frequency of medical examinations per year

The neuropsychiatric consequences of accidental irradiation to ARS patients have been monitored to the present on the basis of one in-patient medical examination per year. All ARS patients are hospitalized in the Radiation Pathology Department of the Institute for Clinical Radiology, RCRM, Kiev.

2.2.2. Type of examinations (laboratory methods and clinical investigations)

The data on the neuropsychiatric aftermath of ARS presented hereafter were based on two research designs: 1) prospective follow-up study (1987–2001), and 2) cross-sectional study with parallel groups (1996–1998).

2.2.2.1. Prospective neuropsychiatric follow-up study of ARS patients (1987–2001)

This follow-up study includes clinical neuropsychiatric examinations together with electroencephalography and rheoencephalography that were available every year. Since 1987 the 110 ARS patients have been enrolled in this study. Of these patients, 105 (95%) were males. At the time of the accident (1986) the age of the patients involved in the study ranged from 20 to 75 years (M±SD=37.44±11.05 years).

According to the data of the "Commission on verification of ARS diagnoses made in 1986" headed by Professor A.K. Guskova, retrospective clinical and karyological analyses and analysis of medical documents enabled to adjust the categorization of the degree of ARS severity in patients originally done in 1989 [1]. The karyological study demonstrated a typical bone-marrow form in 74 out of 110 ARS patients. The last point became a basis of three sub-groups selection among the main study group: NOARS (or ARS-0) — 36 patients with not confirmed ARS diagnosis (average dose [M±SD] of general relatively uniform γ- and β-radiation 0.3±0.3 Gy (the absorbed doses were estimated in the Institute of Biophysics, Moscow, Russia); ARS-1 — 39 patients who had the 1st degree (mild) ARS (1.0±0.61 Gy); ARS-2 — 35 patients survived the 2nd and 3rd degree (moderate to severe) ARS (2.62±1.26 Gy).

A prospective neuropsychiatric follow-up study of ARS patients (1987–2001) uses an *"internal control"*. The NOARS group was used as the control to groups ARS-1 and ARS-2 bone-marrow radiation syndrome consequences on the brain in this study.

During the post-accidental years among these 74 confirmed ARS patients included in the study 6 died: in 1992 one death (sudden cardiac death of ARS-2 survivor at the age of 67); in 1993 two deaths (death of ARS-2 survivor due to myelodysplastic syndrome at the age of 52 and sudden cardiac death of ARS-1 survivor at the age of 42); in 1995 three deaths (death of one ARS-2 survivor due to liver cirrhosis at the age of 42 and death of two ARS-1 survivors of lung tuberculosis at the age of 51 and of adipose embolism due to trauma at the age of 53). In addition, mong the 36 NOARS patients, one sudden cardiac death occurred in 1994 (at the age of 59). As a result, since 1996 among the 110 patients enrolled in the neuropsychiatric study there are 103 survivors: 35 (ARS-0), 36 (ARS-1), and 32 (ARS-2).

Neuropsychiatric and neuro-psychophysiological examinations of ARS survivors (all were right-handed persons) were conducted in from 1987 to 2001 in the Neurology Department of the Institute for Clinical Radiology of RCRM, AMS of Ukraine.

2.2.2.2. Cross-sectional neuropsychiatric study of ARS patients with parallel groups (1996–1998)

This study includes the elaborated unified methodology for neuropsychiatric assessment [2] — neurological and psychiatric examination, neuro- and psychophysiological investigations and pathopsychological testing in the Department of Neurology of the Institute for Clinical Radiology, RCRM.

In the cross-sectional neuropsychiatric study of ARS patients (1996–1998), groups of patients were set up as follows (Table 2.1).

Group I — 70 men who were diagnosed with ARS in 1986. Their age at the time of examination ranged between 31 and 75 years (M±SD=47.2±10.05 years). The internationally verified diagnosis of ARS in 1989 was confirmed in 32 of them. Accordingly Group I was divided into three subgroups: NOARS — 38 patients with no confirmed ARS (average absorbed dose [M±SD] according to the estimations of the Institute of Biophysics, Moscow, Russia — 0.23±0.15 Gy); ARS-1 — 14 patients with mild ARS (0.97±0.53 Gy); ARS-2 — 18 patients with moderate to severe ARS (3.04±1.5 Gy).

Group II — 80 men — cleanup workers ("liquidators") who participated in cleanup operations in or since 1986 and 1987. Dose assessment for the study was based on the official individual doses which were reconstructed by the Department of Dosimetry, RCRM of AMS of Ukraine, Dosimetry Service of the Chernobyl Nuclear Power Plant (ChNPP) and Chernobyl exclusion zone. The absorbed doses ranged between 0.05–1.65 Gy. No one of these liquidators developed ARS. 35 patients were exposed to doses below 0.5 Gy, 45 patients to doses of >0.5 Gy. The examined liquidators were divided into two subgroups according to the character of exposure to ionizing radiation:

Subgroup IIA — liquidators who worked for a short time period (less than 3 months) in the Chernobyl exclusion zone in 1986 and 1987 (n=37), and

Subgroup IIB — liquidators of 1986 and 1987 who have been working for a long time period (3–5 and more years) or still working in the exclusion zone (n=43).

Control group A included 15 practically healthy men. *Control group B* included 15 patients with dyscirculatory encephalopathy (DEP) as a result of arterial hypertension or/and cerebral atherosclerosis. They were used in order to test a hypothesis about clearly cerebrovascular genesis of organic neuropsychiatric disorders in ARS patients. *Control group C* included 20 veterans of the Afghanistan war with posttraumatic stress disorders (PTSD) in order to test a hypothesis about stress-related aetiology of neuropsychiatric disorders in ARS patients

Persons of control groups A, B and C were not Chernobyl accident cleanup workers. They had been exposed only to natural background ionizing radiation. There were no significant differences in age and gender between the main and control groups (Table 2.1).

TABLE 2.1. THE STUDY GROUPS

Group	**Number of patients**	**Age at the time of examination, years (M±SD)**	**Dose, Gy, M±SD**
Group I (ARS)	70	47.2±10.0	***1.80±1.66***
ARS–0 (pre-clinical ARS)	38	46.4±10.5	0.23±0.15
ARS–1 (mild ARS)	14	45.4±8.6	0.97±0.52
ARS–2 (moderate to severe ARS)	18	50.2±10.0	3.04±1.52
Group II (liquidators of 1986 and 1987)	80	47.3±8.7	0.54±0.45
Subgroup IIA (liquidators who worked in the Chernobyl exclusion zone in 1986 and 1987 for a short period (less 3 months)	37	46.0±6.9	0.57±0.36
Subgroup IIB (liquidators who worked in the Chernobyl exclusion zone in 1986 and 1987 for a long period (3–5 and more years)	43	50±11.6	0.47±0.33
Control Group A (healthy)	15	44.1±14.9	—
Control Group B (patients with dyscirculatory encephalopathy)	15	53.1±11.5	—
Control group C (veterans with PTSD)	20	43.4±8.2	—

Routine clinical neurological examinations were carried out on all patients. Psychiatric examinations were performed on the basis of typical psychiatric interviews using pathopsychological and psychometric tests as follows:

- Brief Psychiatric Rating Scale, BPRS (©Overall J.E., Gorham D.R., 1962);
- Scale for the Assessment of Negative Symptoms, SANS (WHO Coordinated multi-centre study on the course and outcome of schizophrenia, 2/93 ©Andreasen N.C., 1984);
- Screening Schedule, WHO 5368.1 MNH (11/78) (WHO Collaborative study on determinants of outcome of severe mental disorders, 1978);
- PTSD Scales: Impact of Events Scale (IES) (©Horowitz M.J. et al., 1979) and Arousal Scale of PTSD (IDA) (©Snaith et al., 1978);
- Unmasking Depression. Self-rating Depression Scale (SDS) (©Zung W.W.K., 1974);

- General Health Questionnaire, GHQ-28;
- Adapted and validate MMPI version;
- Working capacity diagnostic method (test of A. Landolt);
- Wechsler Adults Intelligence Scale (WAIS)

Neuro- and psychophysiological investigations included:

- computerized EEG (cEEG)
- checkerboard reversible pattern visual evoked potentials (VEP)
- brainstem auditory evoked potentials (BAEP)
- assessment of vestibular function
- sympathetic skin response (SSR)
- autonomous nervous system tests
- distant thermography
- rheoencephalography
- ultrasonic dopplerography.

2.2.2.3. Pathology presented (prospective neuropsychiatric follow-up study of ARS patients in 1987–2001)

In 1987–1988 all ARS patients were recognized with "vegetovascular dystonia" or "autonomous nervous system dysfunction" that referred to etiologically heterogeneous abnormalities of diencephalic-limbic-reticular complex. They manifested with fatigue, lability of heart rate and blood pressure, sweating, headache, pain in chest and heart area, back pain, pain in limbs, vertigo, memory and concentration deterioration, weakness, irritability, affective lability, anxiety, sleep disorders, meteotropia etc. Symptoms of vegetative-vascular dystonia were paroxysmal in 75 (68%) patients of ARS group. Certain differences in the diagnosis of mental disorders and diseases of the nervous system in the USSR and the Western countries should be stressed. Thus, term "vegetative-vascular dystonia" currently is not accepted in the West, where such disorders could be classified as posttraumatic stress disorder (PTSD), anxiety, depression or somatoform disorders. However, such interpretation — in our understanding — leads towards underestimation of health effects of exposure to ionizing radiation and an overestimation of the role of psychogenic traumatization following the nuclear accident. The Russian conception of "vegetative-vascular dystonia" in irradiated patients is more close to Penfield's "diencephalic autonomic epilepsy" with a paroxysmal activity focus in the hypothalamus and etiologically heterogeneous radiation-psychogenic "diencephalosis" described by Konuma et al. in A-bomb survivors [3].

In 1990–1991 neuropsychiatric symptoms became more severe and ARS patients were firstly diagnosed with "dyscirculatory encephalopathy" as chronic cerebrovascular disorders. According to the International Classification of Diseases, 10th Revision (ICD-10), such disorders are included in the block "F00–F09 Organic Mental Disorders". The use of the term "organic" does not imply that conditions elsewhere in this classification are "non-organic" in the sense of having no cerebral substrate. In the present context, the term "organic" means that the syndrome so classified can be attributed to an independently diagnosable cerebral or systemic disease or disorder.

Since 1990–1991, the frequency of all kinds of organic mental disorders that was firstly classified as statistically significant "dyscirculatory encephalopathy" increased in all study groups as follows:

NOARS — 0 [1987–1988] versus 6 (19%) [1990–1991], $\chi 2=6.55$, $p<0.05$;

ARS-1 — 0 [1987–1988] versus 7 (20%) [1990–1991], $\chi 2=7.69$, $p<0.01$;

ARS-2 — 0 [1987–1988] versus 11 (31%) [1990–1991], $\chi 2=13.05$, $p<0.001$.

There was a tendency towards more rapid increases of the frequency of all kinds of organic mental disorders in proportion to the ARS severity degree. However, there were no statistically significant differences (according to the Chi-square test) in the frequency of all kinds of organic mental disorders between NOARS, ARS-1, and ARS-2 groups during the whole period of the study.

The time trend of all kinds of organic mental disorders in ARS patients for 1987–2001 is presented in Figure 2.1.

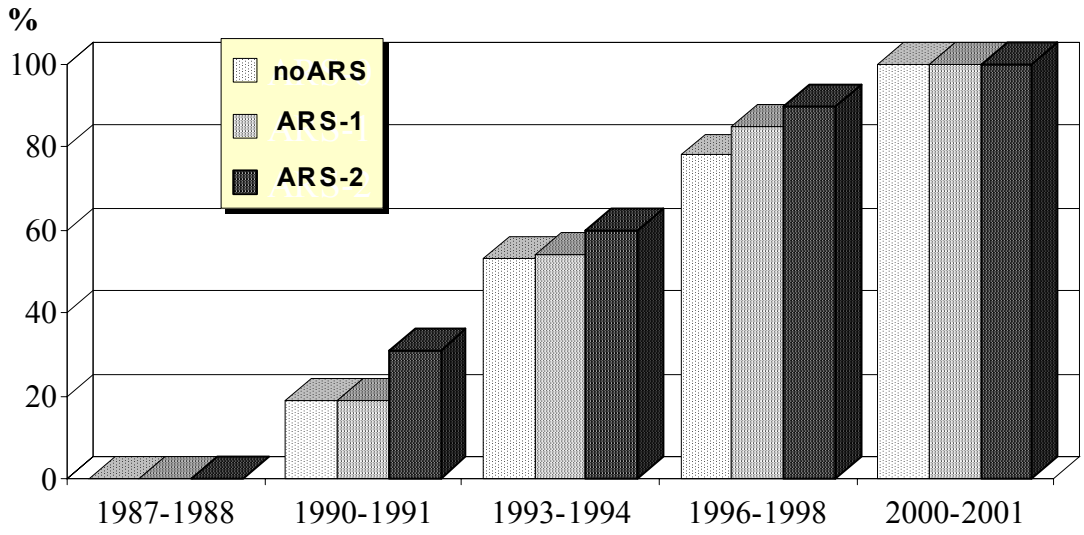

FIG. 2.1. Time trend of all kinds of organic mental disorders in examined groups of exposed patients, 1987–2001. NOARS — exposed persons, no confirmed ARS (n=36 for 1987–1991 and n=35 for 1993–2001); ARS–1 — mild ARS (n=39 for 1987–1991, n=38 for 1993–1994, and n=36 for 1996–2001);ARS–2 — moderate to severe ARS (n=35 for 1987–1991, n=33 for 1993–1994, and n=32 for 1996–2001).

Figure 2.1 shows no significant difference in frequency of all kinds of organic mental disorders in the three examined groups of patients characterized with different mean doses. However, there is statistically significant difference in frequency of F07.0 Organic personality disorder in the examined groups of patients characterized with different mean doses (Fig. 2.2). This disorder is characterized by an alteration of habitual premorbid behaviour. The expression of emotions, needs, and impulses is particularly affected. Cognitive functions may be defective mainly or even exclusively in the areas of planning and anticipating the likely personal and social consequences. The cerebral basis of the organic personality disorder is frontal-limbic dysfunction. The F07.0 Organic personality disorder of the ICD-10 corresponds

to the diagnosis of the Diagnostical and Statistical Manual, 4th ed. (1994) by the American Psychiatric Association (DSM-IV) 310.1 "Personality change due to general medical condition".

The time trend of F07.0 Organic personality disorder in ARS patients for 1987–2001 is presented in Figure 2. Since 1990–1991, there is an increasing frequency of the personality disorder in all ARS patients. However, since 1993–1994 among patients who had moderate to severe ARS, the frequency of this disorder is significantly higher than that in patients with no confirmed or mild ARS.

The current pattern of organic mental disorders in ARS patients is presented in Table 2.2. The main diagnoses in ARS survivors in the delayed period (1996–2001) are F07.0 Organic personality disorder and F06.6 Organic emotionally labile (asthenic) disorder or "Cerebrasthenic syndrome" according to national classification. The F06.6 Organic emotionally labile (asthenic) disorder is characterized by marked and persistent emotional incontinence or lability, fatiguableness, or a variety of unpleasant physical sensations (e.g. dizziness) and pains regarded as being due to the presence of an organic disorder. This disorder is thought to occur in association with a cerebrovascular disease or hypertension more often than with other causes. The frequency of F06.6 Organic emotionally labile [asthenic] disorder is higher among patients with no confirmed ARS and mild ARS. At the same time the frequency of the F07.0 Organic personality disorder increased in proportion to the ARS degree and this is higher in patients who had moderate to severe ARS.

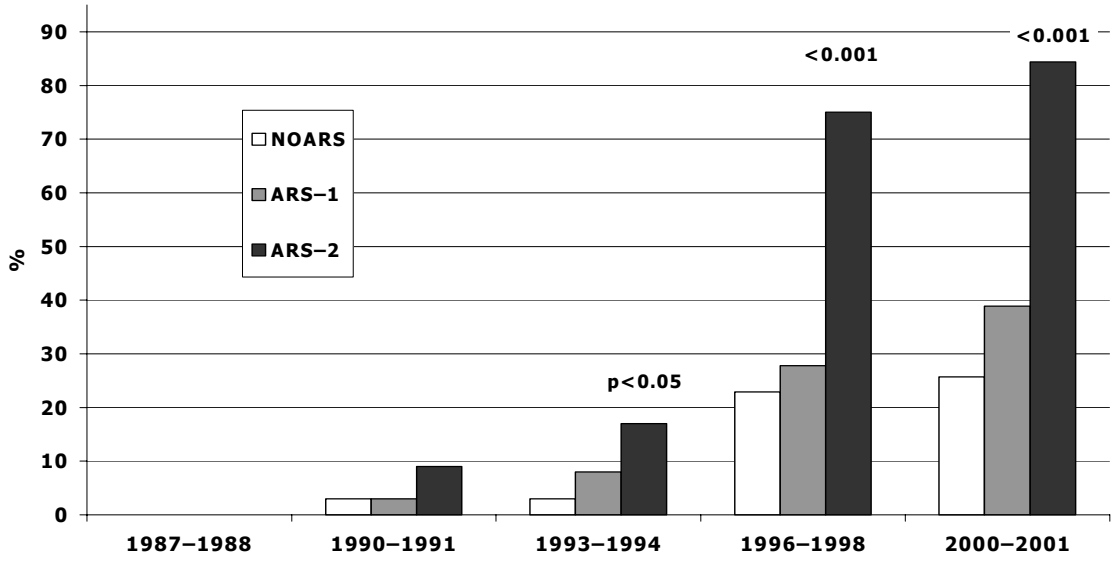

FIG. 2.2. Time trend of F07.0 Organic personality disorder in examined groups of exposed patients, 1987–2001. NOARS — exposed persons, no confirmed ARS (n=36 for 1987–1991 and n=35 for 1993–2001); ARS–1 — mild ARS (n=39 for 1987–1991, n=38 for 1993–1994, and n=36 for 1996–2001); ARS–2 — moderate to severe ARS (n=35 for 1987–1991, n=33 for 1993–1994, and n=32 for 1996–2001).

There are some types of organic personality disorders: labile, apathetic, paranoid, euphoric, disinhibited, aggressive, explosive, mixed, etc. The pattern of organic personality disorders from 1996 to 2001 is presented in Table 2.3. The more frequent type of organic personality disorders in ARS patients is *apathetic*, and it increases in proportion to the dose absorbed (ARS severity degree). The characteristic peculiarities of exposed patients are an absence of "asthenic" organic personality disorders like explosive, disinhibited, aggressive

type together with dominating of "asthenic" disorders like apathetic type of organic personality disorders. This seems to be quite clear differential diagnostic features of mental disorders in exposed patients in remote period after irradiation, namely to dominating of so-called "negative" psychopathological symptoms like apathy, abulia, autism, anhedonia, anergia, etc. A cerebral basis for this symptomatology is the frontal-limbic dysfunction (inhibition), particularly, in the left, dominating hemisphere.

TABLE 2.2. ORGANIC MENTAL DISORDERS IN EXAMINED GROUPS OF EXPOSED PATIENTS, 1996–2001

Disorder	**1996–1998**			**2000–2001**		
	NOARS n=35	**ARS-1** n=36	**ARS-2** n=32	**NOARS** n=35	**ARS-1** n=36	**ARS-2** n=32
Dementia (F02.8)	1 (2.9%)	—	—	1 (2.9%)	—	—
Organic delusional [schizophrenia-like] disorder (F06.2)	—	—	1 (3.1%)	—	—	1 (3.1%)
Organic depressive disorder (F06.32)	4 (11.4%)	4 (11.1%)	2 (6.3%)	5 (14.3%)	3 (8.3%)	2 (6.3%)
Organic anxiety disorder (F06.4)	2 (5.7%)	1 (2.8%)	—	1 (2.9%)	1 (2.8%)	—
Organic emotionally labile [asthenic] disorder (F06.0)	12 ** (34.3%)	15 *** (41.7%)	2 (6.3%)	19 *** (54.3%)	18 *** (50%)	2 (6.3%)
Organic personality disorder (F07.0)	8 *** (22.9%)	10 *** (27.8%)	24 (75%)	9 *** (25.7%)	14 *** (38.9%)	27 (84.4%)

Note: ** — p<0.01 in comparison with ARS-2;
*** — p<0.001 in comparison with ARS-2.

TABLE 2.3. ORGANIC PERSONALITY DISORDERS IN EXAMINED GROUPS OF EXPOSED PATIENTS, 1996–2001

Type of organic personality disorder	**1996–1998**			**2000–2001**		
	NOARS n=35	**ARS-1** n=36	**ARS-2** n=32	**NOARS** n=35	**ARS-1** n=36	**ARS-2** n=32
Labile	—	—	1 (3.1%)	1 (2.9%)	1 (2.8%)	—
Apathetic	4 *** (11.4%)	9 ** (25%)	19 (59.3%)	4 *** (11.4%) ##	12 ** (33.3%)	24 (75%)
Paranoid	2 (5.7%)	1 (2.8%)	2 (6.3%)	2 (5.7%)	1 (2.8%)	2 (6.3%)
Euphoric	1 (2.9%)	—	1 (3.1%)	1 (2.9%)	—	1 (3.1%)
Mixed	1 (2.9%)	1 (2.8%)	1 (3.1%)	1 (2.9%)	—	—

Note: ** — p<0.01 in comparison with ARS-2;
*** — p<0.001 in comparison with ARS-2;
— p<0.01 in comparison with ARS-1.

Accounting for the following three findings detected in ARS patients, namely, 1) an increasing frequency of the organic personality disorder (or a characteropathetic type of psycho-organic syndrome) in proportion to the dose absorbed (ARS severity degree); 2) development of a predominant apathetic type of organic personality disorder in proportion to the dose absorbed (ARS severity degree) and 3) a number of psycho- and neurophysiological peculiarities since 1996, the neuropsychiatric disorders in ARS patients have been classified as "post-radiation dyscirculatory encephalopathy".

2.2.3. Results of clinical and laboratory examinations (cross-sectional neuropsychiatric study of ARS patients with parallel groups, 1996–1998)

2.2.3.1. Neurological examinations

Almost all ARS patients complain of recurrent or persistent headache, limb pain and odd skin sensations, fatigue, vertigo, memory and working capacity deterioration, irritability. According to neurological examinations, severe focal symptoms were absent. At the same time, microfocal abnormalities as convergence weakness, a mild face muscles asymmetry, vestibular dysfunction, delicate pyramidal and extrapyramidal insufficiency, signs of oral automatism (subcortical signs), a mild asymmetry of the tendal and periostal reflexes and coordination disorders were revealed.

Paroxysmal states were typical for 48 (69%) of the ARS patients. These paroxysmal states were recognized as autonomic-vascular paroxysms or Pefield's "diencephalic autonomic epilepsy" with a paroxysmal activity focus at the hypothalamus. The sensoric-algetic and autonomic disorders were diagnosed in 68 (97%) of the ARS-group patients.

Acute radiation and post-radiation dyscirculatory encephalopathy were diagnosed in patients who were exposed to radiation in doses exceeding 4 Gy [4]. Consequently, the sensoric-algetic, autonomic, vestibular-ataxic and epileptic syndromes together with mild pyramidal and extrapyramidal insufficiency are the neurological signs of organic brain damages (encephalopathy) at the remote period of irradiation. The frequency of these symptoms increased following irradiation by 0.5 Gy and more. A direct correlation between the frequency and severity of encephalopathy and the ARS severity degree should be noted. Moreover, in a number of cases there was no correlation between the encephalopathy severity and the degree of cardiovascular system damages, lipid metabolism and blood pressure. It indicates peculiarities of the encephalopathy developing in overexposed persons without atherosclerosis or arterial hypertension present [2, 5–7].

2.2.3.2. Psychiatric and psychological examinations

In 1987–1988, psychopathological manifestations appeared as different variants of the *asthenic syndrome* with pronounced vegetative dysfunction almost in all ARS-group patients. Some patients showed signs of dysphoria, and some others of agitation and explosiveness at that phase. In 1990–1991, a *cerebrasthenic syndrome* and some types of neurotic states prevailed in the majority of patients.

A deterioration of the mental state of patients was recorded 7–8 years after diagnosis of ARS. *Organic mental disorders* were diagnosed in 56% of the patients and their frequency depended on the degree of ARS severity. The same dependency was shown for disorders of psychopathic type. Senestopathies were complicated and supplemented with psychosensory disorders. Apatho-abulic disorders, depression and anxiety symptoms also appeared.

In 1996–1998, organic mental disorders were diagnosed in 84% of the ARS patients with asthenic syndrome revealed in 1987–88. It is considered as transformation of so-called "functional" disorders to encephalopathy. These patients registered pains of various localization, paresthesia and senestopathies. Quite often paroxysmal psychosensory disorders as metamorphopsia and autometamorphopsia were observed. Depressive symptoms increased and became more "anergic". A decrease in the capacity to memorize, store and reproduce of new information (dysmnesia) was observed as well as problems in the use of earlier gained knowledge and everyday skills. A drop in the capacity to concentrate was found. Cognitive dysfunctions were manifested by feelings of suspicion or paranoia and/or excessive anxiety for any abstract question (religion, "justice" or "injustice"), and also by hypochondriac formations which were quite often of supervaluable type. There were changes in speech delivery and flow. The patients also developed a decreased ability to persevere and persist, as well as apathy and abulia.

In 2000–2001, *organic mental disorders* were diagnosed in 100% of the ARS-group patients (including also the non-confirmed or NOARS cases). *A negative psychopathologic symptomatology* and *"anergic" depression* were characteristic in this group 15 years after the first diagnosis of ARS. The clinical picture includes affective flattening (sometimes reaching the degree of apathy), abulic manifestations, anhedonia, a tendency to being alone and social withdrawal up to autism.

The mental state of the ARS-group patients and liquidators was significantly different of that in the control groups. Enhanced concern, blunted or inappropriate affection, emotional withdrawal, as well as suspiciousness dominated in the exposed patients according to the BPRS (Table 2.4). As a whole, the mental capacity to work was reduced according to criteria of efficiency, endurance, accuracy and reliability.

TABLE 2.4. INDICES OF THE BRIEF PSYCHIATRIC RATING SCALE (BPRS)

Index	Group I (n=70)	Group II (n=80)	Group A (n=15)	Group B (n=15)	Group C (n=20)
Somatic concern	4.2±0.2**	4.1±0.2**	1.8±0.1	3.8±0.4*	3.3±0.3*
Anxiety	2.4±0.1*	3±0.2*	1.1±0.1	3.3±0.2*	4.1±0.3**
Emotional withdrawal	3.5±0.2**	2.2±0.2**	0.5±0.1	1.3±0.1*	1.9±0.3*
Conceptual disorganization	0.7±0.1	0.6±0.2	0	0.5±0.2	0.5±0.1
Guilt feelings	1.7±0.2*	1.3±0.2*	0	0.7±0.2	2.5±0.2**
Tension	1.1±0.2	1.6±0.3*	0	1.7±0.1*	2.8±0.3**
Mannerisms and posturing	0.5±0.1	0.4±0.1	0	0.5±0.2	0.8±0.1
Grandiosity	0	0.2±0.1	0	0	0
Depressive mood	2.5±0.2*	3.6±0.2**	1.2±0.2	3.1±0.3**	3.8±0.4**
Hostility	0.4±0.1	0.5±0.2	0	0	1.8±0.2*
Suspiciousness	3±0.2**	2.1±0.2*	0.3±0.1	1.9±0.2*	1.1±0.2
Hallucinatory behaviour	0.3±0.1	0.2±0.1	0	0	0
Motor retardation	2.1±0.1*	1.9±0.2*	0	1.9±0.2*	0
Unco-operativeness	1.5±0.1*	2.4±0.2*	0	0	2.1±0.1*
Unusual thought contents	2.9±0.2**	2.1±0.2*	0.5±0.1	1.3±0.2	1.5±0.2
Blunted or inappropriate affect	3.6±0.2*	2.2±0.2*	0	1.1±0.2*	0.6±0.1
Sum 1–16	30.4±0.4**	28.4±0.5**	5.4±0.2	21.1±0.4**	26.8±0.5**

Notes: * — probability $p<0.05$ relatively to the control group A.
** — probability $p<0.01$ relatively to the control group A.

In 2000–2001, a total *intelligence quotient* (IQ) in the ARS patients was 102.2±14.5 (M±SD), a verbal IQ — 103.2±17.3 and a performance IQ — 100.9±9.0. The cognitive disorders included a worsening of planning, long term goals forming, abilities to mobilize a facility of the personality for these goals achievement, a possibility to foresee of obvious consequences in the future, abilities to development and realization of the alternative problem deciding strategies, as well as simultaneous execution of several tasks. Besides, suspicious or paranoid thinking and/or excessive preoccupation with abstract problems (Eastern religions, "recovery systems" and "correct way of life ", "fairness" and "unfairness"), and unclear speech were also detected.

Affective disorders included mainly affect flattening, up to apathy, with a narrowing of a circle of interests and contacts with the environment, social withdrawing and autism. Depressive disorders were mainly observed in combination with languor, adynamia, hypobulia, lack of initiative. Anxiety-depressive disorders, feeling of despair and an impossibility to influence or change the future were also revealed. Obsessive-phobic and dysphoric states were comparatively fewer.

The negative psychopathological symptoms were studied using SANS (Table 5). A majority of the negative symptoms included unchanging facial expressions; paucity of expressive gestures; poor eye contact; affective non-responsiveness; lack of vocal inflections; poverty of content of speech; increased latency of response; physical anergia; a reduction of recreational interest and activities; a reduction of sexual interest and activity; a tendency to be alone and social withdrawal.

TABLE 2.5. INDICES OF THE SCALE FOR THE ASSESSMENT OF NEGATIVE SYMPTOMS (SANS)

Index	Group I (n=70)	Group II (n=80)	Group A (n=15)	Group B (n=15)	Group C (n=20)
Affective flattening or blunting	2.4±0.1**	2.1±0.2**	0	0.4±0.1	0.7±0.1
Alogia	2.2±0.1**	1.9±0.2*	0	1.3±0.3*	0.4±0.1
Avolition–apathy	2.6±0.1**	2.5±0.2**	0	0.9±0.1*	0.6±0.1*
Anhedonia–asociality	2.7±0.1**	2.6±0.2**	0	0.5±0.2	1.5±0.2*
Attention	2.7±0.2**	2.3±0.2**	0	2.1±0.2**	0.5±0.2

Notes: * — probability $p<0.05$ relatively to the control Group A.
** — probability $p<0.01$ relatively to the control Group A.

According to the above Screening Schedule, 62% of the examined patients have an increased risk of development of severe mental disorders. The results of this schedule have also confirmed a prevalence ($p<0.01$) of the negative symptoms comparatively with the positive ones.

The PTSD study with related scales has shown that all examined ARS survivors were exposed to psychoemotional stress due to the Chernobyl disaster: average score on the Impact of Events Scale (IES) is23.5±1.4 in the Group I and is 27.4±1.2 in the Group II. Memory about the disaster and associated arousal take a leading place in the psychopathology of 8 ARS patients (11%) and of 22 liquidators (27%). This concerns predominantly those who had not been prepared for an emergency and took part in the cleanup works involuntarily. Among the other patients PTSD had no dominant clinical value.

According to the Unmasking Depression Self-rating Depression Scale (SDS) a minimal to mild and a moderate to marked depression were revealed in 41 ARS patients (58%). Severe to extreme depression appears in 7 patients (10%), correspondingly. According to GHQ-28, all examined ARS survivors self-estimated their mental and physical health as significantly worse than usually.

Between 5 and 10 years after ARS, there was a typical "floating" abnormal averaged MMPI profile with a simultaneous increase in both "neurotic" and "psychotic" scales. The MMPI profiles of irradiated persons differ significantly from profiles in the control groups. The patients of Groups I and II distinguished with strongly pronounced stress and personality disadaptation associated with signs of disintegration of intellectual and emotional spheres. Hypochondriac and depressive symptoms were associated with inert thought, dogmatism as well as caution and even hostility in the interpersonal contacts. Chronic feelings of mental discomfort and diffidence, a reduction of general productivity, guilt and inferiority complexes were complicated with signs of apathy and somatic concern.

Thus, the MMPI profile of exposed persons suggests the asthenic type of reactions together with depressive experience complicated with hypochondriac and paranoiac symptoms. Moreover, a significant increase ($p<0.01$) of the schizophrenia, hypochondria, paranoia, epilepsy and odd sensoric perception MMPI-scales together with a decrease of the personality "nucleus" power and intelligence quotient scales were revealed. These MMPI-scales deviations correlated feebly with the level of radiation dose ($r=0.12–0.25$, $p<0.05$ at the force of factor of dose of radiation influence $\eta^2=0.19–0.34$, $p<0.01$). Between 13 and 15 years after ARS, there was still the characteristic "floating" abnormal averaged MMPI-profile with simultaneous raising of both "neurotic" and "psychotic" scales. At the same time, depression and schizophrenia scales dominated.

The neurotic symptoms have no significant correlation with the age and level of radiation dose incurred by the patients. On the contrary, some symptoms (e.g. aggression) were decreased proportionally to the increase of the dose. At the same time such symptoms as lack of interests and initiative, alogia and, particularly, inattentiveness correlated with both the age and a dose. Social and emotional withdrawal, affective flattening, anhedonia—asociality, suspiciousness, motor retardation, unusual thought content, as well as the summarized BPRS-score correlated with the absorbed dose stronger ($r=0.3–0.5$, $p<0.05$) than with the age ($r=0.14–0.34$, $p<0.05$). Mental and behaviour disorders in the ARS patients based on the ICD-10 criteria are presented in Table 2.6.

The schizophrenia-like psychopathology dominates ($p<0.05$) following irradiation at the dose 0.3–0.5 Gy and more. At the same time the affective and somatoform symptoms (anxiety, depression, irritability, somatic concern) prevail ($p<0.05$) in liquidators irradiated at the dose less 0.3 Gy.

2.2.4. Psycho- and neurophysiological studies

As a result of the visual and computerized EEG analyses we found the following patterns of electrical activity in the brain (Table 2.7). The EEG-patterns with interhemispheric asymmetry and paroxysmal activity as discharges of acute and slow waves and "spike–wave" and "polyspike–wave" complexes were typical for the exposed persons.

TABLE 2.6. MENTAL DISORDERS IN THE ARS SURVIVORS ACCORDING TO THE ICD-10 CRITERIA

Mental and behaviour disorders	ICD-10 code	ARS patients (Total=70)
ORGANIC, INCLUDING SYMPTOMATIC, MENTAL DISORDERS:	F00–F09	62 (88 %)
• With cerebrasthenia dominance	F06.6	8 (11 %)
• With brain organic syndrome dominance:	F07; F06	54 (77 %)
Cerebrasthenic type	F06.7	11 (16 %)
Dysthymic type	F06.3	9 (13 %)
Apathetic-abulic type	F07.0	21 (30 %)
Paranoid type	F06.2	6 (9 %)
Explosive type	F07.8	2 (3 %)
Dementia type	F02.8	5 (7 %)
SCHIZOTYPAL DISORDER	F21	9 (13 %)
ENDURING PERSONALITY CHANGE AFTER CATASTROPHIC EXPERIENCE	F62.0	8 (11 %)
SOMATOFORM DISORDERS	F45	9 (13 %)
DYSTHYMIA	F34.1	7 (10 %)

Note. The total rate of mental disorders may exceed 100% because sometimes a patient was diagnosed with more than one disorder (comorbidity).

TABLE 2.7. EEG-PATTERNS AMONG THE EXAMINED PERSONS

EEG-pattern	Group I (n=70)	Group II (n=80)	Group A (n=15)	Group B (n=15)	Group C (n=20)
Organized with α–activity dominance	0	22(27 %)*	12(80 %)*	6(40%)*	12(60)*
Hypersynchronic	7(10 %)	7(9 %)	3(20 %)	2(13 %)	4(20 %)
Flat polymorphous	58(83 %)	55(69 %)	0*	5(33 %)*	2(10 %)*
Disorganized with α–activity dominance	2(3 %)	10(12 %)	0	1(7 %)	2(10 %)
Disorganized with δ–activity dominance	3(4 %)	8(10 %)	0	1(7%)	0
Laterality of abnormal activity:					
– bilateral	14(20 %)	6(7 %)	3(20%)	4(27 %)	3(15 %)
– left-hemispheric	40(57 %)	25(31 %)*	—	1(6 %)*	2(10 %)*
– right-hemispheric	16(23 %)	27(35 %)	—	4(27 %)	3(15 %)

Note. * — probability $p<0.001$ relatively to Group I according to the χ^2 criterion.

The EEG-patterns of irradiated patients varied significantly from the control groups. The normal EEG-patterns were absent in the ARS-group patients. The EEG-patterns with interhemispheric asymmetry, particularly left-hemispheric EEG-patterns with lateralization of abnormal activity towards the left brain hemisphere predominated in patients of the I and II groups [8, 9].

The flat polymorphous EEG-pattern with diffusive δ- and β-power predominantly in the fronto-temporal areas lateralized to the left, dominating, hemisphere together with paroxysmal activity against a background of low-voltage (10–25 μV) EEG was characteristic for the irradiated patients. In addition to the flat EEG, the disorganized EEG-patterns were also typical for the irradiated persons. The disorganized EEG-pattern with α-activity distinguished

with disorganized high-voltage α-activity dominating throughout the brain increased amplitude of β-activity, diffusive θ- and δ-activity of quite high amplitude together with bilateral paroxysmal activity. The disorganized EEG-pattern with θ- and δ-activity was characterized by decreased α-activity against a background of high- or middle-amplitude dysrhythmic EEG. These EEG-patterns testify to organic brain changes and sometimes increased seizure readiness of the brain.

The degree of brain bioelectrical activity disturbances is directly proportional to the value of absorbed dose ($r=0.41$; $p<0.05$) and the age of a patient at the time of examination ($r=0.2$; $p<0.05$). A spectral analysis of brain electrical activity gave the characteristic EEG-pattern for the irradiated patients: a simultaneous increase of δ-(0.5–4 Hz) and β-(>12–32 Hz)-power together with a decrease of θ (>4–7 Hz) and α-(>7–12 Hz)-power (Figure 2.3).

This EEG-pattern was characteristic for both the ARS patients and the examined liquidators who had not developed ARS. It should be stressed, that the examined liquidators were exposed in average to 0.54±0.45 Gy, which is higher than the average dose to patients with non-confirmed ARS (NOARS: 0.23±0.15 Gy). However, the EEG-patterns of patients of the Group I differ from those of the Group II with increased δ-power, particularly in the left fronto-temporal region, and more depressed of θ-power. This EEG-pattern of the irradiated patients suggests structural and functional changes of the brain predominantly in the fronto-temporal cortex (particularly in the left, dominating, hemisphere) and the limbic-reticular-diencephalic complex.

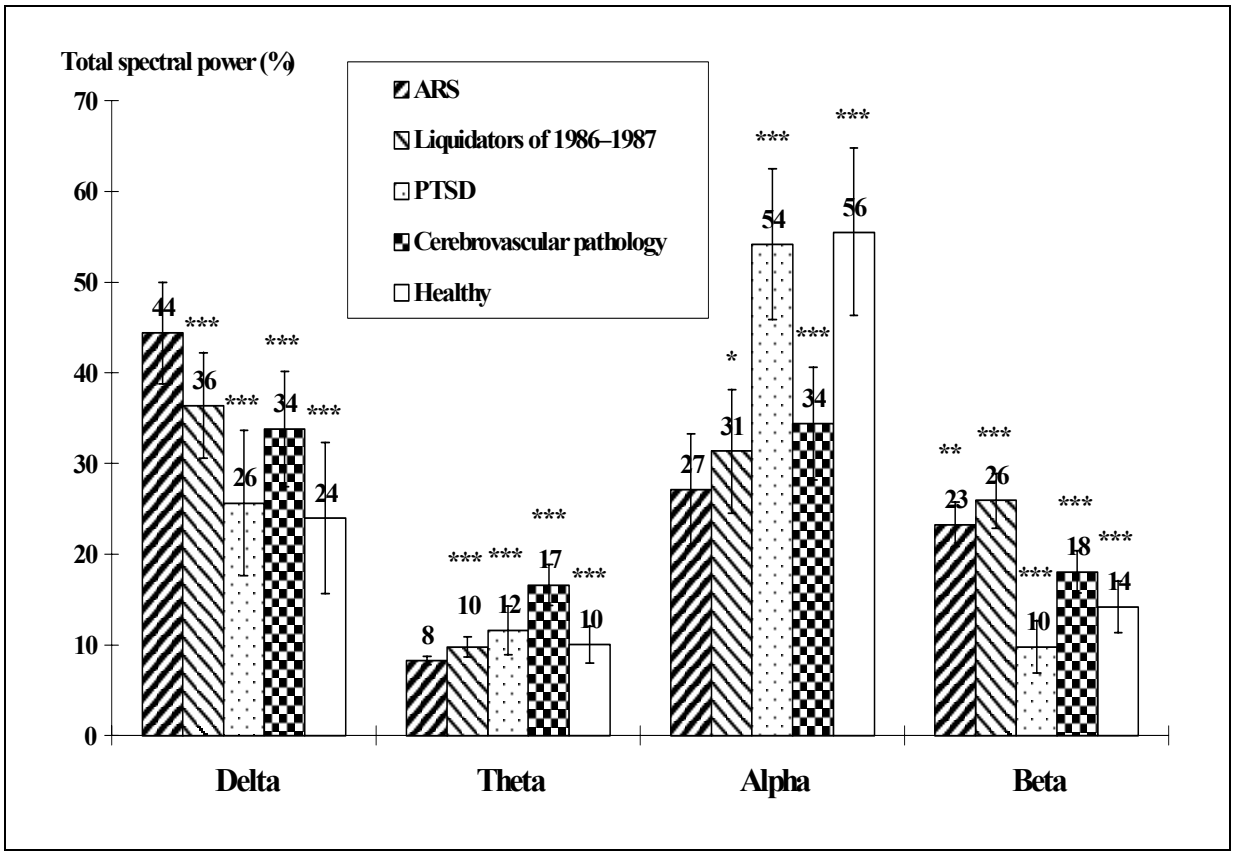

*FIG. 2.3. Results of computerized EEG — total spectral power of EEG main range. Probabilities compared with Group I: * —$p<0.05$, ** —$p<0.01$, *** —$p<0.001$.*

TABLE 2.8. EEG SPECTRAL POWER IN NOARS AND ARS 1–2 PATIENTS

EEG spectral power (%) in leads	**NOARS M±SD**	***t*-test**	**p**	**ARS-1 and ARS-2 M±SD**
Summarized δ (0.5–4 Hz)	35.4±14.3	–2.5	=0.017	45.7±14.6
δ F1	44.6±17.2	–2.4	=0.018	56.9±17.6
δ F7	34.7±14.3	–3.2	=0.002	48.3±14.6
δ F3	40.4±18.1	–2.3	=0.027	51.7±16.4
δ F4	38.0±16.3	–2.1	=0.038	49.1±19.3
δ F8	41.6±16.3	–2.2	=0.029	52.3±16.8
δ T3	35.6±14.3	–3.0	=0.004	48.7±15.9
δ C3	37.1±18.2	–2.1	=0.041	48.9±20.4
δ C4	35.8±16.9	–2.4	=0.019	48.9±19.8
δ T4	35.3±17.1	–2.3	=0.024	46.9±17.4
δ P3	31.5±15.7	–2.4	=0.019	43.8±18.9
δ P2	30.0±16.5	–2.5	=0.016	42.2±17.2
δ P4	28.4±14.8	–2.7	=0.009	40.7±16.0
α F7	28.3±19.8	2.2	=0.034	20.3±17.7

Statistically significant differences in the spectral power of EEG among examined ARS patients were established when this group was divided into two subgroups: NOARS, n=38 and ARS, n=32 (ARS-1 together with ARS-2) -Table 2.8.

The patients with verified ARS differ from those with non-confirmed ARS with significantly increased spectral power of slow (δ) activity, especially in the fronto-temporal areas of the left, dominating hemisphere, as well as with depression of α-activity in the frontal area of the same hemisphere.

The dose-effect relationship for the EEG parameters was observed also in the liquidators of 1986 and 1987. Irradiation at the dose more 0.3 Gy caused an increase ($p<0.001$) of δ-power and a decrease of α-power. The duration of irradiation (work at the exclusion zone) did not influence on these EEG-parameters. Long term work (3 to 5 years and longer) at the exclusion zone and irradiation at doses less 0.3 Gy increased ($P<0.05$) δ-power, and at the doses more 0.3 Gy increased ($P<0.05$) β-power. The linear dose-effect relationship in ARS patients and liquidators was established for δ-power in the left temporal region T_3 (Fig. 2.4).

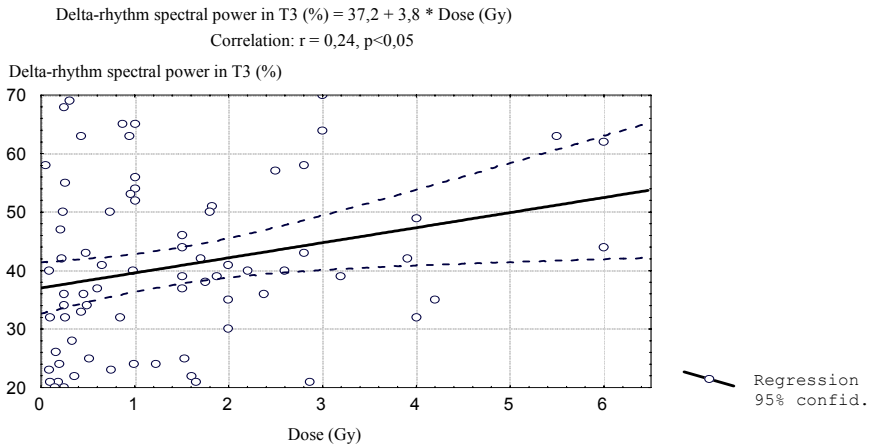

FIG. 2.4. Linear dose-effect relationship in ARS patients and liquidators for δ-power in the left temporal region (T_3) depending on the absorbed dose value.

Analysis of bioelectrical activity in the brain based on use of deflection factors demonstrated significant differences between irradiation aftermath and well-known neuropsychiatric pathology (Fig. 2.5). After irradiation, δ- and β-power dramatically increased, significantly more than at chronic cerebrovascular pathology and PTSD consequences. At the same time θ-power deflection from the mean norm in the irradiated persons was diametrically opposite comparatively with both chronic cerebrovascular pathology and PTSD. A development of cerebrovascular pathology and PTSD is associated with an increase of θ-power (which is generated in hippocampus), however irradiation provoked a depression of this EEG-range that also confirms a pathology of limbic system as the characteristic sign of the post-radiation brain damage.

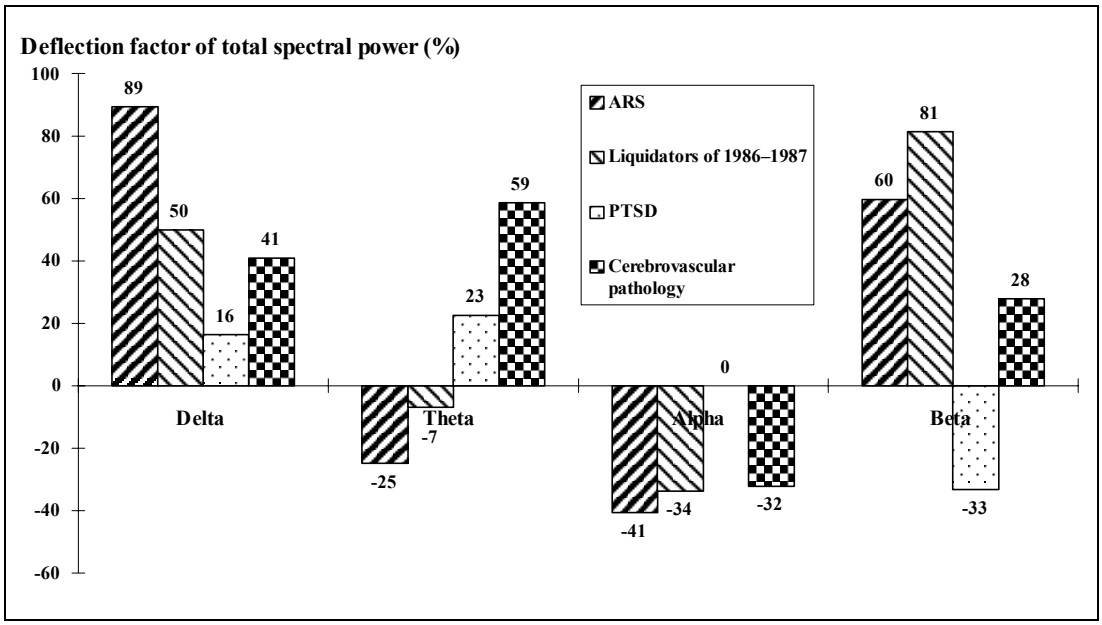

FIG. 2.5. Deflection factors values (%) of total spectral power of EEG main ranges. (The deflection factor was used for detection of the degree and direction of the psychophysiological parameter deviation from the norm. It was calculated according to the formula $Df = (A_1 - A_k) \cdot 100\ \% \div A_k$, *where Df is the deflection factor,* A_1 *is the value of the index to be studied,* A_k *is the mean normal value of this index. The deflection factor is positive if the parameter was increased in a patient comparatively to the norm, and it is negative when the parameter was decreased.).*

Checkerboard reversible pattern VEP and their parameters topographic distribution in the irradiation patients distinguished significantly from the norm. P_{100} amplitude was increased and its latency was decreased; N_{145} and P_{200} latencies were delayed mainly as a result of deformation of the latest VEP components. VEP deformation could testify to organic changes of the brain. VEP acceleration and an increase of their amplitude testify to an increased readiness of the brain for paroxysmal states. Taking into account the absence of visual nerve damage it is possible to suppose that this VEP pattern is associated with an irritation of the diencephalic-limbic-reticular structures together with disorders of sophisticated cortical-subcortical processes of sensoric information processing.

Specific peculiarities of the *brainstem auditory evoked potentials* (BAEP) in ARS remote period are late (III, IV, V) components BAEP deformation, expressed asymmetry of basic components and interpeak intervals as well as V component and III-V interpeak interval latencies increase; V component amplitude decrease; VI (thalamic) component amplitude increase. More over in 6% of the persons who had ARS, it is revealed a significant

lengthening of III-V interpeak interval with sharp deformation of BAEP latest components, that can testify to demyelinization at brain stem level. In ARS remote period the oppression of bottom stem regions structures is predominant. And with it, in some cases irritability phenomena in stem structures, to a greater extent in thalamus is registered, that intensify as the irradiation dose rises.

The most expressed abnormalities of *vestibular function* were observed in the nearest terms after ARS. Later reduction of vestibular dysfunction was registered. In the course of 8 to 10 years of observation a deterioration of vestibular function was registered, that can be explained through organic neurovascular pathology development. There is a direct correlation between vestibular abnormalities severity and the ARS severity degree and, hence, the absorbed irradiation dose.

The type of vestibular reactions also changed in post-accidental years. In the first stage (1986–1987) vestibular dysfunctions were characterized with expressed statokinetic balance disorders. In the last stage (1996–1998 and later) a spontaneous symptomatology was in the foreground, e.g. spontaneous nystagmus and changes of separate parameters of experimental nystagmus, evoked as thermal/caloric or rotary stimulations were also registered. Between 9 and 10 years after initiation of ARS, the experimental nystagmus assumed a tonic character. These changes indicated progression of central regulatory disturbances of the vestibular system.

Thus, the registration of spontaneous and evoked bioelectrical brain activity of a head in ARS remote period testifies to pathology of diencephalo-limbico-reticular structures and associative frontal regions, mainly dominant left hemisphere with expressed abnormalities of central mechanisms of afferentation. The abnormalities of autonomic nervous system functions resulted first of all in changes of a sympathetic skin response (SSR). These changes in ARS patients were as follows: sharp amplitude decrease of SSR hands (156±153 μV on the right and 176±177 μV at the left) and feet (45±35 μV on the right and 45±32 μV on the left), significant increase (on average more than 1,5 times more) of potential duration and, for the most of examined persons, change of its phase structure. At the same time the values of latent periods of SSR did not really differ from the values in control. In research dynamics the gradual fading (SSR amplitude decreased on hands and feet) was registered, and in some cases even the disappearance of SSR, in particular on feet.

The above described clinical data and revealed changes of the SSR peculiarities indicate a mainly central nature of sympathetic nervous system abnormalities (primarily in the hypothalamus), and a decrease in tone and reflex activity of sympathetic vasoconstrictors and sudomotoric skin fibres.

Vagotonic symptoms are predominant in the ARS patients. Abnormalities in the autonomic (vegetative) regulation of the cardiovascular system were revealed in the majority of the patients, who had parasympathetic type of response. In the ARS-1 subgroup the abnormalities of sympathetic type were predominant. (including the mixed type). Moreover, it was established, that the number of cases with vertigo while performing orthostetic test depended on the degree of severity of the ARS. A hypertensive reaction for isometric test was the most frequent in patients of ARS-0 subgroup. So cardiovascular system vegetative regulation abnormalities were registered in ARS remote period as due to floating nerve tone fall of vegetative nervous system sympathetic area, accompanied with vasoconstrictal functional

deterioration, especially in the cases, when it is necessary the urgent adaptation of cardio-vascular system to physical loading. Vegetative abnormalities appeared to be more significant in patients with a lesser degree of ARS severity. This fact reflects multifactor etiopathogenesis of these abnormalities, in origination of which exposure to ionizing radiation is one of pathogenetic factors. These abnormalities are one of pathophysiological mechanisms, that determine complex development of various (sensory-algetic muscle-tone and vegeto-tropho-vascular) displays of *progressing vegetative insufficiency syndrome.*

In more than 75% of the ARS patients the thermographic image of hands, forearms, shins and feet was characterized with hypothermia – "thermoamputation" limb symptom. In addition, it was quite often registered the asymmetry of integument temperature on hips and trunk as well as paroxysmal-distant proportion changes.

Hypertonic and dystonic-hypertonic types of RhEG-curves are *predominant* in ARS remote period. However the most great number of cases of hypertonic type curves was revealed in ARS-2 subgroup patients, that testified to morphological vascular changes of vessels. *Sphygmic blood filling* was also more decreased in the ARS patients with a higher degree of ARS severity. The frequency of sphygmic blood filling interhemispheric asymmetry and cerebral venous circulation disorders was also expected to increase depending on ARS severity degree and exceeded ($p<0.05$) the frequency in control group. The increase in fine brain vessel tone and brain vessel resistance was true more often in the ARS patients, but dependence on a severity degree was not revealed. Using USDG of main neck vessels it was revealed the interhemispheric asymmetry of circulation disorders with predominant disorders in the left hemisphere, mainly in vessel basins left of internal carotid and supratrochlear arteries. At that the changes at terminal vessel level were revealed in 48% of the patients with intracranial blood flow disorders. At the same time in 75% of cases of the control group only initial changes of main neck vessels were revealed.

The changes of brain vascularity certainly depend on the degree of ARS severity, and the number of stable morphological brain vascular disorders predominates in ARS-2 subgroup. Vascular changes also correlate with lipid metabolism, arterial pressure level, eye-ground changes. At the same time it is necessary to mention, that there is no direct correlation between vascular changes and the displays of such neurological syndromes as cerebrasthenic, brain organic, statoco-ordinative and sensory-algetic in some cases. Thus, we can assert, that in these cases the encephalopathy is conditioned not only by dyscirculation mechanism, but, perhaps, direct or indirect exposure to ionizing radiation to brain tissue, i.e. the matter is in encephalopathy of another genesis, with vascular factor as of great, but not fundamental importance, in post-radiation encephalopathy.

Analysis of the relative risk (RR) of neurophysiological abnormalities has shown that ARS increases fivefold the risk of development of brain organization anomalies. Similarly, work at the exclusion zone in 1986 and 1987 increases this risk 3.65-fold and long term work almost fourfold, whereas chronic cerebrovascular pathology and PTSD augment the risk three- and twofold, respectively [2, 7].

The contribution analysis allows to calculate a contribution of the main factors influencing on the brain electrical activity after irradiation. The force of influence of the irradiation dose on an increase of δ- and β-power of EEG is 48% ($F=25.2$; $F_{05}=4.0$; $p<0.05$) and 22% ($F=6.5$; $F_{05}=4.0$; $p<0.05$) respectively, and upon an decrease of θ- and α-power — 44% ($F=21.3$; F-

$_{05}$=4.0; p<0.05) and 26% (F=9.5; F_{05}=4.0; p<0.05) respectively. The force of influence of the duration of work at the exclusion zone on an increase of β-power is 22% (F=10.1; F_{05}=4.0; p<0.05).

At the same time the strength of the influence of age on an increase of δ- and β-power is 13% (F=5.5; F_{05}=4.0; p<0.05) and 25% (F=11.9; F_{05}=4.0; p<0.05) respectively, and upon a decrease of θ- and α-power — 22% (F=10.1; F_{05}=4.0; p<0.05) and 24% (F=11.5; F_{05}=4.0; p<0.05) respectively. It should be stressed the atypical age-related EEG changes in the irradiated patients. In contrast to physiological ageing which accompanied with «slowing» of EEG as an increase of θ-power and a decrease of β-power, the age-related EEG-changes are associated with a decrease of θ-power and an increase of β-power.

Psychological stress (PTSD) does not bear upon δ- and θ-power. At the same time an increase of stress associated with an increase of α-power (the force of influence — 20%; F=9.3; F_{05}=4.0; p<0.05) and a decrease of β-power (the force of influence — 21%; F=9.9; F_{05}=4.0; p<0.05). This signifies that psychological stress provoked diametrically opposite effects on brain electrical activity in comparison with exposure to ionizing radiation.

Cerebrovascular pathology (arterial hypertension and cerebral atherosclerosis) does not influence on spectral power of δ-range of EEG in the irradiated persons. The force of influence of arterial hypertension on an increase of θ- and β-power is 24% (F=11.2; F_{05}=4.0; p<0.05) and 30% (F=15.4; F_{05}=4.0; p<0.05) respectively. The force of influence of cerebral atherosclerosis on a decrease of θ- and β-power is 23% (F=10.6; F_{05}=4.0; p<0.05) and 35% (F=19.3; F_{05}=4.0; p<0.05) respectively, and on an increase of α-power — 32% (F=16.9; F_{05}=4.0; p<0.05).

Comorbidity of physical diseases in the irradiated patients does not influence significantly the changes of spectral parameters of electrical activity in the brain. Thus, psychophysiological disorders in the ARS patients and liquidators of 1986 and 1987 are polyetiological: the age of a patient, psychological stress, cerebrovascular pathology, the duration of work at the exclusion zone all play a part in their genesis. However, a level of absorbed dose has provided a major contribution in the psychophysiological disorders detected. Accordingly, the characteristic psychophysiological pattern of the ARS patients and liquidators of 1986 and 1987 should be considered as the deterministic effect of ionizing radiation [5, 6].

2.2.5. Principles and methods of treatment

The principles of the treatment of neuropsychiatric disorders include complexity, stability and succession between stages (clinical, ambulatory-polyclinic, ambulatory and sanatorium treatment). Basic treatment includes pharmacotherapy and psychological therapy. Neuropharmacology includes vasoactive and nootropic drugs, neuroprotectors, antidepressants (predominantly, selective serotonin reuptake inhibitors — SSRIs) and atypical antipsychotic (if necessary). The correction of *mental disorders* is carried out at syndromological level. It is worth mentioning the importance of *out-patient methods of treatment and rehabilitation* [Nyagu A.I. et al., 1998, Nyagu A.I. et al., 1999].

2.2.6. Ability to work after the acute period or degree of disability

More than 90% of the ARS patients have been disabled. Mental health protection is one of the leading problems, if not the priority for the ARS survivors in the aftermath of the Chernobyl disaster.

2.3. Lessons to be learned from the psychological follow-up of ARS patients

- Fifteen years after the Chernobyl accident neuropsychiatric diseases primarily seem to have emerged in the ARS patients. Neuropsychiatric care in the aftermath of ARS and overexposure to ionizing radiation should be a priority area of attention in the remote period consecutive to accidental irradiation.

- Neuropsychiatric and neuropsychophysiological follow-up studies conducted between 1987 and 2001 confirm that ARS patients who survived after the Chernobyl disaster show progressive structural-functional brain damage: *post-radiation encephalopathy* (ICD-10: T66=unspecified irradiation effects: radiation sickness, along with G93.8=other specified brain diseases: post-radiation encephalopathy, along with F00-F09=organic, including symptomatological mental disorders). The pathophysiological basis for post-radiation encephalopathy is a pathology of diencephalo-limbico-reticular structures and associative frontal regions mainly predominant left hemisphere with expressed disorders of central afferentation mechanisms.

- The diagnostic criteria for post-radiation encephalopathy are [5–7]
  (1) Verified radiation sickness.
  (2) Fast progressive course of neuromental disorders with expressed psychovegetative syndrome predominance 1 to 2 year following the acute ARS period, which develops into organic syndrome of the brain in 3 to 5 years.
  (3) Post-radiation encephalopathy signs like:
    (a) endoformous brain organic syndrome with predominance of senesto- and paranoic-hypochondriac symptomatology in combination with apatho-abulic disorders;
    (b) microfocal neurological symptomatology, mainly of diencephalo-stem level with sensory-algetic, muscle-tonic, vestibular-ataxic syndromes and soft pyramidal and extrapyramidal symptoms;
    (c) progressing vegetative/autonomic insufficiency (the decrease of SSR hands and especially feet amplitude; its value asymmetry; increase of occurrence threshold, and quite often — absence of SSR; decrease of limbic infrared emission («thermoamputation») and its trunk asymmetry; cardiovascular system regulation disturbances as parasympatheticotonia);
    (d) flat or disorganized EEG type with paroxysmal activity, interhemispheric asymmetry with δ- and βpower spectral power predominance;
    (e) deformation and asymmetry of somatosensoric evoked potentials (SSEP) main components at increasing of latent periods and decreasing of early and late components amplitude;
    (f) deformation, decrease of the latent periods and increase of VEP main components amplitude;
    (g) BAEP late (III, IV, V) components deformation, increase of the latent period of V component and III-V of an interpeak interval, decrease of V component amplitude;

(h) the signs of cerebral circulation disorders at absence of its stable disturbances.

(4) Absence of neuropsychiatric pathology of other genesis.

The diagnosis of "post-radiation encephalopathy" was confirmed, if the 1st and the 2nd criteria and not less than three signs of the 3rd criterion were present. In cases, when on the background of ARS, cerebrovascular pathology was developing (arterial hypertension, atherosclerosis) at steady cerebral haemodynamic disorders, the brain organic damage should be classified as post-radiation dyscirculatory encephalopathy.

- *Diagnostic criteria of post-radiation syndrome (encephalopathy) as a proposition for a new F07.3 diagnostic category for ICD-10.* We propose to classify organic mental disorders in ARS patients in the remote period as *post-radiation syndrome (encephalopathy)* which includes significant personality changes, impairment of cognitive and thought functions, impairment of memory, difficulty in concentration and performing mental tasks, apathy, abulia, social estrangement, anhedonia, fatigue, headache, dizziness. We propose to include this syndrome as **F07.3 Post-radiation syndrome (encephalopathy)** in the Chapter F00–F09 Organic, including symptomatic, mental disorders of the ICD-10.

- Therapeutic resistance of mental health abnormalities is determined by a composite influence of unfavourable factors of the Chernobyl accident, where radioactive and psychogene consequences are of the greatest importance, the influence of which is becoming stronger because of social-economic problems in the post-Soviet period. These aspects lead to extremely complicated and multimorphic clinical pictures of mental and, in particular, psychosomatic disorders, which are very difficult to be corrected [2, 7].

- The current Ukrainian system of rendering treatment-prophylactic care in a sphere of mental health protection in the survivors as a result of extreme situations, in particular the Chernobyl accident, is not effective enough, mainly due to organizational reasons:
  - there is no *psychiatric service for extreme situations* in this country;
  - there is no *united co-ordinated centre for mental health protection* for survivors of extreme situations;
  - there are no multiple-discipline treatment-prophylactic institutions giving medical help to the survivors as a result of the Chernobyl disaster, *specialized psychiatric and narcological beds and/or departments* structured in accordance with multiple-discipline treatment-prophylactic institutions. As a consequence, practically any problem of mental health abnormalities of the survivors appears to be unsolvable at existing multiple-discipline treatment-prophylactic institutions giving them medical care. For this reason, adequate medical care is not frequently given to this significant group of patients.

  Effective protection of mental health is possible only by simultaneously addressing the neuropsychiatric, personal, somatic and social spheres of the lives of the survivors. In this regard, to establish a National Service for mental health protection in survivors is a problem at the present time.

- *Inadequate social rehabilitation*. Now, perhaps, the only more or less reliable social guarantee is an acknowledgement of a disability to work, i.e. an invalid status. The patients' desire to obtain the status of invalid is in many respects caused by the necessity to find social and, foremost, material protection. It is more advantageous to be an invalid than

healthy in current circumstances. The prejudice from this situation (caused reportedly by imperfect legislation) is obvious: along with the growing social burden for this country, an aggravation of psychosomatic pathology is taking place as well as the development of a passive personality and a reinforcement of the 'victim complex'. In this connection, a *social measures system* is needed that will provide the following basic aspects:

— a medical guarantee;
— employment with possible training and retraining for a new profession;
— social facilities and privileges for those who work;
— material support;
— involvment in civil activity.

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Chapter 3

HEALTH CONSEQUENCES AMONG THE LILO ACCIDENT VICTIMS, MEDICAL MONITORING IN GEORGIA, FRANCE AND GERMANY

J.-M. Cosset, D. Jikia, R.U. Peter, G. Souchkevitch, I. Turai

3.1. Short description of the accident

The accident took place in Lilo, a small Georgian city located 25 kilometers East of Tbilisi (Georgia). Before 1992, a training camp for the Soviet Army was installed in the city. Russian soldiers had available a number of radioactive sources for training (search of radioactive materials on battlefields, detection and management of sources). In 1992, the camp was transferred to the Georgian Army, and then used for training of Georgian frontier troops. Several radioactive sources had been left by the Soviet Army in the training camp, most of them apparently were in protective containers. Some of the radioactive sources were subsequently found by Georgian soldiers (mostly unaware of their nature) and were responsible for the severe lesions listed below. It should be noted that the precise circumstances of the accidental exposures were extremely difficult (and often impossible) to reconstruct, either because the soldiers did not realize the dangers of the small pieces of metal what they found, or because they were extremely reluctant to speak about it, with some feeling of being "guilty" of having manipulated such material. Even the patients with very severe hand lesions have never recognized that they had handled something resembling the sources.

The first event was noted in July 1996, when a young Georgian recruit exhibited fever, together with atypical lesions of both hands, of the abdomen and of the left thigh. At that time, the precise diagnosis was almost impossible, and the patient was treated for "serum disease" [1]. In December 1996, five other soldiers exhibited nausea, vomiting, associated with multiple skin lesions, some of them necrotic. The patients were at that time treated for a "polyform exudative erythema". In May–June 1997, five more soldiers presented with various skin ulcerations. The diagnosis of radiation injury was established in August 1997 only, by two physicians who had arrived from Moscow.

A first radiation hot spot was detected on August 26, 1997, near the underground shelter. On September 13, 1997, a cesium-137 source, with an activity of 164 GBq, was removed from the pocket of a soldier's winter coat. Since this coat was also used as a blanket by several soldiers, this source was probably responsible for the lesions presented by most of the victims. Another Caesium source, with an activity of 126 GBq, was found buried at about 30 cm deep in the soil of the soccer field. Eight other caesium sources, with much lower activity, were found in various places in the camp. A low-activity Cobalt-60 source, used for calibration, was also found. Finally, about 200 night shooting guides with Radium 226 were discovered at various sites in the camp.

There were eleven accidentally exposed victims [1]. Considering the necrotic lesions, the local doses probably exceeded 25–30 Gy. Mean total body doses were subsequently estimated both with the conventional cytogenetic technique using dicentrics and rings count (in France and Germany) and by Electron Spin Resonance (ESR) obtained from the study of tooth enamel or of bone pieces (in case of finger amputation) in Russia. Table 3.1 shows the results obtained by both techniques for all 11 patients.

TABLE 3.1. INDIVIDUAL (TOTAL BODY) DOSES, GY

Patient	Cytogenetic (corrected)	ESR
1 AN	4.2	No data
2 EP	5.9	4.5
3 CG	1.5	1.4
4 TK	1.1	1.5
5 GL	0.2	No data
6 BZ	0.6	0.7
7 GG	1.1	1.3
8 SO	0.7	0.1
9 ID	4.1	0.4
10 VZ	0.2	No data
11 SN	0.6	0.1

The analysis of these results show that there was an acceptable (and sometimes excellent) agreement between the two techniques, except for patient 9, maybe because of a particular inhomogeneity of the exposure (with low irradiation of the tooth enamel).

3.2. Diagnosis and treatment in the acute phase of the disease or injury

3.2.1. Degree and type of initial injuries for each patient

Patient 1 (AN)
Numerous skin lesions were disseminated on the fingers and were characterized by thinness of the skin, telangiectasias, aponeurotic retractions, fingers blocked in flexion and loss of the index nail. The most severe lesions were radionecrosis of the last phalanx of the right thumb, the pulp of the left thumb and the left middle finger. On the left thigh a 10 cm × 6 cm necrotic lesion was found, surrounded by fibrous tissue, profoundly modified by previous surgery. On the right thigh an 8 cm × 3 cm lesion with a superficial zone of necrosis was found. The front side of the lower part of the thorax presented a zone of fibrosis (6 cm × 4 cm) with depigmentation and telangiectasia.

Patient 2 (EP)
Three cutaneous sub-cutaneous "punched out" round lesions of radionecrosis (3–4 cm diameter) were found on the right musculus triceps brachia as well as on the middle part of the right side of the back and on the right musculus quadriceps femoris, just above the kneecap. Multiple, more or less bleached scars were visible on the whole body (total number 33).

Patient 3 (CG)
The principal lesion was on the anterolateral part of the middle third of the right thigh. Several necrectomies had already been performed without it being possible to cover the wound. An extensive loss of substance was found : the lesion was atonic, superinfected, with necrotic tissue on the surface and a fibrous muscle deep down. It was surrounded by a halo of inflammation but no lymphadenopathy was found. There was severe muscular wasting and a flexion deformity of the hip. The morphological and functional picture seemed poor. The

lateral necrosis area was found to be 12 cm in diameter and the other one at the anterior surface was 2 cm × 3cm. Additionally, retractions due to fibrosis were found in the thumb, index and middle finger of the right hand.

Patient 4 (TK)
Radiation injury was found on the outer part of the right thigh, situated at the junction of the middle third and the lower third of the thigh. This lesion presented as a necrosis of 5 cm diameter, sharply demarcated and pushed out. The adjacent tissues and muscles of the whole thigh were oedematous and tense, indicating that major local/regional extension might occur, with a major inflammatory reaction.

Patient 5 (GL)
At the lower extremity of the left leg, above the lateral malleolus, a 3 cm × 2 cm ulcer was found. It was sharply contoured, with a reddish basis ; it had a yellow coating and was surrounded by an erythema. At the front of the left foot, a white macule was observed of 1.5 cm diameter, irregularly contoured and surrounded by a brown border of 5 mm. In the middle of the white spot several dark brown macules of some 2 mm in diameter could be seen. At the right medial malleolus a 3 cm × 1.5 cm white discoloration with palpable induration was found. Onychodystrophy was noted on the left great toe.

Patient 6 (BZ)
A 7 cm × 2 cm ulcer was found on the right thigh above the knee joint. It was sharply but irregularly contoured with a yellow coating at the basis. An erythema surrounded the ulcer. At the lower extremity of the right leg a sharply contoured white macule of 1.2 cm × 5 cm was found. There was an ulcer of 1 cm × 0.8 cm covered by a central haemorrhagic scab in the lower extremity of the left leg.

Patient 7 (GG)
A 5 cm × 6 cm sharply contoured ulcer with a yellow coating was found on the right thigh. An erythema surrounded the ulcer. In the region of the breastbone, a sharply contoured red spot (macule) of 1.2 cm × 1.4 cm was observed.

Patient 8 (SO)
A sharply and irregularly contoured ulcer of 3.5 cm × 4 cm, with a yellow coating in the centre and surrounded by an erythema, was found on the left thigh.
A sharply contoured white macule of 2 cm diameter was found on the right thigh.

Patient 9 (ID)
In the region of the lower thoracic vertebrae a 2.2 cm × 2 cm ulcer was found: it had a yellow coating and was surrounded by an erythema. Eleven white macules of up to 2.5 cm diameter were observed in the region of the chest, abdomen and back. A white macule of 2 cm × 2 cm with palpable induration was found on the left shoulder. In the right gluteal region an ulcer with a diameter of 0.5 cm was noted.

Patient 10 (VZ)
In the upper area of the right arm, a sharply contoured and deep ulcer of 1.5 cm × 1 cm was observed. It was surrounded by an erythema and induration. Additional diagnosis: pityriasis versicolor.

Patient 11 (SN)
An ulcer of 1.8 cm was found on the left thigh ; it was sharply contoured, flushed, flat and surrounded by an erythema.

3.2.2. Initial management of patients in Georgia

Patient 1 (AN) had to be hospitalized several times in Georgia. In May 1997, a left tight necrectomy was performed at the Russian Hospital of Tbilisi, but a thin skin graft attempt was unfortunately unsuccessful. All the other patients, except Patients 7 and 10, were hospitalized for various periods of time in Georgia. The treatments permitted epithelialization of a number of lesions, which healed completely (usually leaving depigmented scars), while some other skin lesions deteriorated, with a necrotic aspect.

3.2.3. Initial management of patients at the Institut Curie, Paris, France

Two victims (Patient 1 (AN) and Patient 2 (EP)) arrived in Paris on October 22, 1997, and were immediately hospitalized in the Radiotherapy / Radiopathology Department of the Institut Curie [2]. Patient 1 (AN) never left France, where he married in 1998. The numerous lesions (see description above) had to be treated almost continuously from October 1997 to September 1999, with seven hospitalization periods, for a total of 9 months at the hospital. The patient had to be anaesthetized eight different times, these anaesthesias allowing the surgeons to perform 28 different surgical procedures. Patient 2 (EP) remained hospitalized from October 1997 to January 1998, when he could return to Georgia, after three surgical interventions (needing three general anaesthesias) allowing healing of the lesions of the right thigh, of the right arm and of the back.

3.2.4. Initial management of patients in the French Armed Forces Percy Hospital, Clamart, France

Patient 3 (CG) and 4 (TK) also arrived on October 22, 1997 in France. They were hospitalized in the Surgery department (Thermal burns Unit) of the Hospital Percy, a military hospital. To our knowledge, these two patients were the first ones with radionecrosis who benefited from a three-steps graft technique which was initially developed for the treatment of severe deep thermal burns. After complete removal of the radionecrotic tissues, the three steps were as follows :

Step 1: Porcine skin xenograft
Step 2: Xenograft was replaced with a synthetic dermal matrix (INTEGRA)
Step 3: The matrix, colonized by the fibroblasts of the patient himself, was covered with a thin skin autograft.

With satisfactory evolution, the two patients could return to Georgia at the beginning of 1998.

3.2.5. Initial management of the patients at the Federal Armed Force Hospital, Ulm, Germany

The seven other patients (Patients 5 to 11) arrived in Germany on October 29, 1997 [3, 4]. They all benefited from more or less sophisticated surgical procedures adapted to their lesions (see above for details).With satisfactory evolution after surgery, all patients but one could return to Georgia after about two months of hospitalization (end of 1997). For one patient (Patient 6 (BZ)), the German specialists had to face difficult problems, with radiation-induced synovitis of the right knee and associated complications. Four surgical interventions were

necessary for this patient between October 1997 and April 1998. He could only be released in June, 1998, and returned to Georgia.

3.3. Patient follow-up in the delayed period

Patient 1 (AN)
As previously mentioned, this patient had to be treated almost continuously, in hospital or on an outpatient basis, for almost two years, with as many as 28 different surgical procedures. Since September 1999, no complementary treatment was necessary. In 2001, the patient is alive and in good general health, but with very severe hand sequelae (partial amputations of some fingers, finger retractions) which will probably need additional surgery. In spite of severe cosmetic sequelae of the left thigh, there was no major functional impairment and he is able to walk normally. Psychological status, according to his wife and friends, is far from optimal. He has been unable to find regular work until now.

Patient 2 (EP)
After he left Paris in January 1998, the patient had to be rehospitalized and treated several times. In May–June, 1998, he was hospitalized in Obninsk (Russia), where a right thigh lesion, which initially healed, reopened, just above the one treated in France. Surgical treatment (rotation skin flap) was successfully performed by Russian surgeons. Almost one year later, in April–June 1999, the patient had to be rehospitalized in Obninsk for the surgical treatment of three new lesions. In November 1999, he came to Paris (Institut Curie) for a follow-up consultation. He then had to be kept in hospitalization for the surgical therapy of three additional necrotic lesions. He was able to return to Georgia in December 1999. In 2001, a pre-necrotic lesion of the back will possibly have to undergo a new surgical procedure. The patient complains of various symptoms (weakness, nausea, headache) and of a nervous breakdown. He is azoospermic (sterilized by the accidental exposure).

Patient 3 (CG) The patient had to be rehospitalized in Tbilisi (Georgia) in September 1998, for amputation of fingers DI and DIII of the right hand. In 2001, the skin condition is satisfactory (with cosmetic sequelae). The patient complains of weakness, nausea, dyspepsia and depression. Asthenospermia was diagnosed.

Patient 4 (TK)
In April 1999, the patient was rehospitalized in Obninsk (Russia) for a localized secondary ulceration in the area which was grafted in France (see above). This secondary radionecrosis was successfully treated by a skin graft. In 2001, the skin condition can be considered as satisfactory (with sequelae). The patient also complains of weakness, nausea, headache and depression. He is oligospermic.

Patient 5 (GL)
In July 1998, a complementary surgical treatment of a previously treated lesion of the left malleolus was necessary in Obninsk (Russia).

Patient 6 (BZ)
No complementary treatment was necessary for this patient after his initial treatment in Ulm (Germany). In 2001, the skin condition is satisfactory (with cosmetic sequelae). The patient is oligospermic. He complains of general weakness, but his psychological status is correct.

Patient 7 (GG)
In July 1998, a recurrent radiation ulcer (right thigh) required surgery in Obninsk (Russia). In 2001, the skin status is correct, the patient is oligospermic and complains of general weakness and depression.

Patient 8 (SO)
No complementary treatment was needed after the initial treatment in Ulm. In 2001, the skin condition looks satisfactory. The patient is oligospermic and complains of general weakness. His psychological status is correct.

Patient 9 (ID)
In July 1998, a recurrent radiation ulcer of the left shoulder had to be surgically treated in Tbilisi (Georgia) and then in Obninsk (Russia). In 2001, several skin lesions still pose a problem and will possibly have to be treated. Patient is oligospermic. He complains of general weakness, headache, dyspepsia. His psychological status is correct.

Patient 10 (VZ)
No complementary treatment was needed. In 2001, the skin condition is satisfactory. The patient presents asthenospermia. He also complains of general weakness, headache, dyspepsia and depression.

Patient 11 (SN)
No complementary treatment was needed after the initial management in Germany. In 2001, his skin condition is satisfactory. The patient shows asthenospermia. He complains of weakness, headache, dyspepsia and depression.

3.4. Conclusions

After the initial treatment in France and Germany, the eleven patients could reasonably be considered cured, or at least consolidated. However, subsequent follow-up confirmed the appearance of delayed health effects, and the necessity for consequent medical support. Overall, seven patients, among eleven, had to be rehospitalized (sometimes several times) for complementary treatment(s). This was linked either to the recurrence of radionecrosis in a previously treated area, reopening or to the emergence of new radionecrotic lesions in areas previously not treated in France or Germany.

Consequently, the main lessons learned from this accident are :

(1) Skin lesions which spontaneously healed and appeared stable at the initial examination can deteriorate, with secondary reopening, a long time (months-years) thereafter.

(2) Satisfactory initial surgery did not prevent in all cases some secondary (often localized) radionecrotic ulcerations that should be followed up for a year, or even years.

(3) A number of sequelae were responsible for a severe impairment of the quality of life of the patients; functional sequelae (finger amputations…) for some of them, cosmetic sequelae for almost all patients, oligo or azoospermia in all cases, and various psychomatic symptoms and nervous breakdowns. Hence, attention should be paid to general health status of patients what should be monitored properly for a long period (years) involving immunological treatment and psychotherapeutical methods.

(4) These patients are at an increased risk for secondary malignancies (leukaemias, myelodysplasias, solid tumors). Long term annual follow-up, up to 15–20 years and probably more, is therefore mandatory for all eleven victims of the Lilo accident.

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Chapter 4

MEDICAL FOLLOW-UP OF THE LOCALIZED RADIATION INJURIES OF THE VICTIM OF THE PERUVIAN RADIATION ACCIDENT

M. Zaharia, L. Pinillos-Ashton, C. Picon, A. Heredia, M.E. Berger, R.E. Goans, R.C. Ricks, I. Turai

4.1. Description of the accident

The accident happened on 20 February 1999 at the Yanango hydroelectric power plant, which is located in jungle in the San Ramon District of Junin Department, approximately 300 km east of Lima. On the morning of Saturday 20 February 1999, a welder and his assistant started to repair a weld of a 2 m diameter pipe. At 13:00 both went for lunch.

The welder and his assistant came back from lunch at 14:00 and continued with the repairs to the pipe. One hour later, the radiographer started to use ultrasonic test equipment to examine the pipe, but the equipment failed and it could not be repaired. At some time during the day the source became detached from the camera. At approximately 16:00, the welder picked up the unshielded ^{192}Ir source, with his right hand and placed it in the back right pocket of his trousers (at the time of writing the investigation has not established how the source came to be outside the camera).

After the welder had picked up the radioactive source he continued to work, spending much of the time in the pipe. He claims that he was sitting working and changing of position that he did not determined well. He was wearing loose fitting denim jeans and at around 21:00 he felt a pain in the back of his right thigh. He left work at approximately 22:00 and took a minibus home. The ride lasted about 30 minutes and there were 15 other people in the minibus.

When the welder arrived home at approximately 22:30, he reportedly complained to his wife about the pain and she looked at his posterior right thigh and noted a red area of skin. He took off his jeans and, with the source still in the pocket, placed them on the floor. He visited a local doctor who told him he had an “insect bite” and that he should put a hot compress on the area. The welder´s wife meanwhile spent about five to ten minutes squatting/sitting on the jeans where the source was, while she breastfed their 18-month-old child. Two other children who were at home, a girl of ten and a boy of seven, were about two to three metres from the source for approximately two hours. After discussing his pain with his wife, the welder remembered the source in his jeans pocket, took it out with his right hand and carried it to the bathroom which was about four metres away outside the house (at approximately 23:00 hours).

At 01:00 on 21 February, the operator of the company arrived at the welder´s home and asked whether he had seen the source. The welder went to the bathroom and carried the source in his hands to the door. The radiographer told him to throw the source onto the street and recovery actions were initiated [1].

The event was notified to a staff member of the Technical Office of IPEN at 10:20 on Sunday, 21 February. He contacted the radiation physicist of IPEN and the head of the Radiotherapy Department of the Instituto de Enfermedades Neoplásticas (INEN) in accordance with and

agreement to assist radiation injured patients. At 13:30 The welder was admitted to hospital, 20 hours after. In the INEN Doctors initiated a medical examination of the welder and other potentially exposed persons. Clinical analyses were performed (blood counts of all persons) The first conclusion was that only the welder had been severely exposed.

4.2. Diagnosis and treatment in the acute phase of the injury in Peru

On February 21, 1999, the patient was admitted to the National Cancer Hospital (INEN) in Lima approximately 20 hours after exposure to the radioactive source. The hospital physicians noted, during the physical examination, an area of erythema on the patient´s right upper posterior thigh. He was immediately given hydration (Glucose intravenously, 2 L in the first 24 hours and then 1 litre per day for 20 days) and a course of Ciprofloxazin (500 mg orally every 12 hours) and Dexamethasone (8 mg intravenously every 8 hours). He also received a Naprosyn-like compound for pain relief. On February 22, day 2 after irradiation, a blistering lesion surrounded with large inflammatory halo appeared on the mid-upper line of the rear surface of the right thigh (Photo 4-1 in the Annex).

Next day, the blister became larger (4 cm × 1 cm to 5 cm × 1 cm) at the junction of the thigh and the buttock. The first bone marrow aspiration from iliac crest proved changes compatible with reactive type granulocytic hyperplasia with severe deviation to the right. Initial dosimetry was performed by the Peruvian physicists on the third day of the patient´s admission using the Prowess 3000 treatment planning computer system (Table 4.1). On February 24, a drastic reduction in the lymphocyte count was observed (Table 4.2).

On February 25, erythema of the posterior right thigh and blistering lesion 4 cm × 4 cm was noted. The patient was switched to Clindamycin (300 mg/8h) and Ciprofloxazin (dosage increased to 750 mg/12 h) .

TABLE 4.1. DISTRIBUTION OF DOSES BY DEPTH AS CALCULATED BY INEN (PERU)

Organ-Distance	Dose (cm)	(Gy)
Skin	1	9966
Soft tissue	2	2508
Soft tissue	3	1110
Soft tissue	4	617
Soft tissue	5	388
Soft tissue	6	265
Soft tissue	7	191
Femur	8	143
Femoral artery	8	143
Soft tissue	9	111
Soft tissue	10	88
Gonads	18	23
Bladder	20	18
Rectum	20	18
Thyroid	90	-

On February 26, a computed tomography (CT) scan was performed and revealed a markedly swollen right thigh with extensive subcutaneous oedema, loss of the posterior fascial margins and swelling of almost all muscle groups of the thigh, centred between 10 and 20 cm below the hip X ray of pelvis and bones revealed no bone or joint lesions. On March 1, extended superficial erosion surrounded by a large dusky (hyperpigmented) inflammatory area in the rear surface of the right thigh on day 9 (Photo 4-2).

TABLE 4.2. HAEMATOLOGICAL EVOLUTION

		HAEMATOLOGY			
	Normal range	Leucocytes 4000–11000	Lymphocytes 1500–4000	Neutrophils 2500–7000	Platelets 100 000–400 000
	Day 1 (20 Feb. 99)	7600	1 500	6000	250 000
	Day 2 (21 Feb. 99)	7100	1 064	5822	248 000
	Day 5 (24 Feb. 99)	6000	120	5880	252 000
	Day 8 (27 Feb. 99)	4200	42	4074	294 000
	Day 10 (01 Mar.99)	3800	304	3420	280 000
	Day 11 (02 Mar. 99)	3700	111	3515	
	Day 13 (04 Mar. 99)	5000	200	4650	239 450
	Day 15 (06 Mar. 99)	5200	312	4784	240 000
	Day 17 (08 Mar. 99)	6000	300	5580	232 000
	Day 20 (11 Mar. 99)	5200	52	5096	
	Day 22 (13 Mar. 99)	5800	290	5220	
	Day 26 (17 Mar. 99)	4100	205	3854	147 000
	Day 31 (22 Mar. 99)	3100	310	2759	
L	Day 34 (25 Mar. 99)	1500	30	1440	99 900
E	Day 35 (26 Mar. 99)	2500	175	2275	152 000
U	Day 36 (27 Mar. 99)	2000	340	1580	157 500
C	Day 37 (28 Mar. 99)	4000	160	3720	109 000
O	Day 38 (29 Mar. 99)	4200	420	3696	210 000
M	Day 39 (30 Mar. 99)	3600	540	2988	156 000
A	Day 40 (31 Mar. 99)	7900	474	7347	
X	Day 41 (01 Apr. 99)	8200	410	7708	112 000
	Day 42 (02 Apr. 99)	6100	854	5002	164 000
	Day 43 (03 Apr. 99)	8500	425	7990	187 300
	Day 44 (04 Apr. 99)	13 200	792	11 748	326 400
	Day 45 (05 Apr. 99)	18 100	1 810	15 385	238 500
	Day 46 (06 Apr. 99)	11 400	1 368	9234	360 000
	Day 47 (07 Apr. 99)	7300	1 460	5256	272 000
	Day 49 (09 Apr. 99)	8800	1584	6512	343 000
	Day 50 (10 Apr. 99)	25 700	771	24 158	377 000
	Day 51 (11 Apr. 99)	20 000	2000	14 400	469 000
	Day 52 (12 Apr. 99)	12 100	1210	9922	562 000
	Day 56 (16 Apr. 99)	8000	1840	5840	685 000
	Day 59 (19 Apr. 99)	13 400	1340	11 524	666 000
	Day 61 (21 Apr. 99)	15 900	1431	12 879	698 000

Table 4.2. (cont.)

	HAEMATOLOGY			
Normal range	Leucocytes 4000–11000	Lymphocytes 1500–4000	Neutrophils 2500–7000	Platelets 100 000–400 000
Day 62 (22 Apr. 99)	11 800	118	11 682	582 000
Day 66 (26 Apr. 99)	13 400	670	11 524	520 000
Day 70 (30 Apr. 99)	13 900	556	12 232	
Day 72 (02 May 99)	13 500	540	12 555	696 000
Day 75 (05 May 99)	11 200	1120	9856	759 000
Day 82 (12 May 99)	7100	1278	5467	629 000
Day 87 (17 May 99)	8300	581	7470	
Day 91 (21 May 99)	8700	348	8178	468 000
Day 98 (28 May 99)		Transfer to France		

Physical examination on March 6, revealed a superficial ulcerated lesion 8 × 8 cm, surrounded by a dark halo of 12 × 12 cm with the subcutaneous tissue being indurated, and the presence of genital herpes lesions. On March 9, administration of Ciprofloxazin was suspended. Zinnat 500 orally three times a day and Acyclovir (Zovirax) one tablet every 8 hours was started. The patient was experiencing intensive pain that made it difficult for him to move his right leg. On March 15, hyperpigmented reaction of the lesion on day 23. The lesion edges were well defined and the skin was peeling off in some areas surrounding the central lesion. The patient had begun to complain of numbness in the outer right thigh and hypersensitivity in the inner part. The herpetic lesions, disappeared in a week, so administration of Zinnat and Zovirax was suspended.

One month after the accident, the patient's deteriorating health was evident [2]. He had lost 7 kg in weight, was in intense pain, laid on his left side almost all the time. Nerve involvement was suspected and subsequently diagnosed with nerve-conduction studies. Clinically, the patient now presented with a sensory deficit present in the outer right thigh and hypersensitivity on the inner aspect. On his right thigh there was a 10 × 10 cm lesion which was 2 cm deep. The subcutaneous fat was undergoing necrosis and the underlying muscle was faintly visible. The edge of the lesion was dark and firm. The lesion appeared to be a superinfected ulcer covered with a fibrin crust (Photo 4-3).

A team of US experts, recruited by the IAEA at the request of the Peruvian Government [1], arrived on March 19 to consult with the Peruvian physicians regarding details of the accident, treatment protocols, lessons learned, etc. The team noted the slightly depressed blood counts indicating low level whole body irradiation, estimated to be between 1 and 3 Gy [2]. Upon observation of the wound and surrounding area, body hair was noted to be firmly attached in the perineal region and to the skin of the leg just below the wound. This observation was significant for biological dosimetry purposes because epilation usually occurs about three weeks after an exposure greater than 3 Gy. The team at this time discussed the potential need for a right hemipelvectomy which was suggested by the main author, and noted that surgeons experienced in the procedure were available in Peru**.** Although a majority of the IAEA team

and the Peruvian physicians felt this procedure would be necessary, the team elected to defer the procedure until the patient's haematological status improved because the patient was approaching the nadir in blood counts. In addition, they recognized discrepancies between biological effects observed and the calculated doses. In this time period, the source was calibrated and found to be somewhat less than the 1.37 TBq originally reported. Measurements indicated that its activity was approximately 0.962 TBq (26 Ci).

Uretro-cystoscopy was done on March 23, showing normal mucosa in the bladder. *Radiation neuropathy of the sciatic nerve on the right side* was diagnosed. For this reason continuous infusion of morphine to the patient was performed in order to relieve the pain.

By March 24, vesicles and blisters in the proximal third and medium part of the second and third fingers of the right hand were found. On the following day, electromyography was done which showed denervative signs of the sciatic right nerve of the subacute type incipiently affecting the peroneal and tibial branches. The nadir of all peripheral haematological parameters was observed.

On March 26, second Bone marrow aspiration from iliac crest: bone marrow with severe hypoplasia corresponding to significant exposure to radiation of this area of the body. It was necessary to fix an epidural catheter because of severe pain. Administration of haematopoietic granulocyte colony stimulating factor (G-CSF Leucomax, 300 micrograms per day) was started.

On March 30, the patient had fever (39 C) for the first time. The necrotic ulcer appeared to be infected with pus. The culture of pus was positive for klebsiella and Streptococcus aureus. The patient received Clindamycin (600 mg intravenously, every 8 hours) and Cefoterazone Sulbactan (7.5 g intravenously every 12 hrs). By March 31, physical examination revealed ulcerated lesions of both gluteal regions and scrotum. On the right hand there were erythema of the hypotenar and vesicles on the palms.

By April 2, Leucomax was stopped owing to an observed significant rise in white blood cell counts. On April 5, the patient presented melena. A gastroscopy was done and erosion and haemorrhage were detected in the prepyloric area. Citomegalovirus in glandular cells of the stomach was found. A stress gastric ulcer was diagnosed. The patient was put on inhibitors (150 mg tablets of Ulceran were give orally every 8 hours) the level of testosterone was significantly reduced to 29 ng/dL (normal values are 300–1000 ng/dL in adult men).

On April 7, haemoglobin decreased to 7.9 g/L (the normal value is 15–17 g/L at the high altitude of the patient´s residence) and whole blood transfusion (two units) were performed. Infection of the liquor was infected with Streptococcus epidermitis was detected and the patient was given Vancomycin (1 g intravenously every 12 hours). On 10 April the second whole-blood transfusion (two units) was performed.

On April 13, blistering of the right hand palmar surface of the 2^{nd}, 3^{rd}, 4^{th}, and 5^{th}, fingers on day 52 **(**Photo 4-4). By 16 April magnetic resonance imaging (MRI) of the pelvis and thighs was carried out: diffused oedema was found to be most expressed in the superior limit of the psoas muscle, the iliac, and the muscles of the right paravertebral area. There was a major swelling of the gluteus muscles and the medial and posterior compartments of the thigh. At this level an ulcerated lesion was observed. The oedema went down to the soft tissues of the knee joint. At the level of the bone marrow there was discrete oedema of the right iliac bone. No significant changes of the femur bone marrow were found by MRI.

A culture of pus secretion was made on 19 April of the necrotic ulcer: it contained Enterobacter and Staphylococcus aureus. Amikacyne was started (1 g intravenously every 24 hours). At this time (on day 60) local radiation injury (erythema and dry desquamation) developed in the inferior external part of the right leg.

On April 23, the third bone marrow aspiration from sternum showed hyperplasia as a compensatory reaction of non-irradiated bone marrow. On May 3, the huge necrotic lesion (30 × 20 cm) went deep into the muscular layers, requiring surgical debridement of the right thigh (Photo 4-5).

On May 11, the pathology report confirmed Lozenge (rhombi) of skin and subcutaneous tissue of size 15.5 cm × 12 cm × 2.5 cm including a deep ulcer of 13.5 cm × 10 cm with irregular borders in which fibrin and necrotic tissue were seen. The deep ulcer involved the thigh muscles. *Microscopic report* besides ulcers with extensive post-radiation necrosis of the skin, subcutaneous fat and striated muscular tissues, there was also vasculitis, fibrosis and degeneration of the superficial nervous branches on the surface and surgical borders. Treatment sessions in a chamber of hyperbaric oxygen were started. The patient went to the hyperbaric oxygen chamber for one hour daily for the next 20 days.

On May 21 electromyography revealed worsening of the lesion of the sciatic nerve which caused chronic and progressive suffering. There was no functional innervation of the muscles dependent on the peroneal nerve and posterior tibial nerve. The patient was put on Tegretol 200 mg three times per day to relieve pain.

On May 25, the report of the cytogenetic study of bone marrow showed normal chromosomes (46 X,Y), however, the cell count in the sample was very poor.

Meanwhile, the pathology report and slides were sent to medical consultants at REAC/TS in the USA and a right hemipelvectomy was again advised, along with triple antibiotic therapy. However, surgical intervention was postponed because of the risk of sepsis. Despite surgical debridement, antibiotic therapy, and hyperbaric therapy, there was no sign of healing, and the patient was in constant need of medication for severe pain.

4.3. Treatment in the subacute period in France

On Day 91 after exposure, the patient was transferred to the Burn Treatment Centre of the Percy Hospital in Paris, France, according to the offer of the French Government. The treatment strategy in Paris was to use the latest artificial skin-graft techniques, which had been used with success in a previous radiation accident (Lilo, Georgia). At this time, the massive radionecrosis of the posterior thigh now extended to an area 30 × 40 cm, with swelling, infection, necrosis, serous leakage, and an inflammatory border. Pain control for this patient continued to be a serious clinical issue.

Subsequent surgical exploration and debridement of the area revealed that the lesion had extended to the femur and to the sciatic nerve. Porcine xenografts, applied on June 1 and July 8, failed to stimulate granulation, and a purulent necrosis developed despite intensive antibiotic therapy. On August 16 (Day 170) the right hip was disarticulated and a left iliac colostomy was performed, unfortunately the surgical specimen was disregarded and no pathology and electron spin resonance dosimetry were done. The patient left the Burn Centre on Day 205 after the accident for transfer to a rehabilitation centre. By late September, the radionecrosis and superficial infection had extended to the perineum, including the anal

sphincter and scrotum. In addition to the perineal radionecrosis, the patient developed a urethro-vesical fistula, which subsequently required urethral reconstruction. On Day 230, Oct. 17, 1999, the patient was returned to Peru because of the gravity of both his psychological and his physical conditions.

4.4. Follow-up in the delayed period in Peru

Upon arrival in Peru, the patient was found to be profoundly depressed and in poor pain control. By November 10, the patient had received a intratecal application of phenol with good success. He was also able to be relieved from narcotics because of the success of the phenol application. However, at this time, the perineal area became infected with *Klebsiella* and drug-resistant *Pseudomonas*, apparently nosocomial. Blood cultures were negative, and the patient was begun on Imipenem (1g each 8 hours IV) for 14 days.

In Dec. 1999 the entire perineum contained large infected ulcerated lesions (Photo 4-6). Following repeated debridements an urethral fistula has developed (Photo 4-7). Infected ulceronecrotic lesions were also noted on the distal aspect of the left leg and on the ankle (Photo 4-8) which reopened in April 2000 (Photo 4-9). At that time, surgeons in Lima did not feel that a graft could be successful and opted to perform local wound care with sequential debridement.

In May of 2000, the patient was transferred from Lima to an intensive care unit in a hospital near his home town (Arequipa). Because of severe psychological issues, close family contact has proven to be of significant therapeutic value.

Therapy to date (Oct. 2001) has included local wound care. This therapy has been successful; some granulation tissue has formed around the edges of the perineal wound leading to some closure of the necrotic perineal area with formation of granulation tissue and progressive fibrosis.

4.5. Follow-up of the radiation injury of the patient's wife

On the evening of the and prior to discovery of the ^{192}Ir source accident (20 Feb. 1999), the patient's wife sat on the jeans containing the source for 20 to 30 minutes while she nursed their 18-month old child. She subsequently developed a circumscribed area of wet desquamation in the S4-S5 posterior dermatome. At the end of March 1999, dry desquamation extended as far as the lateral edge of the S1 dermatome (Photo 4-10). This area has healed moderately well with local wound care, but the patient has experienced delayed tissue necrosis and scarring by Oct. 1999 (Photo 4-11).

Photo 4-12 illustrates most of the delayed effects of her acute local radiation injury in May 2001: a central area of necrotic soft tissue, extensive peripheral fibrosis, dilated superficial capillaries, small veins and arteries (telangiectasia), and a fragile epidermis. The patient required surgical treatment in June 2001, and is being followed regularly (Photo 4-13). She had no complaints because of her treated radiation injury, which healed well, in Dec. 2001.

4.6. Comparative dose estimates

Because of the unusual health physics issues presented in this case, dosimetry estimates have been performed by Instituto de Enfermedades Neoplásticas (INEN; Peru), Institut de

Protection et de Sûreté Nucléaire (IPSN; France) and REAC/TS. Initial theoretical dosimetry studies were performed using the Prowess 3000 treatment-planning computer system by INEN, Lima (as discussed in Section 4.2). Monte Carlo simulation of organ dose has been performed by IPSN with a mathematical phantom and the well-established code Morse. A similar simulation was performed by REAC/TS staff with the more recent code MCNP 4b implemented on the adult anthropomorphic MIRD phantom. Table 4.3 presents preliminary results of these calculations.

In general, dosimetry for this accident should be considered approximate because of the complexity of the source-organ geometry and the uncertain time-dependent spatial position of the industrial radiography source. However, there is reasonable agreement on most dose values where it is possible to make a direct comparison. The MIRD phantom does not appear to be well suited for gonad dose from this geometry because of the over-attenuation of ^{192}Ir photons and the lack of consideration of potential streaming effects. The gonad dose from the MIRD model here is, therefore, likely an underestimate. Research to further refine these dose values with a more anatomically correct mathematical phantom is under way [3].

TABLE 4.3. CALCULATED ORGAN DOSES (Gy)

Organ	INEN (Peru)	IPSN (France)	REAC/TS (USA)
Skin	9966	11 752	10 080
Sciatic nerve	—	25–30	25–35
Femur/femoral artery	143	188	80–120
Sigmoid Colon	—	—	22
Gonads	23	28	11
Bladder/rectum	18	21	16

4.7. Conclusions

There are a number of unusual aspects of this accident. While the calculated doses were higher than the biological and clinical indicators would suggest, there were uncertainties in source location and duration of exposure. There were major discrepancies in the calculated organ doses and the doses assessed in biological (cytogenetic) and clinical dosimetry. One good explanation for the difference is the unstable location of the source over the thigh and the marked inhomogeneity of exposure. The bone marrow in the skull, cervical spine and upper thorax have likely had enough stems cells to prevent severe marrow depression.

The local tissue reaction also was less than expected. The patient was treated with dexamethasone until approximately day 30 post-exposure. It was stopped at that time due to infection of the wound, and the necrosis and radiation induced changes around the wound and perineum. Dexamethasone appears to have played a role in decreasing the early clinical effects but it does not seem to have affect on long term outcome. It is not clear whether early

hemipelvectomy would have affected the outcome, although it would have saved the patient´s long, painful and expensive hospital course.

This is one of the first case of local radiation injuries in which cytokines were used. Most cases of local radiation injury do not have significant bone marrow depression. G-CSF was given at day 34 post-exposure but whether this had a beneficial effect in this case is unclear for some experts. A number of authors feel that the response to cytokines depends on the degree of the injury. In our opinion, the depression of bone narrow is dose dependant, for this reason more damage will influence to the bone marrow and will be expressed in the peripheral blood examination as can be seen in Table 4.2.

4.8. Lessons learned

There are uncertainties associated with physical dose estimates based on the observed biological effects. These uncertainties could have been diminished if histopathological and electron spin resonance studies had been carried out on the tissues from the amputated leg. Unfortunately, the amputated tissue had been discarded and was unavailable for study.

Amputated tissue from highly exposed persons can provide an additional source of dose information that could help in the subsequent treatment of the patient. Care needs to be taken to ensure that such tissue samples are kept until it is certain that they are no longer required.

Hemipelvectomy was considered three weeks post-exposure and prior to involvement of the perianal region, but a decision was made to delay the procedure and to graft over the lesion in an attempt to save the irradiated limb. The grafting techniques failed and the limb was amputated a few months later. While it is not possible to know whether early hemipelvectomy would have prevented involvement of tissues of the perianal region, physicians in charge of patient care in any similar accidents in the future should give careful consideration to *extensive surgical therapy*, taking into account physical and biological dosimetry and consulting experts with experience in localized radiation injuries.

Psychological support provided by the family is a very strong additional factor of treatment efficiency even in very severe cases having bad prognosis. Thus, the sooner return of the radiation accident patient to his/her place of habitat is urged and recommended.

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Chapter 5

FOLLOW-UP OF DELAYED HEALTH CONSEQUENCES OF THE ISTANBUL RADIOLOGICAL ACCIDENT AND LESSONS TO BE LEARNED FROM ITS MEDICAL MANAGEMENT

B. Günalp, K. Ergen, I. Turai

5.1. Short description of the accident

5.1.1. Place, date, circumstances

A serious radiological accident occurred in Istanbul, Turkey, in December 1998. Two transport containers, one had a spent ^{60}Co radiotherapy source, were transferred in February 1998 from licensed premises in Ankara to unauthorized premises in Istanbul. After several months the premises were sold together with the source transport containers. The new owners, not realizing what was in the packages, sold them as scrap metal. Ten scrap metal dealers started to dismantle the containers on 13 December 1998. The steel shell of containers was peeled off using oxyacetylene torch, mechanical tools and also an excavator. They managed to open the containers. Shortly after they removed shielding plug and drawer assembly, six of them had nausea that rapidly progressed to vomiting and stopped working. They thought their sickness was due to lead poisoning and they buried lead containers but the source remained at the junkyard, adjacent to the family house two weeks. On 27 December 1998, the scrap metal, including the source, was loaded onto a truck by hand and with a shovel, and taken to a large scrap metal dealer in the same area. The source remained at this second junkyard under a pile of scrap metal till its recovery on 10 January 1999 [1].

5.1.2. Radioactive source

The radioactive source, cause of the accident, contained ^{60}Co and its activity at the time of the accident was 3.3 TBq (91 Ci). The source capsule was intact and there was no contamination.

5.1.3. Number of victims, estimated individual doses

Based on clinical and haematological findings acute radiation syndrome (ARS) was diagnosed in ten adults. Their doses were estimated to be between 3 and 5 Gy for the first five adults, about 2 Gy for patients No. 6 and 7, and about 1 Gy for another three persons. The owners of the second scrap yard, three persons, received doses between 0.4 and 0.8 Gy.

5.1.4. Degree and type of initial injuries

All patients were exposed externally. Five patients developed a moderate degree of ARS. One of them also had acute local radiation injury on his right hand. Five patients developed a mild degree of ARS.

5.2. Diagnosis and treatment in the acute phase of the radiation disease and injury

5.2.1. Methods applied prior to admission at hospital

Six out of the ten persons who were present during the dismantling (either working or observing) felt unwell, started to vomit and these symptoms continued all night. On the next day they went to a nearby private clinic where they were treated symptomatically as food

poisoning was the first diagnosis. The accident victims repeatedly consulted different medical doctors over the following 4 weeks, complaining of weakness, emesis, diarrhoea, and/or loss of appetite. Nevertheless, haematological check-ups were not performed and radiation sickness was not suspected.

On 8 January 1999 two scrap collectors who were feeling sick, 2-N.I. and 5-I.I., applied to another private hospital, where radiation sickness was first suspected and reported to Çekmece Nuclear Research and Training Centre (ÇNAEM). The radiation accident was confirmed on the same day. On 9 January 1999 the first blood samples were taken from the above mentioned two patients, as well as from person 7-A.I and G.I. (the visiting son and wife of 5-I.I.) for cytogenetic dose assessment by the Biodosimetry Laboratory of CNAEM.

On 9 January, the above mentioned three patients (No. 2-N.I, 5-I.I. and 7-A.I.) were transferred to the state owned Haseki Hospital. Four other adults (1-M.I., 4-K.I., 9-A.S. and 10-E.D.) who had also participated in the dismantling of the containers four weeks earlier and had some discomfort and weakness since that time, were also admitted to the same hospital. During the next two days 4 more adults (11 in total) and 7 children were admitted to the Haseki State Hospital with suspicion of overexposure. After completion of their haematological and biodosimetric examinations, one adult (A.Y.) and 7 children were discharged from the hospital as no evidence of overexposure had been found.

From 9 to 15 January, 404 persons concerned about their possible exposure applied for medical or haematological check-up as a result of information issued by CNAEM and the media reports about the accident. Triage was made according to the patients' lymphocyte, granulocyte and platelet counts.

5.2.2. Diagnosis and treatment methods applied in the hospital

According to patients blood counts ARS was diagnosed in 10 patients. Their detailed initial blood counts from 9 and 10 Jan. 1999 are given in Table I together with the patients' codes. The white blood cell counts of Patients 1, 2, 3, 4, and 5 were at a level of about 10% of the mid-value of the normal range, lymphocytes were not detectable, while platelets were as low as 1–3% of normal values [2].

TABLE 5.1. INITIAL BLOOD COUNTS OF THE ISTANBUL RADIATION ACCIDENT VICTIMS ON THE DAY OF THEIR HOSPITALIZATION

Patients' code	Date of hospitalization	White blood cells ($\times 10^3/\mu L$)	Lymphocytes ($\times 10^3/\mu L$)	Platelets ($\times 10^3/\mu L$)	Hb (g/100 mL)	Hct (%)
1-M.I.	09-01-99	0.6	ND	1.0	8.8	25.5
2-N.I.	09-01-99	0.4	ND	6.0	8.6	26.5
3-H.I.	10-01-99	0.4	ND	1.0	9.8	31.2
4-K.I.	09-01-99	0.9	ND	3.0	7.4	22.5
5-I.I.	09-01-99	0.3	ND	1.0	9.6	30.0
6-H.G.	10-01-99	1.4	0.6	17.0	11.0	34.6
7-A.I.	09-01-99	3.0	0.7	32.0	11.3	36.0
8-H.S.	09-01-99	5.0	1.9	61.0	14.0	44.0
9-A.S.	11-01-99	3.8	1.0	26.0	14.0	38.0
10-E.D.	11-01-99	3.7	1.2	40.0	13.3	37.4
Normal range ($\times 10^3/\mu L$)		4.3–11.0	1.5–4.0	150–350	14–18	43–52

ND = not detectable

On 12 January 1999, the five most severely affected patients (No. 1–5.) were transferred from the Haseki Hospital to strictly isolated single rooms at the Department of Haematology of the Cerrahpasa Medical Faculty of Istanbul University. Bone marrow biopsy was performed from patients 1–5 on 13 January 1999 and showed severely hypocellular bone marrow.

Blood samples were taken for cytogenetic dosimetry by Cekmece Nuclear Research and Training Centre (CNAEM) Istanbul, Turkey on 9 and 11 January; Institute for Protection and Nuclear Safety, (IPSN), Clamart, France; National Radiological Protection Board, (NRPB), Chilton, UK and Department of Radiation Genetics and Chemical Mutagenesis, Leiden University Medical Centre, (LUMC), Leiden, The Netherlands on 13 and 14 January. Blood samples from ten patients with confirmed acute radiation syndrome (ARS) were conveyed to each institute where they were processed by the laboratories' routine procedures. In addition CNAEM examined a further 20 subjects who were assessed to have received lower exposures.

All laboratories undertook routine analysis for dicentric chromosome aberrations; additionally IPSN and LUMC carried out micronucleus analysis; IPSN, NRPB and LUMC also examined translocations using fluorescence *in situ* hybridisation (FISH). The biological dose estimates based on the frequencies of dicentric chromosomes and micronuclei indicated whole body doses between 2 and 3 Gy in Patients 1, 2, 3, 4 and 5, about 2 Gy in Patient 6-H.G. and a dose range between 0.5–1.0 Gy in Patients 7–10. Translocation aberration analysis was performed using FISH technique and it was shown that the dose estimates derived from translocations are about 20% higher than those from dicentrics (Table II). This could indicate that over the first month the dicentric — and micronuclei — yields did indeed reduce and thus the dose values estimated by dicentrics and micronuclei may be underestimate the doses by about 20%.

5.2.2.1. Treatment of patients at the hospital:

The massive platelet transfusions were applied during the first week of hospitalization to prevent any severe bleeding. In addition to platelet transfusions, whole blood and erythrocyte transfusions were also carried out, as shown in Table 5.3.

TABLE 5.2. PROTRACTED DOSE ESTIMATE ON THE BASIS OF ANALYSES OF TRANSLOCATIONS AND DICENTRICS

Patient	Dose, Gy, based on	
	Translocations	Dicentrics
1-M.I.	2.8	2.2
2-N.I.	3.2	2.3
3-H.I.	3.9	3.1
4-K.I.	3.0	2.5
5-I.I.	2.7	2.5

TABLE 5.3. NUMBER OF UNITS OF BLOOD COMPONENTS TRANSFUSED TO PATIENTS 1–5 AND 7 WITHIN 12 DAYS

Patients' code	Whole blood	Platelets	Erythrocytes
1-M.I.	1	14	5
2-N.I.	1	22	3
3-H.I.	1	3	0
4-K.I.	2	19	8
5-I.I.	6	31	0
7-A.I.	1	9	0

Patients 1–5 were treated in a similar manner with the same antibacterial, antiviral and antifungal drugs and dosages of cytokines. The total dose of G-CSF used for bone marrow stimulation between 12–23 Jan. 1999 was 48 million units (48 M U) for patients 1–5 (8 μg/kg/day), while for patients 6–7, who were in less severe condition, a daily dosage of 5 μg/kg was applied and in total 30 M U was administered. Single additional dose (48 million Unit/day) administrated to P4 due to WBC counts drop to 1800/mm^3 on 31 January 1999.

The daily doses of antibacterial, antiviral and antifungal drugs administered to patients 1–5 for the three weeks from 12 January to 1 February are given in Table 5.4. These proved to be very effective in the prevention of infectious complications.

TABLE 5.4. MEDICATION ADMINISTERED TO THE ARS PATIENTS TO PREVENT INFECTIOUS COMPLICATIONS

12–22 Jan. 1999	Meronem (Meropenem), iv 3 × 1 g Amikasin (Amikacin), iv 1 × 1 g Vancocin (Vankomycin), iv, 3 × 500 mg Acyclovir (Zovirax), iv, 3 × 250 mg Triflucan (Flukanazol), iv, 1 × 200 mg Bactrim forte (Trimethoprim-sulfamethoxazale), po, 2 × 800/160
23 Jan.–01 Feb. 1999	Cipro (Cyprophloxacine 1x1), p.o., 2 × 500mg Triflucan (Flukanazol), iv, 1 × 100 mg Bactrim forte (Trimethoprim-sulphamethoxazale), po, 2 × 800/160

5.2.3. Duration and places of hospitalization

The five most severely affected patients were hospitalized at the Department of Haematology of the Cerrahpaşa Medical Faculty Hospital for 45 days. The five other mild degree ARS patients were hospitalized at the Haseki General Hospital between 15 to 40 days.

5.2.4. Results of treatment of the acute phase of the disease

By 24 January (following a 12–14 day hospitalization period):

- the bone marrow of all ten patients had recovered and the cytokine (G-CSF, Neupogen) therapy was stopped after 11–12 days of administration in Patients No. 1–4 and after 6 days in Patients No. 5–7,

- none of the patients needed any more transfusion of blood components,
- none of the ARS patients became systemically infected and all had a good prognosis.

Three of the patients were discharged from the Haseki Hospital on 25 January.

5.3. Follow-up in the delayed period

5.3.1. Frequency of medical examinations (in-patient or out-patient)

The patients were followed-up once per month for the first three months, once every three months during the first year and once every 6 months for the following years.

5.3.2. Type of examinations (laboratory methods and clinical investigations)

The patients were followed-up with CBC and routine biochemical analysis.

5.3.3. Pathology

Progression of the local radiation injury
Patient 1-M.I. was admitted to hospital with moist desquamation on his second and third fingers of the right hand due to high local dose. These injuries were healed by the time of discharge from the hospital.

In April 1999, an X ray examination of the right hand showed a slightly thinner bone tip of the first phalanx of 2nd finger where the skin had also become thinner.
In July 1999, the three phase bone scintigraphy showed slightly decreased perfusion and X rays revealed osteoporosis and soft tissue atrophy on the tip of the first phalanx of the second finger of the right hand. Flexion limitation of the proximal interphalangial joint was noticed. No sign of infection sign or pain was present. Abnormal sensation on the right 2nd finger tip was expressed . The other fingers were functioning normally.

In November 1999, the three phase bone scintigraphy showed absence of perfusion at the distal (end) phalanx of the 2nd finger and this phalanx had to be amputated. In February 2000, 14 months after the acute local radiation exposure, Patient 1-(MI) was admitted to hospital with swelling and erythema on the 3rd finger of his right hand and a deep ulceration on distal interphalangial joint of this finger of right hand (Photo 5-1 in the Annex).

Three-phase bone scan and magnetic resonance (MR) imaging were performed. Both imaging modalities showed increased perfusion and oedema, consistent with soft tissue inflammation of the 3rd finger. Lesions were regressed by wound cleaning with antiseptic solutions, avoidance of trauma and skin hydration.

5.3.4. Results of clinical and laboratory examinations

Patients clearly benefited from *bone marrow stimulation* by G-CSF, started on 12 Jan.1999. This growth factor induced a rapid recovery of the white cell lineage, which reached a level of 10 000/mm^3 in all patients in 4 to 11 days. As usual, after a leucocyte 'peak' due to G-CSF, the white blood cell counts normalized within a few days (see Fig. 5-1 in the Annex). The haematological chart of all ten patients has been followed-up since their discharge from the hospital. First they were examined weekly for 4 months, then quarterly and semi-annually (Table 5.5). The haematological chart of Patient 1-(MI) for a period of over one year is shown in Figure 5-2 in the Annex.

TABLE 5.5. HAEMATOLOGICAL FOLLOW-UP OF PATIENT NO. 1

Dates	WBC	Lympho	Platelet	Hgb	Hct	Transf	Other
09.01.1999	600	ND	1000	8,8	25,5	1u WB	
10.01.1999	700	ND	8000	9,0	10,7		
11.01.1999	400	ND	7000	10,7	32,2		
12.01.1999	500	300	7000	9,7	27,2	1P,1WB	Neup.
13.01.1999	500	300	4000	9,4	25,0	1 u Plt	Neup.
14.01.1999	400	400	26000	7,8	20,8	1uE,1uP	Neup.
15.01.1999	600	600	13000	7,6	20,0		Neup.
16.01.1999	500		21000	7,4	20,4	1 uE	Neup.
17.01.1999	600	400	19000	7,7	22,4		Neup.
18.01.1999	900	400	13000	7,1	19,4	1uE,1uP	Neup.
19.01.1999	1800		9000	7,4	20,0	1uE,1uP	Neup.
20.01.1999	4200	600	9000	8,3	22,7	1uP	Neup.
21.01.1999	8500		18000	8,2	23,2	1uE,1uP	Neup.
22.01.1999	12700		25000	12,7	25,0		Neup.
23.01.1999	9400	1000	26000	9,5	26,4		
24.01.1999	7100		33000	9,7	27,0		
25.01.1999	6300	800	37000	9,5	26,3		
26.01.1999	6600	900	43000	9,4	27,0		
27.01.1999	5000	800	54000	9,1	25,8		
28.01.1999	4400		72000	9,2	25,6		
29.01.1999	4600	1000	90000	9,4	26,0		
30.01.1999	3500	500	105000	8,5	25,5		
01.02.1999	3500	800	156000	10,2	28,8		
02.02.1999	3600	900	163000	10,1	28,8		
03.02.1999	3500	700	165000	10,7	29,9		
04.02.1999	4400	900	190000	11,4	32,8		
05.02.1999	2800	600	174000	11,1	31,2		
06.02.1999	3200	700	150000	10,7	30,1		
07.02.1999	3500	800	151000	11,8	32,9		
08.02.1999	3200	700	137000	12,0	34,5		
09.02.1999	4100	900	123000	12,0	34,2		
10.02.1999	3900	800	126000	13,0	35,9		
11.02.1999	4300	900	116000	13,0	36,6		
12.02.1999	4100	800	118000	13,0	36,6		
14.02.1999	4600	800	125000	13,0	37,5		
15.02.1999	3800	700	120000	13,4	38,5		
24.02.1999	6700	1139	120000	7,5	20,8		
03.03.1999	7700	700	136000	16,0	46,1		
11.03.1999	5100	900	176000	15,7	44,7		
16.03.1999	4900	800	186000	15,8	45,7		
18.04.1999	3300	700	175000	15,0	47.9		
17.04.2000	5500	1500	166000	17,0	48.4		
17.10.2000	5000	1100	159000	17,0	48.5		
11.09.2001	5500	1500	161000	16,1	46.3		

Heading key: WBC=white blood cells, Lympho=Lymphocytes, Transf.=transfusion of whole blood (WB) or blood component (P=platelets, or E=erythrocytes); Neup.=cytokine treatment with Neupogen.

Bone marrow biopsy was performed before and after the cytokine treatment. The results of this procedure are shown in Table 5.6.

TABLE 5.6. RESULTS OF BONE MARROW BIOPSY OF PATIENTS 1–5

Patients	13 January 1999	17 February 1999
1-M.I.	Highly hypocellular bone marrow. Marrow areas were occupied with fat cells. There was no precursor haematopoietic cell. Just a few lymphocytes and plasma cells were identified.	Normocellular bone marrow (40% cellularity); Erythroid hyperplasia, normoblastic maturation, focal megaloblastic differentiation, high Fe score, relative decrease in myeloid series, continuous maturation, and normal megakaryopoiesis.
2-N.I.	Hypocellular bone marrow (5% cellularity), rare erythroid islands, normoblastic maturation, relative increase in lymphocytes and plasma cells.	Normocellular bone marrow (50% cellularity); Erythroid hyperplasia, normoblastic maturation, focal megaloblastic differentiation, high Fe score, relative decrease in myeloid series, continuous maturation, and focal increase in megakariocytes and slight dismegakaryopoiesis.
3-H.I.	Hypocellular bone marrow (15% cellularity); significant increase in immature cells (promyelocytes), absence of mature myeloid cells and megakaryocytes, rare erythroid islands. Normoblastic maturation. Relative increase in lymphocytes and plasma cells. Findings of recovery from aplasia.	Normocellular bone marrow (35% cellularity); Erythroid hyperplasia, normoblastic maturation, focal megaloblastic differentiation, high Fe score, relative decrease in myeloid series, continuous maturation, sufficient megacaryocytes and slight dismegakaryopoiesis.
4-K.I.	Hypocellular bone marrow (2% cellularity), relative increase in lymphocytes and plasma cells.	Bone marrow cellularity 20-40%; erythroid hyperplasia, normoblastic maturation, focal megaloblastic differentiation, high Fe score, relative decrease in myeloid series, continuous maturation, sufficient megacariocytes and slight dismegakaryopoiesis.
5-I.I.	Hypocellular bone marrow (20% cellularity), promyelosit increase, absence of mature myeloid cells, high Fe score, relative increase in lymphocytes and plasma cells.	Normocellular bone marrow (35% cellularity); Erythroid hyperplasia, normoblastic maturation, focal megaloblastic differentiation, high Fe score, relative decrease in myeloid series, continuous maturation, sufficient megacariocytes and slight dismegakaryopoiesis.

Biological dosimetry was carried out; the pooled results are presented in Table 5.7.

TABLE 5.7. POOLED RESULTS OF DOSE ESTIMATES TO PATIENTS NO.1–10 BASED ON ANALYSES OF DICENTRIC ABERRATIONS AND OF MICRONUCLEI FREQUENCIES IN TWO LABORATORIES

Patients	Assumed exposure time on 13-12-98, hours	Protracted dose by dicentrics, ± SE, Gy	Estimated dose by micronuclei Gy
1-M.I.	6	2.2 ± 0.3	2.1
2-N.I.	7	2.3 ± 0.4	2.5
3-H.I.	6	3.1 ± 0.3	2.7
4-K.I.	7	2.5 ± 0.2	2.5
5-I.I.	7	2.5 ± 0.5	2.2
6-H.G.	6	1.8 ± 0.2	1.6
7-A.I.	2	0.9 ± 0.1	0.7
8-H.S.	2	0.6 ± 0.1	—
9-A.S.	3	0.8 ± 0.2	0.7
10-E.D.	2	0.6 ± 0.2	—

5.3.5. Principles and methods of treatment

The primary goal of therapy was a reduction in both the depth and duration of leucopenia. There is a quantitative relationship between the degree of neutropenia and the increased risk of infectious complications. As the duration of neutropenia increases, the risk of secondary infections also increases. It is for these reasons that adjuvant therapy with granulocyte-colony-stimulating factor (G-CSF) (Neupogen) was applied and proved valuable in the treatment of the severely irradiated persons even one month after irradiation.

5.3.6. Ability to work after the acute period or degree of disability

Although patients complain of weakness and fatigue after discharge from hospital, all of them have returned to their usual work at the time of writing.

5.4. Conclusions

1. Although accident victims applied to several out-patient clinics and hospitals, their symptoms were not initially diagnosed as being caused by radiation exposure. This situation has occurred in many other reported accidents — medical doctors are frequently not able to recognize a radiation injury. Early diagnosis, and treatment, can be crucial, and in some cases even life saving.

2. With adequate supportive care, platelet transfusions and granulocyte stimulation by G-CSF — when indicated —, return to safe levels of all blood components can be achieved within a few days.

   2.1. The clinical evolution observed in this case confirms, that even with rather severe haematopoietic syndrome due to accidental whole body irradiation of a few grays (about the $LD_{50/60}$), the use of allogeneic bone marrow transplantation is not indicated. (It is rather contra-indicated, due to graft complications to be anticipated in this specific context [2]) .

   2.2. Use of cytokines assisted the haematopoietic recovery even one month after the radiation exposure (with a dose of 3–4 Gy to the whole body), and is a useful means of treatment in such cases as it shortened the period of neutropenia, thus prevented the development of systemic infections (sepsis) that may lead to fatality. Adverse effect of G-CSF on platelet recovery was not observed.

   2.3. Use of cytokines can be recommended for treatment of radiation induced severe bone marrow aplasia when spontaneous hematopoetic recovery has not started yet according to extensive bone marrow examination.

3. At the late phase of local radiation injury, skin lesions are susceptible to reopening due to progressive vasculitis. A vascular necrosis and reopening of lesions were observed 11 and 14 months after the local radiation exposure. Local antiseptic solutions and skin hydration were effective for their care.

REFERENCES TO CHAPTER 5

[1] INTERNATIONAL ATOMIC ENERGY AGENCY, The Radiological Accident in Istanbul, IAEA, Vienna (2000).

[2] INTERNATIONAL ATOMIC ENERGY AGENCY, WORLD HEALTH ORGANIZATION, Diagnosis and Treatment of Radiation Injuries, Safety Reports Series No. 2, IAEA, Vienna (1998).

Chapter 6

MEDICAL TREATMENT AND PSYCHOLOGICAL FOLLOW-UP OF THE TOKAIMURA ACCIDENT VICTIMS

G. Suzuki, T. Hirama

6.1. Short description of the accident

6.1.1. Place, date, circumstances

A criticality accident occurred at a nuclear fuel conversion facility, JCO Co., Tokaimura, Ibaraki Prefecture, Japan, on Sept. 30, 1999, where 3 workers were engaged in a special work for making a homogeneous solution of 18.8%-enriched ^{235}U-uranyl nitrate in a precipitation tank. The precipitation tank had a water jacket around it for cooling and the water jacket happened to work as a neutron reflector. The use of a precipitation tank for this purpose was illegal, and the workers did not understand that it might cause a criticality reaction. Upon pouring 14.5 Kg U into the tank by stainless steel bucket, super-criticality condition was achieved (the position of workers O. and S. is shown in Figure 6-1 in the Annex). They saw blue-white light and heard a gamma-alarm ringing in the room. Two workers (O. and S.) left the scene immediately but a supervisor (Y.) who was exposed in the next room stayed there for a while trying to contact with radiation safety personnel. The criticality reaction continued for 19.5 hours, and total number of fissions was calculated to be 2.5×10^{18}.

6.1.2. Number of victims, estimated individual doses

These three persons received significant external neutron and gamma ray doses and suffered from acute radiation syndrome (ARS). Contamination by fission products was negligible. Doses they received were estimated by several methods (Table 1). In addition, 169 workers of JCO were irradiated during their stay in the facility (0.06–47.4 mSv) or during mitigation operations (0.7–48 mSv). Low-grade irradiation was delivered to 3 ambulance personnel (4.6–9.4 mSv) and 57 health physicists from other institutions (0.1–9.4 mSv). Two hundred seven residents in 350 m radius from the facility received low-grade irradiation (0.01–21 mSv).

6.1.3. Degree and type of initial injuries

The heavily irradiated three workers had prodromal signs and symptoms. Judging from the signs and symptoms as well as lymphocyte counts in the peripheral blood on day 0, Patients O., S. and Y. were diagnosed as “lethal”, “very severe”, and “mild to moderate” degree of ARS, respectively (Table 6.1). There were no skin injuries on day 0.

6.2. Diagnosis and treatment in the acute phase of the disease

6.2.1. Pre-hospital period

One or two minutes after leaving the scene of the accident Patient O. lost his consciousness and vomited. He seemed to experience an epilepsy attack, though there was no previous history of epilepsy. His colleagues tried to insert a stick between jaws to prevent airway occlusion by vomitus. He woke up 1 or 2 min later but was drowsy for another 20 or 30 min. He experienced diarrhoea several times thereafter. Patient S. felt numb sensation from shoulders to hands immediately after exposure, and it continued for 24 hours. He started

vomiting one hour after exposure. He did not experience diarrhoea. Patient Y. only felt nausea during transportation by helicopter.

An ambulance arrived at JCO Co. 11 minutes after the accident but could not leave until one hour later for a hospital where the primary care could be administered for radiation accident victims. Finally, three patients were transferred to the National Mito Hospital, about 20 km away from JCO Co, after the negotiation between the National Institute of Radiological Sciences (NIRS) and the hospital. The Ibaraki Prefecture Government had appointed the hospital as the secondary hospital by the Nuclear Disaster Prevention Plan. At the Mito Hospital, they made the primary care for the victims, surveyed body surface contamination from fission products, and analysed the blood chemistry and blood cells. Since three patients seemed to receive high doses causing ARS, it was decided to transfer them to NIRS by helicopter with continuous drip infusion. NIRS had been appointed as the tertiary hospital by the Guideline of Nuclear Disaster Prevention issued by the Nuclear Safety Commission. Drip infusion was decided for Patients O. and S. because of the loss of body fluid by diarrhoea, vomiting, and sweating due to high body temperature. Three patients arrived at NIRS 5 hours after exposure.

6.2.2. Diagnosis and treatment methods applied at the hospital

Vomitus and cloths that absorbed sweat were radioactive, and the gamma spectra-analyses demonstrated the presence of neutron-activated radionuclides. By this observation, we realized that a criticality accident occurred in JCO. Co. Upon arrival at NIRS, blood samples were taken for routine blood examination, HLA typing and cytogenetic dosimetry. Patients O. and S. had high fever of more than 38.5 degree C, and generalized erythema on their front surface of body. Patient O. complained tenderness upon touching on salivary glands, right arm, fore chest and upper abdomen. Patient S. complained tenderness on salivary glands. Initial dose estimation was done using lymphocyte counts (Fig. 6-2 in the Annex), the frequency of ring chromosome by a premature chromosome condensation (PCC) method, and the content of Na-24 in the blood (Table 6.1) [1, 2]. After irradiation, the cell cycle is arrested for a few days, which hampers the effectiveness of conventional chromosomal analysis for dosimetry. A new PCC method suitable for high dose-exposure had been established in NIRS. Patients O. and S. were irradiated quite near the precipitation tank. Therefore, the dose distribution was naturally inhomogeneous in the body. Moreover, as neutron tends to lose its energy after penetrating into the body, the dose distribution of neutron was even more inhomogeneous. Thus, the estimated radiation dose in Table 6.1 was mean dose, and the frontal skin dose of Patient O. was estimated about 40 Gy in total by gamma and neutron.

TABLE 6.1. DOSE ESTIMATION

Method of estimation		Patient O.	Patient S.	Patient Y.
Prodromal Signs and Symptoms (GyEq)		>8 (>20)	4–6	2 >
Lymphocyte Numbers (GyEq)		>10	6–10	1–4
Chromosome Aberration (PCC) (GyEq)		> 20	7.8	2.6
Na-24 content	Neutron (Gy)	5.5	2.9	0.81
	Gamma (Gy)	8.5	4.5	1.3

GyEq = Gy equivalent to gamma dose

Patient O. received more than 20 Gy equivalent to gamma dose and would develop a complex syndrome, i.e., the hyper-permeability of endothelium, acute gastro-intestinal (GI) syndrome, acute bone marrow (BM) syndrome, radiation skin injury and chronic fibrosis of lung and kidney. Patient S. received about 8 Gy equivalent to gamma dose and would develop mainly acute BM syndrome, radiation skin injury and fibrosis of lung and kidney. Patient Y. received about 2 Gy equivalent to gamma dose and would develop moderate acute BM syndrome 3–4 weeks after exposure.

For the treatment of hyper-permeability of endothelium, i.e., generalized oedema, pulmonary oedema, ascites, and pleural effusion, administered were high dose pentoxifylline (600–900 mg/d), m-prednisolone (up to 1000 mg/d), and diuretics. Pentoxifylline and m-prednisolone were administered in attempting to reduce the production of cytokines especially tumour necrosis factor-α (TNF-α) from irradiated and inflamed tissues. On the third day, Patient O. was transferred to the department of emergency medicine, the University of Tokyo Hospital, for the ICU care; assisting the respiration and monitoring the cardiovascular dynamics by a Swanganz catheter and the water-electrolyte balance. According to these real time analyses, the doses of diuretics and catecholamine, and the volume of electrolyte solution and plasma transfusion were determined. In addition, the drainage of ascites and pleural effusion was performed.

For the prevention of acute GI syndrome, selective digestive tract decontamination (SDD) with KM (later replaced by VCM or TOB), polymyxin B, and amphotericin B was started immediately after admission. Patients were fed with sterilized food supplemented with elementary diet in a bioclean room, and received parenteral alimentation supplemented with L-alanyl-glutamine (20 g/d). Prophylactic administration of broad-spectrum antibiotics and G-CSF was also started from the first day of admission in order to control the bacterial translocation from GI tract and respiratory tract.

For the prevention of BM failure in Patients O. and S, the transplantation of haematopoietic stem cells was performed as mentioned below. For the prevention of radiation pneumonitis or renal sclerosis, high dose pentoxifylline and radical scavengers such as vitamin C and tocopherol (1000 mg/d) were administered. Patients O. and S. were transferred respectively to the University of Tokyo Hospital on 3rd day and the Medical Research Institute, University of Tokyo, on 5th day in order to receive stem cell transplantation. Patient Y. was treated in the NIRS hospital.

6.2.3. Stem cell transplantation

Patient O. was transplanted with peripheral blood stem cells from an HLA-A, B, C, DRb fully identical sister on the 7th and 8th day. MTX, FK506 (later CyA) and Pred were used for the prevention of GVHD. The levels of CyA and FK506 in the plasma were monitored every day or every other day in order to keep the therapeutic range of immunosuppressant. G-CSF had been re-administered after the peripheral blood stem cell transplantation (PBSCT). WBC recovered more than 1000/mm^3 10 days after PBSCT, although platelet did not recover in his clinical course. Chromosome analyses repeatedly demonstrated that more than 99% of cells were donor origin. There were no sings of graft vs. host disease (GVHD).

Patient S. received the cord blood from a 5/6-matched donor (HLA-A, DRb loci-identical but HLA-B locus haplo-identical) on the 10th day. By the cord blood transfusion, 2×10^7/kg of CD34$^+$ cells were transplanted. Anti-thymocyte globulin (ATG), CyA and Pred were used for

the prevention of GVHD. G-CSF, EPO and TPO were administered after transplantation. WBC recovered more than 1000/mm^3 16 days after transplantation. Chromosome analyses demonstrated that the recovered haematopoietic cells and lymphocytes were the mixture of donor (female) and autologous (male) cells. Stable mixed chimerism was a sign of no GVHD. This mixed chimerism ceased one and half month later by the disappearance of donor cells. Platelet was recovered one month after transplantation in S.

Mild protocol of GVHD prophylaxis was used for Patient S., because we wished to avoid the toxicity of MTX against mucosal membrane in the GI tract. In case of cord (umbilical) blood transfusion (CBT), T cells in the cord blood are immature so that the severity of GVHD after CBT is generally low. About 80% of CBT cases developed very mild GVHD (grade 0-II) after CBT in Japan. The mild GVHD prophylaxis with ATG, CyA and Pred tends to make a state of mixed chimerism according to the literature.

6.2.4. Clinical course of Patient O

Serum amylase levels elevated for 3 days, and the isoenzyme analyses indicated the amylase came from salivary glands. Right forearm of Patient O. had been seriously irradiated during he held a funnel by right hand. As a result, rhabdomyolysis occurred in the right forearm and the serum levels of CPK and myoglobin increased up to 5060 IU/L and 1490 ng/ml, respectively. Right arm became dry gangrene finally. In order to control the respiration, the intubation was performed on day 10 after putting him under deep sedation. The sedation was helpful for the control of pains on right arm and radiation burns that appeared over entire front surface of his body 2–3 weeks after exposure. Skin lesions were blisters all over the front surface of body, which ruptured on the next day. Sometimes new blisters appeared and ruptured again in the skin area where old blisters ruptured a week before. The skin lesions progressively worsened and the epidermal layer was completely lost in almost all frontal body surface area 2 months later. Skin lesions were treated with povidone-iodine and an ointment containing bacitracin and fradiomycin sulphate twice a day, and covered by siliconized gauze. Allogeneic cultured epidermal cell-sheet was used to cover the raw surface but failed. The volume of exudates from burn increased along with the clinical course and was about 1000–4000 ml/day.

Although acute GI syndrome was suppressed, watery diarrhoea began from 25th day and it became tarry 7 weeks after exposure. It was difficult to make a differential diagnosis between atrophic gastroenteropathy due to irradiation, GVHD, and gastroenteropathy with microangiopathy due to overdoses of immunosuppressants. The radiation-induced microangiopathy in the GI tract results in the atrophic gastro-enteropathy. Since the biopsy of atrophic gastro-enteropathy might induce uncontrollable bleeding, we did not perform biopsy. As to GVHD, there were no increase of liver enzymes, soluble IL-2R, nor IFN-gamma producing lymphocytes in peripheral blood. Recently, a new disease entity is separated from “pseudo-GVHD”, i.e., gastroenteropathy with microangiopathy due to overdoses of immunosuppressants. After discussions, we increased the dose of m-prednisolone in order to suppress GVHD if any. However, we could not control diarrhoea.

He received 1–7 L of fresh frozen plasma every day to maintain the osmotic pressure. In spite of this, he developed ascites, pleural effusion, and pulmonary oedema again, which decreased the respiratory function. On the 60th day, cardiac arrest occurred suddenly when he was about to receive an X ray examination. He was successfully resuscitated one hour later. Multi-organ

failure progressed after this ischaemic episode and he died on 84th day. There had been no episode of clinical infection throughout his course.

6.2.5. Clinical course of Patient S

Serum amylase levels elevated for initial 3 days that derived from salivary glands. Primary erythema and swelling of skin disappeared within a couple of days after exposure. Skin lesions reappeared 2 week later. First, he complained just pain on face, the upper part of chest, hands and fingers, ankles, and toes. A few days later, small lesions with dark red colour appeared, and they turned into blisters one week later. At the same time, the lesion expanded progressively. Skin lesions also appeared 4–5 weeks after exposure on thighs, scrotum, arms and abdomen. Burn surface was treated with silver sulphadiazine or an ointment containing fradiomycin sulphate, and covered with siliconized gauze. Except for skin lesions on face, head, neck, hands, and feet, other skin lesions were epithelializated spontaneously. Three months later, residual raw surface areas were covered by either an allogeneic epidermal cell-sheet or cadaver's skin. Although Patient S. did not receive any immunosuppressants at that time, the allogeneic skin graft was accepted. Transplanted skin as well as regenerated skin gradually became sclerotic 5 months after exposure.

Clinical course of Patient S. was rather stable until March 1, 2000, when he suffered from aspiration pneumonia of MRSA, and subsequently from acute respiratory distress syndrome (ARDS). ARDS and MRSA infection were successfully controlled, but pulmonary lesions remained. GI tract bleeding started, which was hard to control. He was transferred to the department of emergency medicine, the University of Tokyo Hospital on Apr. 10. Destructive pneumonia and the sclerosis of chest wall reduced the respiratory function and he died by respiratory failure on Apr. 27, 2000, the 211st clinical day.

6.2.6. Clinical course of Patient Y

Initial therapeutic strategy for Patient Y. was principally the same as for the other two patients. For the maintenance of body fluids, electrolytes and plasma were infused under central venous pressure monitoring. Similarly, measures to help bone marrow recovery and prevent infection included the administration of G-CSF, SDD until the stool culture was negative, prophylactic use of antifungal and antiviral reagents and reverse isolation when necessary. His diabetes mellitus was controlled with rapid type insulin in combination with diet therapy. His hypertension was not a factor in the hospitalized situation. We also used pentoxifylline to improve microcirculation and L-glutamine to facilitate the recovery of the intestinal epithelium. Examples of the haematological parameters of Patient Y. are shown in Fig. 6-1. His neutrophil counts initially responded to G-CSF and increased, then started to decline in a stairwise pattern and reached a nadir on day 21. He was kept under reverse isolation while being neutropenic. The decrease of the platelet count necessitated three episodes of platelet transfusion. His neutrophil and platelet counts made gradual recovery thereafter. The haemoglobin value decreased from about 170 g/L to 100 g/L. The lymphocytes were decreased to about 0.5E9/L and showed gradual recovery. Serum immunoglobulin levels were grossly normal. Bone marrow taps on Day 1 showed hypocellularity with decreased erythroid series and some morphologically abnormal megacaryocytes. Among other laboratory findings, serum amylase increased to 1094 IU/L on Day 2 and was judged to be mainly of salivary origin by isoenzyme analysis. Uric acid was elevated by about 10 mg/L compared to his previous value. Although his clinical course was principally without any episodes of overt infection, the CRP value and erythrocyte sedimentation rate increased transiently, with the

only possible focus of infection being the gums. Unexpectedly, he showed transient hypoxia (PaO2: 62.6 mmHg) starting on the day of exposure, for which oxygen was given via a nasal prong. An respiratory function test showed a slightly decreased DLCO value. His hypoxia was also associated with computed tomography findings suggesting interstitial oedema of the lung. Although he did not show desquamation of the skin that is characteristic of high dose exposure to the organ, he exhibited spotty epilation as well as marked retardation of beard growth. In addition, his oral mucosa showed fragility so that he sometimes had localized painless defect of the oral mucosa without his knowing. These symptoms were judged to be caused by irradiation and gradually improved during admission.

Patient Y. had transient bone marrow suppression 3–4 weeks after exposure, which was controlled by platelet transfusions and G-CSF. Since he was a supervisor of other two accident victims, he felt guilty for involving them in the accident. He needed mental support by a psychiatrist. He was discharged from NIRS on the 82nd day.

6.2.7. Psychological support

Consultation with a psychiatrist was arranged shortly after their admission to the NIRS and started on October 1, the next day of the accident. Psychiatrists from the nearby Chiba University Hospital were invited and interviewed the three patients. In the very acute period they evaluated the psychiatric status of the patients and provided support. While treating the three patients, the NIRS hospital was in an unusual situation, not only because the intensive treatment of the patients was done around the clock but also because a lot of visitors, physicians and administrative personnel came in to see the patients. As a result, the ward was more crowded and noisier than is usually the case.

After the Patients O. and S. were transferred out of the NIRS hospital, one of the psychiatrists took the responsibility to interview Patient Y. regularly. The accident was the biggest topic of the year among the mass media in Japan, whose reports, however, were often misleading and erroneous, and likely to cause unnecessary psychological stress to Patient Y. The treating team and Patient Y. discussed about the issue and agreed that he should keep away from reading newspapers and watching TV for a while.

6.2.8. Duration and place of hospitalization

Patient O. stayed at the NIRS hospital from Sept. 30 to Oct. 2, 1999, when he was transferred to the department of emergency medicine, the University of Tokyo Hospital. He died on Dec. 22, 1999, and it was the 84th clinical day.

Patient S. stayed at the NIRS hospital from Sept. 30 to Oct. 4, when he was transferred to the Medical Research Institute, University of Tokyo. He was transferred to the department of emergency medicine, the University of Tokyo Hospital on Apr. 10, 2000. He died on Apr. 27, 2000, and it was the 211th clinical day.

Patient Y. stayed at the NIRS hospital. He was discharged from the hospital on December 20, 1999. The duration of his hospitalization was therefore 82 days. His discharge was planned several times, but finally was decided largely based on non-medical, social factors relating to coverage in the media and heightened public scrutiny.

6.3. Follow-up in the delayed period

6.3.1. Frequency of medical examinations (in-patient or out-patient)

After being discharged, Patient Y. visited the NIRS in January, April and November of 2000 and June of 2001 following the advice of the staff physicians of NIRS.

6.3.2. Type of examinations (laboratory methods and clinical investigations)

Typically, Patient Y. stays at the NIRS hospital for a couple of days whenever he visits and undergoes medical examinations including complete blood count, serum chemistry, hormones and some tumour markers, FACS analysis of peripheral blood leucocytes, bone marrow tap and urinalysis. Chromosome analysis of peripheral blood lymphocytes and computed tomography analysis of the chest are also done to follow-up his initial changes. He also sees ophthalmologist, cardiologist, dentist and psychiatrist during his stay.

6.3.3. Pathology

No pathological finding that could be associated with the exposure has evolved in Patient Y. after he was discharged in December 1999.

6.3.4. Results of clinical and laboratory examinations

Patient Y. has exhibited two episodes of retinal haemorrhage without major consequences, once during the first admission and again at his June 2001 check-up. They were regarded as being associated with diabetes and not with the irradiation. Although he continues to have gingivitis, the fragility issue has been over and he recently underwent a tooth extraction without major complications. His diabetes and hypertension are principally being treated by his primary physician near his residence, and are becoming more pronounced as he has gained about 8 kg since the time of discharge. His hair has fully grown by January of 2000. No signs of skin change have been noted except for a transient atopic dermatitis, which healed without sequelae with topical administration of anti-histamines. The computed tomography of the chest and respiratory function test have remained problem-free.

6.3.5. Ability to work after the acute period or degree of disability

Although Patient Y. is physically well enough, his social situation keeps him away from going back fully to work. Soon after he went back to work, he, as the only survivor of the crew who were directly involved in the accident, was arrested in October of 2000 and subsequently sued together with several key members of the company. As of August 2001, he is on trial, through the end of which he is ordered not to contact any members of the company.

6.4. Lessons learned from the follow-up of the victims

(a) It is demonstrated that prompt and radical prophylaxis of infection by SDD, systemic administration of broad-spectrum antibiotics and G-CSF can modify the clinical outcome of ARS. It is noteworthy that no clinical infection occurred in Patients O. and S. when WBC counts were less than 500 for 2 and 4 weeks, respectively. Moreover, acute GI syndrome was completely suppressed in these patients.

(b) Stem cell transplantation from peripheral blood or cord blood has been performed in Patients O. and S. without GVHD. It is essential to analyse HLA types of patient and his or

her family members as soon as possible. The degree of HLA matching is critical for the prevention of GVHD. HLA typing for A, B, C, and DRb loci is recommended. Moreover, DNA typing can further characterize the fine specificity of HLA type. Since DNA typing can be done for any tissue, it is convenient for lymphopenic patients.

(c) Non-myeloablating protocol of bone marrow transplantation has been reported in literature, which may reduce the toxicity of MTX on exposed skin and mucosa.

(d) Medical measure must be developed for the prevention of a subacute form of gastroenteropathy and chronic fibrosis / sclerosis of tissues in future.

(e) In a radiation accident in an industrial setting such as the Tokaimura accident, in which the trigger to the accident is easily recognizable whereas the real cause of the accident, such as inadequate education of the operator, is not self-revealing, the victim operator may become the one who is accused, either socially or legally, regardless of the appropriateness of the accusation. Therefore, the extremely difficult social situation and resultant psychological stress that confront the victim need to be recognized and addressed with as early as possible with the help of appropriate specialists.

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Chapter 7

STRATEGY FOR DIAGNOSIS AND TREATMENT OF SEVERE LOCAL RADIATION INJURIES

P. Gottlöber, M. Steinert, R.U. Peter

7.1. Introduction

Ionizing radiation causes severe acute and chronic reactions in skin. Considerable progress has been made in the last few years in the understanding of the underlying pathomechanisms. In contrast to older concepts focusing mainly on the antiproliferative effects of ionizing radiation on hypothetic stem cells, recent scientific progress demonstrated that these radiation-induced cutaneous reactions are caused by complex interactions between anti-proliferative and proinflammatory processes, involving a variety of cytokines, growth factors and their receptors, and adhesion molecules, in a clinically well-defined time pattern, for which the term cutaneous radiation syndrome (CRS) has been coined [1, 2].

7.2. Pathophysiological aspects and clinical management

Generally, the course of cutaneous radiation syndrome (CRS) follows a distinct clinical pattern. The stages of CRS are summarized in Table 7.1. Within minutes to hours after exposure, an erythematous rash develops, which may be associated with a burning itch [1, 2]. This prodromal stage is transient in nature. These effects most probably are caused by initial transcriptional activation of proinflammatory cytokines such as IL-5, Il-6, and TNF-alpha [3–6] in epithelial cells as well as in endothelia. Activation of cutaneous mast cells then leads to histamine liberation, which again sets off a whole cascade of inflammatory cytokines in the neighbouring tissue. After this prodromal stage a so-called latency phase of clinically inapparent reactions follows. On the subcellular level, however, it is assumed that a balanced pattern of pro-and anti-inflammatory processes involving pro-inflammatory cytokines, growth factors and their receptors, as well as anti-inflammatory cytokines such as TGF-ß and IL-10 occurs.

Consecutive and primary induction of adhesion molecule expression in keratinocytes and endothelial cells [5, 7] leads to pooling of neutrophilic and eosinophilic granulocytes, which by release of H_2O_2 may again generate oxidative stress to the affected tissue. Once the inflammatory processes prevail, the result is the manifestation stage, which is then characterized either by erythema and eventually discrete scaling, or by subepidermal blisters and necrotizing ulcers. Sometimes a subacute stage with a vasculitis of subcutaneous and muscular vessels and local haemorrhages occurs 1–3 weeks after the peak of the manifestational stage.

In the further progress a change of the cytokine pattern occurs: anti-inflammatory cytokines, such as TGF-ß prevail in basal keratinocytes as well as dermal fibroblasts, the inflammatory infiltrate changes to predominantly perivascularily orientated lymphocytes of the CD 4+ helper subtype [8]. TGF-ß1 as such, though important for wound healing, is a strong inducer of collagen synthesis in dermal and subcutaneous fibroblasts. As such, increased collagen production leading to fibrosis appears a natural biological consequence of irradiation. Therefore radiation fibrosis is the characteristic feature of the chronic sequelae xerosis, as well as hyper- and hypopigmentation are characteristic features, apart from epidermal atrophy,

radiation keratosis, teleangiectasias, radiation lentigo and subungual splinter haemorrhages (Fig. 7-1, in the Annex). Fibrosis and epidermal atrophy may be followed by secondary ulceration [1, 2, 9]. With a latency of years and decades (15–35 years) basal and squamous cell carcinomas may develop [10–12]. The time course depends on several factors such as the applied radiation dose, radiation quality, individual radiation sensitivity, the extent of exposure, contamination and absorption and volume of the skin.

TABLE 7.1. CLINICAL STAGES OF THE CUTANEOUS RADIATION SYNDROME

Stage	Latency	Persistence	Symptoms
Prodromal stage	minutes-hours	0.5–36 hours	erythema, pruritus
Manifestation stage	3 weeks	1–2 weeks	erythema, pruritus, bullae, ulcer
Subacute stage	16 weeks	months	erythema, ulcer
Chronic stage	years	unlimited	keratosis, fibrosis, ulcer epidermal atrophy, teleangiectasias, hyper- and hypopigmentation, angioma
Late stage	>10 years	unlimited	as in the chronic stage angioma, basal and squamous cell carcinomas

TABLE 7.2. DEGREE OF SEVERITY OF SKIN INJURY AFTER RADIATION EXPOSURE

Symptom	Degree 1	Degree 2	Degree 3	Degree 4
Erythema	minimal transient	moderate, isolated patches, <10% BS	marked, isolated patches, 10–40% BS	severe, >40%BS
Itching	none or slight	slight and intermittent	moderate and persistent	severe and persistent
Sensation	none	slight pain	tolerable pain	severe pain
Swelling/oedema	present, asymptomatic	symptomatic, tension	secondary dysfunction	total dysfunction
Desquamation	absent	patchy dry	patchy moist	Confluent
Blistering	rare with sterile fluid	often with sterile fluid	bullae with sterile fluid	bullae with haemorrhage
Ulcer/necrosis	epidermal	dermal	subcutaneous	muscle/bone involvement
Hair loss	thinning	patchy, visible	complete, reversible	complete, irreversible
Onycholysis	absent	partial	partial	Complete

In frame of the project “Medical treatment protocols for radiation accident victims as a basis for a computerized guidance system”, in short METREPOL, a new approach was developed in the medical management of radiation accidents with respect to diagnostic procedures and therapeutic options based on the recognition and evaluation of health impairments after acute radiation exposure.

The Manual on the management of the acute radiation syndrome for the first time comprises defined algorithms for diagnosis and therapeutic decisions, which include components of different organ systems, by means of which so-called response categories (RC) have been established [13]. The degree of severity for the cutaneous syndrome are listed below.

7.3. Diagnostics

For diagnostics of the cutaneous radiation syndrome the following procedures are used: 7.5 MHz to 20 MHz-B-scan-sonography, thermography, capillary microscopy, profilometry, nuclear magnetic resonance imaging, bone scintigraphy and histology [14].

The 20 MHz-sonography (Figure 7-2 in the Annex) is a frequently used, reproducible, non-invasive method for evaluation of skin thickness and skin density in patients with cutaneous radiation fibrosis [15–17]. The 20 MHz-scanner with an axial resolution of about 80 µm and a lateral resolution of 200 µm is suitable to investigate epidermis, dermis and subcutaneous fat tissue up to a depth of about 10 mm. The depth of cutaneous radiation ulcers can be determined by sonography before and during therapy. The 7.5 MHz-sonography is a well established, non-invasive procedure for evaluation of dermis, subcutaneous fat tissue, muscle fascia and musculature. Radiation fibrosis of subcutis and deeper radiation ulcers can be determined by 7.5 MHz-sonography [14–17].

Thermography is a useful method for quantification of the skin temperature and heat loss of the body [18]. The skin surface temperature and the emitted heat from the body surface are connected with the cutaneous vessel system. The measurement of the skin surface temperature and heat loss from the skin is an indirect parameter for the vascularization of the skin. Such techniques like infrared thermography, microwave thermography and liquid-crystal-contact-thermography are available. There is a significant lower local skin surface temperature in patients with necrosis. A significant higher skin temperature was observed in patients with inflammations.

Capillary microscopy is a non-invasive method for a qualitative and quantitative evaluation of the capillaries of the stratum papillare of the dermis [19]. The capillaries of the nail fold of fingers or feet are dilated in patients with the manifestation stage of CRS. The capillaries are smaller and rare in patients with the chronic stage of CRS. Additionally subungual splinter haemorrhages may be visible in distal parts of the nail bed in these stages [20].

Profilometry is the most common method to quantify the skin topography in two and three dimensions [14]. The analysis of the vertical and horizontal distribution of the furrows gives information on skin surface.

Nuclear magnetic resonance imaging is an non-invasive, well-established approach for the examination of the signal intensity of dermis, subcutaneous fat tissue, muscle and bone [14].

Morphological changes can be discovered. The increase of the signal intensity in the nuclear magnetic resonance imaging is the result of fluid in the tissue which may occur through inflammation, oedema or necrosis. A reduced content of fluid in the tissue leads to a decrease of signal intensity . With nuclear magnetic resonance imaging the extent of skin ulcers in radiation exposed patients could be evaluated. A disadvantage of this method is the lacking ability to discriminate between necrosis and inflammation. Bone scintigraphy allows information about the activity in bone under radiation ulcers.

Histology is an invasive method for determination of CRS. The histology of the manifestation stage/subacute stage of CRS demonstrate dilated blood vessels, oedema and multiple infiltrations consisting mainly of neutrophils and eosinophils. The histology of the chronic stage/late stage of CRS is characterized by epidermal atrophy or akanthosis, fibrosis of the dermis, rare lymphohistiocytic infiltrations, dilated blood and lymphatic vessels in the upper dermis, hypo- and hyperpigmentation and a loss of skin appendices [2, 14].

7.4. Treatment

7.4.1. Conservative treatment

Treatment has to focus on the stage of CRS and the avoidance of additional risk to the patients. The prodromal and manifestation stages are characterized by inflammatory processes. Anti-inflammatory creams e.g. linoleic acid (Linola Fett^{R}, Wolff, Bielefeld) cream should be used as basic treatment. Additionally, nonatrophogenic local steroids e.g. Mometasonfuroate (Ecural^{R}, Elocon^{R}, Schering-Plough, New Jersey) should be used to reduce the inflammation. Systemic steroids (0.5–1.0 mg/ kg prednisolon equivalent) should be applied in patients with extensive affected skin areas after check of contraindications to reduce the dermal and muscular vasculitis [2, 21]. If the patients suffer from pain, analgesics should be given. Treatment with desloratadine, (Aeirus^{R}, Essex, Munich, Germany) a non-sedating and mast-cell stabilizing antihistamine, induce a marked relief of burning itch. Additional therapy modalities which have been reported to be of value in the manifestation stage are heparinization and antibiotic prophylaxis for bacterial infections [20–22].

Xerosis is one of the symptoms of the chronic stage of CRS. The basic therapy with a specific ointment containing linoleic acid (Linola Fett^{R}, Wolff, Bielefeld) lead to a marked decrease of initially severely increased transepidermal water loss. Teleangiectasias caused discomfort due to sensation of a burning itch and heat, which disappeared after therapy by Argon Laser. Tretinoin cream 0.005% (Epi Aberel^{R}, Janssen Cilaf, Germany), applied once daily, lead to a clearance of focal and patchy radiation keratoses. In more extensive lesions, oral application of retinoids should be recommended [13, 20, 22].

Radiation fibrosis is characterized by an increase of collagen fibres by affected fibroblasts. If left untreated, persistent cutaneous fibrosis may give rise to ulcerations. Various approaches have been undertaken to antagonize this chronically inflammatory process, among these systemic and topical application of superoxide dismutase, systemic application of pentoxifylline and alpha-tocopherol and proteinase inhibitors [23–26]. Interferon gamma inhibits collagen production by human dermal fibroblasts. Interferon gamma should be scheduled on a low-dose regimen, 2-3 $\times$ 100 μg/week s.c. for 6 months, then once per week for another 6 months. A decrease in skin thickness could be observed 6 months after initiation of therapy [27, 28].

Cutaneous radiation ulcer should be treated with topical dressings of Tetrachlorodekaoxide (TCDO). TCDO induce considerable granulation and re-epithelialization in ulcers. Additionally, hydrocolloid dressings or topical thrombocytic growth factors could be used [13,22]. A recent interesting alternative are wound dressings with semipermeable fibres (Biocell^{R}, Germany) a systematic evaluation of this new approach is pending.

7.4.2. Surgical treatment

If the conservative therapy of radiation ulcers or radiation fibrosis is not successful, a surgical treatment should be performed. When radiation exposed skin reveals tumorous changes, a local recurrence as well as malignoma such as squamous cell carcinoma or basal cell carcinoma must be excluded. If the conservative therapy of radiation induced ulceration shows no success, methods of plastic surgery should be performed [29].

The problem of radiation exposed skin includes radiation fibrosis, which often affects not only skin, but also subcutaneous tissue including musculature and bone.

The surgical therapy of the cutaneous radiation syndrome includes two steps:

1. a spacious debridement of radiation exposed skin and altered tissue
2. the covering of the skin lesion using a sufficiently vascularized flap.

The following possibilities of plastic surgery are available: mesh graft, full thickness graft, transpositional flap, distant flap and free flap [29]. When the ground of the wound is well vascularized after debridement mesh graft and whole graft can be used. After superficial cutaneous radiation either a whole or a mesh graft onto a well vascularized muscle is indicated (Figs 7-3 and 7-4 in the Annex).

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Chapter 8

STRATEGY AND TACTICS FOR STIMULATION OF HAEMOPOIESIS IN PATIENTS DEVELOPING THE ACUTE RADIATION SYNDROME

T.M. Fliedner, D.H. Graessle, C. Paulsen, K. Reimers

8.1. Introduction

This paper is essentially based on the outcome of a concerted research action of the European Communities entitled "Medical Treatment Protocols for Radiation Accident Victims as a Basis for a Computerized Guidance System" (METREPOL) which was conducted as a joint effort between research establishments in Paris, Oxford, Rotterdam, Munich and Ulm. The results of this concerted action have been published by the British Institute of Radiology in 2001 with the following title: "Medical Management of Radiation Accidents: Manual on the Acute Radiation Syndrome" [1]. In this manual, experience was used from more than 800 case histories of persons that were subjected to whole body radiation exposure during radiation accidents. A total of 70 accidents in 14 countries provided the material for the manual including data on medical management and follow-up of the Chernobyl and Tokaimura accidents presented in detail in this Technical Document.

These case histories form the core of an international database system entitled SEARCH (System for Evaluation and Archiving of Radiation Accidents based on Case Histories) [2].

The haematopoietic cell renewal systems are of paramount importance in the clinical management of the acute radiation syndrome for two reasons. First of all, the haematopoietic tissue is distributed throughout the skeleton characterized by an enormous haematopoietic cell turnover as well as by a high radiation sensitivity. Furthermore, it is regulated to act as one organ by humoral factors and by a continuous monitoring of stem cell content in the bone marrow units by a migration stream of circulating haematopoietic stem cells. Therefore, the haematopoietic blood cell response patterns after total body exposure to ionizing radiation reflect in a very precise way the extent of damage to the entire organism and are able to predict the probable clinical course of the patient and allows preparation for the different treatment options. Thus, it is obvious that the haematopoietic cell renewal system is of high diagnostic significance in the management of the acute radiation syndrome.

Secondly, the haematopoietic tissue is also of crucial importance for the principle survival chance of an exposed person. If haematopoietic regeneration can be achieved, then other organ radiation impairments may well have a chance to be successfully treated. Due to modern treatment options such as stem cell transplantation as well as growth factor therapy, the vulnerability of the haematopoietic system is not any longer the limiting factor in radiation accident survival of victims. The critical question that remains is whether the subsequent multiorgan damage can be overcome by appropriate therapeutic methods.

Therefore, this chapter presents first the structure and function of the haematopoietic cell renewal systems and their relevance for the acute radiation syndrome. Secondly, it addresses the question of the strategic approaches to assess the severity of radiation injury to haematopoiesis. And thirdly, it is its purpose to briefly summarize the approaches to treat haematological consequences of whole body radiation exposure.

8.2. Structure and function of haematopoietic cell renewal systems

In clinical radiation accident management, it is of paramount importance to recall the principle structure and function of the haematopoietic system. The blood cell forming bone marrow is distributed throughout the skeleton. More than 200 bones are, in principle, endowed in their marrow cavity to produce haematopoietic cells. This widely distributed bone marrow has an overall size of about 2600 g of which about 1500 g are active in producing the blood cells that the human being needs in order to maintain its integrity in changing environments. It has been calculated that the bone marrow contains 126×10^{10} cells and that the marrow cell production can be assessed to be 18.8×10^{7} per kg body weight/hour. The blood cell forming bone marrow is not a "cell culture" that is "accidentally" localized within the bone cavity. Rather, one should recall that the blood cell forming bone marrow is a highly specialized organ with a specific neurovascular structure. There are nutrient capillaries and a complex sinusoidal system operating in an encapsulated situation not permitting growth volume changes of the organ unit as such. Furthermore, it is important to stress that the blood cell formation in the bone marrow is regulated by unmyelinated and myelinated nerve fibres as well as by stimulating and inhibiting humoral factors. This situation has recently been reviewed [3].

Of particular importance for radiation accident management is the knowledge about the *function of the different haematopoietic cell renewal systems*. The granulocytic cell renewal system produces every day 120×10^{9} blood granulocytes. An equal number of cells is lost from the blood per day. The life expectancy of granulocytes has been measured to be about one day. This means that every day the entire granulocyte pool is turned over once. This fact is of paramount importance for radiation accident management as will be highlighted below.

Every day, 200×10^{9} erythrocytes are being produced in the bone marrow and are lost from the blood. The life span, however, of erythrocytes is in the order of 120 days. Therefore, after acute radiation exposure, it takes weeks rather than days before the red cell count becomes critical unless there is thrombocytopenic bleeding influencing the number of red cells in the peripheral blood.

The number of platelets produced per day is in the order of 150×10^{9}. An equal number is removed every day from the blood. One has to consider the life expectancy of blood platelets to be in the order of 10 days. Therefore, if there is a complete destruction of the megakaryocytic system, one would expect that the blood platelets decrease to critical "thrombopenic" levels within the first 10 days after radiation exposure.

As far as lymphocytes is concerned, one has to recall that these cells are very heterogeneous regarding their function. In addition, the life span of lymphocytes is very different depending on the functional role of a particular lymphocyte. Nevertheless, one can calculate that this very heterogeneous group of cells has a turnover of 20×10^{9} per day. The response of lymphocytes after total body radiation exposure is often used as a first indicator of severity of exposure. However, lymphocytes (unlike the other blood cells) are "recirculating" cells. They enter the blood stream via the lymphatics and are emigrating out of the blood stream back into the lymphatic tissue [4]. Thus, after total body or a significant partial body exposure (upper body), this process of recirculation of lymphocytes is interrupted almost instantaneously. Therefore, the early response of lymphocytes is first of all caused by the impairment of recirculation. In addition, lymphocytes, unlike the other blood cells, are cells with a potential of further replication, proliferation and differentiation. Thus, they are also radiation-sensitive. This

radiation sensitivity can be tested in cell culture studies using phytohaemagglutin as a mean to induce cell proliferation [5].

Among the mononuclear cells in the peripheral blood (summarized as "lymphocytes") are cells of a completely different quality: haematopoietic stem- as well as progenitor cells. The fact that haematopoietic stem cells are part of the blood leucocyte population was first discovered by Goodman and Hodgson (1962) [6]. The research group in Ulm studied systematically the physiology and pathophysiology of circulating stem- and progenitor cells [7–10]. Today, it can be assumed that $CD34^+$ cells, CFU-mix, GM-CFU and BFU as well as other progenitor cells are part of the normal "adult" blood stem cell population with a turnover between about $2–50 \times 10^9$ per day [7, 11].

Since the blood stem- and progenitor cells as well as the stem- and progenitor cells in the haematopoietic bone marrow are very radiation-sensitive, it goes without saying that after exposure to whole-body irradiation the number of stem- and progenitor cells in the bone marrow as well as in the peripheral blood are decreased almost momentarily. The D_0 of stem- and progenitor cells in human beings has been reviewed by Nothdurft [12]. In human beings, the D_0 values are between 0.6 and 1.6 Gy. The in vitro sensitivity of GEMM-CFC was determined to be 0.57 Gy while the D_0 for GM-CFC was 0.86 Gy and for BFU-E 1.13 Gy.

Similar sensitivities were found for haematopoietic stem cells in several mammalian experimental animals [10]. These data mean — for all practical purposes — that a total body radiation exposure in the LD50 range reduces the stem cell pool dramatically to less than 10% of normal almost instantaneously.

In summary, haematopoiesis is of crucial significance for radiation accident management for the following reasons. First, it is distributed through the entire skeleton and therefore, homogeneity or inhomogeneity play a major role in the development of haematopoietic failure and in any recovery process. Secondly, blood cell concentrations (granulocytes, lymphocytes, platelets and red cells) are maintained through continuous replacement of old cells by means of new cells, and therefore reflect the type and extent of radiation damage. Thirdly, cell production in active sites of haematopoiesis is continuously controlled and maintained by blood stem cell traffic and by humoral factors determining largely the capacity to overcome haematopoietic failure after whole body radiation exposure.

As far as the significance of the haematopoietic system for radiation accident management is concerned, one should recall that in radiation accidents rarely, if ever, a homogenous whole body exposure will occur. Therefore, it is extremely difficult to assess any “exposure dose” to the widely distributed haematopoietic stem cell pool. For instance, if the upper body has received the major radiation exposure, then it is most likely that in the lower part of the body there are bone marrow sites with less radiation exposure and therefore with a higher probability of autochthonous regeneration. These relatively less exposed sites may produce new stem cells that are migrating through the blood stream to repopulate more heavily exposed bone marrow sites. Therefore, any inhomogeneity of whole body radiation exposure increases the chance of an autologous haematopoietic recovery.

8.3. Pathophysiological principles for the response of haemopoiesis to whole body radiation exposure

If one is applying the pathophysiological principles of the response of haematopoiesis to whole body radiation exposure to a concrete patient, the following observations can be made:

In Fig. 8-1a, one can see the blood cell changes in the first 4 weeks after essentially lethal whole body radiation exposure. The data shown are taken from the Tokaimura accident review [13].

It is of great interest to note that the *leucocytes* (WBC) of Patient A show a significant initial granulocytosis with values up to about 30 000 per mm^3 within 24 hours (Fig.8-1a in the Annex). For about 4 days the leucocyte count remains above 5000 (normal range). Thereafter, one sees a precipitous drop of leucocytes to reach minimal levels after 5–6 days. Thereafter, for another 10 days, there is hardly any leucocyte countable in the peripheral blood. Beyond day 15 one sees a leucocyte recovery which is due to the successful engraftment of peripheral blood stem cells. The peripheral blood stem cell transplantation was performed on day 5 and 6.

As far as the *lymphocytes* are concerned, they drop to essentially zero within 2 days after exposure. However, already within 24 hours one can see that there are hardly any lymphocytes left in the blood. A recovery is not recognizable essentially within 20 days. As far as platelets are concerned, one can recognize a progressive decline within 5 days with a slight shoulder between Day 5 and Day 10. The course of platelets is of course influenced by platelet transfusions that had to be given in order to combat thrombocytopenic bleeding. In order to recognize the significance of haematopoietic cell renewal for the diagnosis and prognosis of the acute radiation syndrome, it is of paramount importance to understand why the blood cell changes occur the way they do. This can be derived schematically from Fig. 8-1b.

The first key element to understand the behaviour of granulocyte changes in the peripheral blood is to recognize that the transit time of the maturing-only pool ($t_b + t_c$) of granulocytic cells is about 4 days (14). If one assumes a situation — "Case 1" — whereby the dividing maturing pool of granulocytic precursor cells (t_a) is completely eradicated by ionizing radiation, then one would expect that the maturing-only cells mature to become neutrophilic granulocytes and are released into the peripheral blood. Since these maturing-only cells ($t_b + t_c$) are relatively radioresistant, one would expect that a normal granulocyte concentration is maintained for up to about 4 days. If the dividing maturing compartment (t_a) (transit time about 6 days) is completely eradicated by ionizing radiation, then one would expect a precipitous drop of granulocytes in the peripheral blood between days 4 and 6 with a granulocyte disappearance halftime of about 7 hours. Thus, a severe granulocytopenia by Day 5–6 would indicate that the dividing maturing pool of granulocyte precursors was essentially destroyed by radiation. The stem cell pool (St. + P. Cells), which is even more radiosensitive than the cells in the dividing maturing pool, is obviously eradicated also and would not be able to restore the granulocytic cell renewal system.

If one would assume, "Case 2", that the ionizing radiation would *not* affect the dividing maturing pool (which is an unrealistic assumption), but would *only* affect the stem cell pool (St. + P. Cells), then the entire behaviour of the blood response curve would be different. Under these circumstances (only stem cell eradication), one would expect a continuing

granulocyte production for about 10 days (4 + 6 days) before then the system fails. Under these (theoretical) considerations, one would have a precipitous drop of cells between Day 10 and 12.

Thus, the granulocyte pattern in Patient A (Fig. 8-1a) may well be interpreted to mean that, first of all, the entire stem cell pool as well as the dividing maturing pool of granulocytes has been eradicated indicating an essentially "irreversible damage" to the blood cell replication and production. Otherwise, the pattern of granulocytes would be different as seen in cases of essentially reversible damage of the haematopoietic system. This granulocyte response is schematically depicted as "Case 3" in Fig. 8-1b. In this scheme, it is assumed that the cells in compartment t_b and t_c continue to mature and to be released into the blood for about 4 days. Thereafter, there is a phase of "degeneration" due to the fact that the pool of "dividing-maturing" cells (M1, M2, M3 and M4) is partially damaged so that there are cells that enter the pool $\neq t_b$ and t_c and are released into the blood. Thus, there is a granulocyte decrease between days 5 and 10 but the shallower slope indicates the continuation of some proliferation and maturation in t_a. At the same time, there will be a regeneration of cells in the pool of stem- and progenitor cells (St. + P. Cells) somewhere in the marrow of an irradiated person, resulting in a recruitment of cells in the t_a pool, resulting in newly regeneration granulocytes ("regeneration"). Therefore, the granulocyte pattern of "Case 3" is compatible with an onset of an "abortive rise" and the resulting slope of granulocyte concentration is indicative of a potentially "reversible damage" to the system (see later haematological grading H3).

Secondly, it is of interest to interpret the early granulocytosis. It is known from experimental studies [15] that there is a bone marrow stress syndrome resulting in a severe and immediate granulocytosis. Unlike the platelet system and the red cell system, there is in granulocytopoiesis a relatively large reserve of mature granulocytes in the bone marrow as well as in the so-called marginal blood pool that are mobilized under "stress conditions" [15]. This mobilizable granulocyte pool is released into the peripheral blood as a "stress reaction". The more severe the stress is, the higher is the granulocytosis in the peripheral blood.

As far as the interpretation of the thrombocyte curve is concerned, it appears sufficient to state here that a biomathematical model of the megakaryocytic-platelet curve indicates how such a precipitous drop of platelets can occur [16]. Very similar to the argumentation of the pathophysiology of the granulocyte changes one has to state that if the platelets disappear from the peripheral blood even earlier than 10 days, one has to consider that the entire megacaryocyte plus the stem cell system is destroyed by ionizing radiation and that there is even a thrombocytopenia caused by premature removal of platelets from the peripheral blood (reduction of life span of platelets as in ITP (idiopathic thrombocytopenic purpura)). Such a premature precipitous drop of platelets together with the typical granulocyte pattern of most severe granulocytopenia within 5 days is indicative of an irreversible damage of the haematopoietic stem cell pool. This severe damage is confirmed also by the lymphocyte depression due to severe impairment of lymphocyte recirculation as well as lymphocyte radiation sensitivity. Thus, the early blood changes observed (within 6 days after irradiation) in granulocytes, platelets and lymphocytes can be taken together as a response pattern are indicative of an *irreversible haematopoietic damage which only can be overcome by stem cell transplantation*.

In summary, if there is within 24 hours an extensive granulocytosis combined with an extensive lymphopenia and an early "downhill course" of thrombocytes, then the likelihood of a severe, if not irreversible, damage to the stem cell pool can be assumed.

The experienced haematologist will of course perform one or several bone marrow aspirations to obtain a bone marrow particle smear for cytological evaluation. Such a bone marrow particle smear would indicate within 24 hours after exposure severe cytological abnormalities, such as nuclear oedema, increased karyorhexis and karyolysis and, beginning after 24 hours, mitotically connected abnormalities (clumpy metaphases, binucleated cells, cytoplasmic bridges, etc.) [17].

One of the lessons learned from reviewing radiation accident victim case reports is that within 24 hours the experienced haematologist can state with high probability whether one must expect an essentially irreversible damage of haematopoiesis or whether there is a chance for survival leading to the proposal of using stimulatory factors to induce haematopoietic recovery.

The time and space for this paper does not allow a detailed description of the pathophysiological mechanisms resulting in the haematological changes that can be observed after total body radiation exposure and the reader is referred to appropriate references [1].

8.4. Strategic approaches to assess the severity of radiation injury to haematopoiesis

In 1965, Bond, Fliedner and Archambeau [18] suggested on the basis of reviewing the experimental radiobiological literature that radiation-induced lethality can be best explained as a consequence of a perturbance of cellular kinetics. The authors showed very clearly that all signs and symptoms of the acute radiation syndrome both in animals and in man are the consequence of the interaction of ionizing radiation with the different most critical cell renewal systems of the body, such as haematopoiesis, gastrointestinal, mucous membranes and other cell renewal systems, such as the skin.

The enormous wealth of data collected in the international SEARCH database system confirm the reproducibility of clinical signs and laboratory symptoms in accidentally whole body exposed human beings. This lead to the conclusion that a *sufficient number of biological indicators of effect and repair are available very early after radiation exposure to assess the severity of effect, to predict the most likely outcome and to decide on the principle modes of treatment of the acute radiation syndrome and especially of the effects on haematopoiesis*.

To examine this proposal, a concerted action entitled "METREPOL" [1] was started by the European Commission's Nuclear Fission Safety Programme to find a consensus regarding the indicators to be used in radiation accident management.

Fig. 8-2 shows the METREPOL approach for the triage phase of radiation accident management. If there is a suspicion of an accidental total or significant partial body exposure, the diagnostic process consisting of establishing the case history, the physical examination, the laboratory tests and additional diagnostic measures will result in an organ-specific grading of the severity of radiation effect. This will allow the establishment of a *grading code* resulting in a *response category* (RC) for a given time point after the acute radiation exposure. The logic behind this approach was taken from clinical medicine: in oncology it is well established to use a grading code (TNM-classification) to describe the severity of a cancer lesion in order to plan the appropriate therapeutic measures. What is of importance to a medical doctor is to assess the 4 most important organ systems as to the severity of damage.

The most important organ systems are the neurovascular system, the haematopoietic system, the cutaneous system and the gastrointestinal system. For each organ system, 4 degrees of damage were identified. For each degree of severity, the question as to whether an autochthonous recovery is possible or not has to be posed or whether specific therapeutic measures might be indicated if an autochthonous recovery is not possible or most unlikely (Fig. 8-3).

For each organ system several indicators are recommended to be used to classify a patient according to a degree of severity code relevant to the question of spontaneous recovery or not. The diagnostic approach taken in this triage process would require the systematic evaluation of 25 indicators as a function of time after acute exposure (Fig. 8-4). As far as the haematopoietic system is concerned, this grading approach relies on the response pattern of granulocytes, thrombocytes and lymphocytes as a function of time as well as on the question of the manifestation of infection and/or blood loss.

Using this approach recognizing not only the haematopoietic system but the neurovascular system, the cutaneous system and the gastrointestinal system as well (Fig. 8-4), it is possible to determine the grading code and, on that basis, the response category for a given time after exposure (see Fig. 8-5).

As far as haematopoiesis is concerned, the systematic assessment of signs and symptoms allows within 24 hours the first prediction of the possible clinical course and the therapeutic measures to be taken. The appropriate response category for a given patient is firmly established for the haematopoietic organs within 5–6 days. In the example given in Fig. 8-5, one can see that for a patient with a moderately damaged neurovascular system (N2), with a grading code H3 for haematopoiesis (meaning that autologous recovery is possible), with hardly any evidence of a cutaneous syndrome and with some evidence of a gastrointestinal damage, such a grading leads to a RC3 on the second day after exposure.

In Fig. 8-6, the early blood cell pattern characteristic of an irreversible damage to the haematopoietic system, is shown for several radiation accidents. Such a pattern for a grading code H4 includes progressive decrease of granulocytes towards day 5 and day 6 to severely granulopenic levels, a progressive decline of platelet counts in the peripheral blood towards day 10 and a severe decline of lymphocytes within 1–2 days. This pattern is compatible with the assumption of an *essentially irreversible damage of the haematopoietic stem cell pool* throughout the blood cell forming bone marrow.

In contrast, the blood cell changes in patients assigned to the grading code H3 can be characterized as follows: the granulocyte do not show the excessive granulocytosis during the first 3 days as it is seen for grading code H4. There is some decline of granulocytes, but on Day 5 and Day 6 there is still a measurable granulocyte level in the peripheral blood and the nadir of granulocytopenia is only seen between Days 20–25 (for a pathophysiological explanation see Fig. 8-1b).

As far as platelets are concerned, it can clearly be shown (Fig. 8-7) that there is an initial shoulder for the platelets during the first 10 days. A severe thrombocytopenia develops only between Days 20–30. The platelet numbers in the graph are higher than they would be, if no platelet transfusions were given. A slow recovery occurs beyond Day 25.

The pathophysiological basis for this type if behaviour of granulocytes and platelets is given in Fig. 8-8. In the above mentioned monograph on Mammalian Radiation Lethality: A Disturbance of Cellular Kinetics [18] it was postulated that this type of granulocyte and platelet response after ionizing whole body radiation can be explained by the so-called "injured cell hypothesis" (Fig. 8-8). In this hypothesis, it is assumed that acute radiation exposure results in an almost instantaneous death of more than 95% of haematopoietic stem cells. The final recovery after acute radiation commences from the intact or completely repaired haematopoietic stem cells (time parameters on the abscissa are derived from rodent experiments). The hypothesis further postulates that the radiation exposure results in the production of "injured stem cells". These are cells that are injured and repaired to such an extent that they can undergo a limited number of cell replications before their clone dies out. If such assumptions are made, all biomathematical models indicate that there would be an "abortive rise". This is the reason for the particular pattern of granulocytes assigned to a characteristic for a grading code H3 and also the shoulder seen in the platelets. If one is analysing the bone marrow in these human beings, one can find between days 5 and 10 evidence of some haematopoietic recovery and a significant number of mitotically connected abnormalities indicating the attempt of the bone marrow to recover from the inflicted radiation damage.

In Fig. 8-9 granulocyte values and platelet values are plotted for 21 Chernobyl victims who were accidentally exposed during the night of April 26, 1986[*] [19]. These patients in essence would be assigned initially to the severity grade H3. These cell plots indicate very clearly the early abortive rise between the first 15 days after radiation exposure, the nadir of granulocytes and of platelet counts between days 20 and 30. In all these patients there was a spontaneous recovery of haematopoiesis and during the first year there seems to be a slight overshoot of numbers and then a slow progressive return of counts into the normal range.

This METREPOL approach to classify patients after acute radiation exposure into "severity groups" that are prognostically meaningful regarding especially the therapeutic measures to be taken, allows a number of conclusions. The assessment of blood cell changes (granulocytes, lymphocytes and platelets) allow the medical doctor to determine the severity of damage and hence the grading (H4, H3, H2 and H1) for the haematopoietic tissue within a maximum of 5–6 days after exposure. Such a haematological grading allows one to answer the following question: Is there a high probability of a reversible or an irreversible damage to the haematopoietic tissue distributed throughout the skeleton?

The haematopoietic grading should be considered as an integral part of the entire triage process and allows the medical doctor to determine the response category comprising the severity of radiation-induced damage to the most critical organ systems (neurovascular, cutaneous, gastrointestinal and haematopoiesis). The systematic assessment of 25 indicators of effect that can be easily determined during the first few days after radiation exposure of the critical organ systems are sufficient for a patient grading and, if necessary, performing the appropriate therapeutic measures.

The METREPOL approach is not relying on any "physical dosimetry". It acts on *indicators of effect and repair* without necessarily disregarding indicators of exposure (physical dosimetry). The justification for such an approach is that in most, if not all, radiation accidents there is a

[*] This study was done in close collaboration with Prof. Bebeshko and his team in Kiev and Prof. Baranov and his team in Moscow.

high probability of an inhomogeneous exposure. However, the haematological damage depends very closely on the extent of radiation effects of the haematopoietic stem cell compartment, which is distributed throughout the body and interconnected by blood stem cell traffic. Therefore, any inhomogeneity of exposure acts in favour of the recovery potential of the patient and may allow a spontaneous recovery of haematopoiesis in spite of the extent of damage on other organ systems, such as the skin. The details of this approach and the scientific reasoning can be found in Ref. [1].

8.5. Approaches to the treatment of haematological consequences of whole body radiation exposure

The details of recent approaches to treat radiation accident victims suffering from an acute radiation syndrome are comprehensively covered in the METREPOL manual [1]. Therefore, it is sufficient to give in this review the principles used to propose therapeutic options.

In Fig. 8-10 one can derive the logic of the approach. Patients suffering from the RC1 will experience an autologous recovery. Therefore, the only therapy necessary will be general support of recovery processes in affected organs, but no specific therapy is usually needed. Of importance is that patients classified on the basis of organ-specific grading codes into the category RC1 can be taken care of on an out-patient basis. They do not need hospitalization. However, what is important is to register all signs and symptoms in the course of disease and to establish beyond doubt that they have had an exposure to ionizing radiation (for instance, by chromosomal analysis). This is important, not only for clinical reasons, but also for forensic reasons and later juridical claims.

Patients classified into RC2 will also experience an autologous haematological recovery. The examples for patients in RC2 derived from the database system SEARCH indicate that sometimes supportive care is needed and in case of a manifestation of infection during the treatment phase or evidence of a slight blood loss (nose bleeding, petechiae, erythrocytes in the urine) some medical doctor may feel obliged to give a blood transfusion or a platelet transfusion or to administer antibiotics. For these patients, medical wards are sufficient, if there is appropriate haematological-oncological, neurological or dermatological consultation services.

From the viewpoint of haematology, the patients assigned to RC3 and to RC4 require the most intensive attention. In the case of RC3 an autologous recovery is possible, if all modern tools and techniques of therapy of an extensive but nevertheless transient haematopoietic failure can be applied and used. Therefore, these patients should be admitted to haematological-oncological services, which are used to treat cancer patients with high-dose chemotherapy. The respective medical services will usually have available protected environment beds which allow an essentially "gnotobiotic" treatment. These patients are vulnerable to their own endogenous microbial flora during the time of haematopoietic failure. These patients may also need the services of an intensive care unit. They will be the patients that benefit most from growth factor therapy in order to enhance haematopoietic recovery.

If the clinical judgement shows that a patient belongs to RC4, it is clear that a spontaneous haematopoietic recovery from the haematopoietic stem cell pool is most unlikely. In this case, the first and most important approach is to select a stem cell source. Since in most cases autologous stem cells are not available (except in the situation where the patient has an

identical non-irradiated twin), one has to look for an appropriate histocompatible donor. The stem cells can be taken from the bone marrow, but it may well be that enough can be removed from the peripheral blood, such as was done in Tokaimura in 1999. There may also be a chance to use cord blood cells (as in Tokaimura in 1999), however, one must be aware of the fact that for an adult a cord blood donation might not give enough stem cells. It may well be that one has to use a non-identical donor and this would require to initiate all the steps that are necessary as in any allogeneic stem cell transplantation. This means also that this type of treatment need and can be done in hospitals that are used to perform stem cell transplantation in oncological patients.

The specific therapeutic approaches for the different *haematological grades of severity* of effect can be summarized as follows: *treatment options grading H1* (autologous recovery certain): first, it is recommended to use a general support approach of the recovery processes. Usually no specific haematological therapy is required. Therefore, out-patient care may be sufficient. Regular examinations to confirm the initial grading code as well as the response category is recommended. Secondly, it can be expected that in these patients the platelet levels do not drop below 50×10^9/L but slight platelet count depression may be observed between Days 15 and 30. Thirdly, the manifestation of bacterial infection is usually not seen, since the blood granulocyte level is maintained at a sufficient level of more than 2×10^9/L. Should, however, infection occur, it is advised to determine the antibiotic sensitivity of the microbial flora in order to give the best possible antibiotic treatment.

Therapeutic options grading H2 (autologous recovery likely): in these patients, a general support for overcoming the consequences of radiation exposure is advisable. The principle treatment strategy is to bridge the days of haematopoietic failure determined by the nadir of granulocytes and platelets between about Days 15 and 30. In these cases substitution therapy may be necessary: platelet transfusions should be given to maintain a platelets concentration, if possible, of more than 20×10^9/l. The time during which platelet support may be needed in this category may be 5–10 days. As indicated later for H3, one transfusion requires 4 blood donors. Thus, in H2, the number of volunteers for 1 patient may be a minimum of 20. Stimulation therapy using growth factors may be indicated. The period of granulocytopenia without growth factor therapy may be up to 10 days. Since growth factors may also affect the relative differentiation of stem cells into the various haematopoietic cell lineages, one should restrict the administration of growth factors to patients in whom the time of a haematopoietic failure is too long. Further supportive therapy using antibiotics, fungostatic or antiviral drugs should be administered on the basis of observed signs and symptoms.

Treatment options grading H3: these patients are severely sick and require a lot of general support. However, the principle of haematopoietic treatment is to bridge the days of haematopoietic failure, since the stem cell pool may well recover spontaneously. On the basis of this assumption, substantiated by findings within the first 10 days after exposure, the therapeutic option consists of "substitution therapy". Platelet transfusions may need to be given to maintain platelet concentrations, if possible of more than 20×10^9/L. One should be aware of the fact that this type of platelet support may require a lot of donors. Patients in H3 may experience a thrombocytopenic period of 20 days. Therefore (if platelets are given every other day), 40 blood donors are needed. If a hospital has to treat only 10 patients of this category, a total number of 400 blood donors may become necessary. In these patients, it might be advisable to stimulate granulocyte recovery and to decrease the risk of bacterial infection by using growth factor therapy (G-CSF and GM-CSF) to shorten the period of

granulocytopenia. Thrombopoietin (TPO) may be useful in combination with G-CSF. However, more clinical research needs to be done to validate the usefulness of TPO in the treatment of the acute radiation syndrome. Furthermore, it is of importance to reduce the risk of bacterial infections, either from endogenous or from exogenous sources. Therefore, it is reasonable to induce a "gnotobiotic state" and maintain it in a germfree environment. This can be done by the administration of non-resorbable antibiotics and the maintenance of the patient in a protective environment. Systemic antibiotics should be used whenever there is clinical evidence for the development of bacterial or other infections. Furthermore, antifungal and antiviral therapy should be used as indicated.

Treatment options grading H4 (autologous recovery most unlikely): Patients classified in this response category are of course very severely ill. As far as the haematopoietic system is concerned, they pattern recognition of the haematopoietic blood cell changes in the first 3–6 days clearly indicates that there is no chance for an autochthonous recovery of the stem cell pool within a reasonable time period. Therefore, all preparatory steps for a stem cell transplantation are essential. Of particular importance is the early blood sampling to try to use whatever lymphocytes are left to determine the histocompatibility code. This would then foster the search for a suitable stem cell donor. As a rule, it will be an allogeneic donor, either to donate bone marrow or to donate blood stem cells. If it turns out to be impossible to find a suitable bone marrow or blood stem cell donor, then cord blood cells is a real alternative. In any event, the success or failure of stem cell transplantation treatment relies on the administration of a sufficient stem cell number. Clinical evidence indicates that one needs from the bone marrow 3×10^6 $CD34^+$ cells/kg body weight. If one is collecting stem cells from the peripheral blood (after appropriate mobilization), then $2–4 \times 10^6$ $CD34^+$ cells should be in the transfusate/kg body weight. As far as cord blood stem cells is concerned, one should have 0.3×10^8 total nucleated cells/kg body weight. One should, however, be aware, that it takes at least 10 days to expect the first newly formed granulocytes in the peripheral blood. Therefore, one should monitor the likelihood of haematopoietic recovery in the first 10 days after exposure by bone marrow examination. It is also necessary to make sure that the blood platelet concentration remains higher than $10–20 \times 10^9$/L. The time period during which platelets may be needed is difficult to predict: it depends on the speed of platelet recovery. Since there may be competition between granulocytic and thrombopoietic stem cells in the stem cell pool, one should consider whether growth factor therapy would potentially influence the balance between granulopoietic and thrombopoietic cell differentiation. It is of interest to know that in some patients that have received stem cell support and simultaneously growth factor therapy, the platelets had a difficulty to recover as one would have expected it.

8.6. Concluding remarks

It should be stressed that in this strategic paper only the haematological aspects of acute radiation syndrome were considered in some detail. In the real accident situation, however, all other critical systems are involved to a larger and smaller extent: the neurovascular system, the cutaneous system or the gastrointestinal system. The acute radiation syndrome is a multiorgan syndrome requiring, for treatment, all tools of clinical medicine. Therefore, for the grading codes RC3 and RC4 only the well established hospitals with most, if not all medical services are suited to take care of radiation induced disorders. The METREPOL approach as laid down in the Manual of the Acute Radiation Syndrome [1] recognizes the complexity of managing patients with the acute radiation syndrome. In this paper, only the surface of

possibilities and limitations of treating the acute radiation syndrome could be touched. Therefore, the reader is requested to consult the original monograph [1].

8.7. Summary

1. Information on the health consequences of accidental whole body exposure to ionizing radiation is available in internationally available data base systems for more than 800 persons from more than 70 radiation accidents in 14 countries worldwide [1].
2. The haematopoietic system plays a major role in the diagnosis of the acute radiation syndrome and its extend of damage inflicted not only on the haematopoietic system as such but also on the entire body. This is due to the distribution of haematopoiesis and of its stem cell pool in many skeletal bones ("the bone marrow") and the maintenance of a sufficiently sized stem cell pool by a continuous migration stream of stem cells via the blood stream between the sites of haematopoiesis.
3. During the first week after accidental whole body radiation exposure, it is essential and also possible to assess the extent of damage to the haematopoietic system to such an extend that prognostic conclusions can be drawn. For clinical management, it is of paramount importance to know whether the bone marrow in general and the stem cell pool in particular are damaged to such an extent that a stem cell transplantation (source: peripheral blood, bone marrow, cord blood, foetal liver) is the only way to achieve a haematopoietic recovery of granulocytes, platelets and erythrocytes as well as of the immune system.
4. The use of the "Response Category"-Classification based on organ system specific grading codes allows the medical doctor to determine appropriate therapeutic strategies utilizing the specific expertise of the different medical specialties. It is also of high relevance for selecting the appropriate medical services to handle the patients based on their clinical expressions of the acute radiation syndrome.

5. From the viewpoint of haematology, the key question is whether the haematopoietic stem cell pool is damaged to such an extend that an autochthonous recovery cannot be expected within a clinically reasonable time (for instance 4–5 weeks), or whether a spontaneous recovery can be expected. The METREPOL-concept suggests that in the first case (recovery essentially improbable = grade 4) the patient should be treated similar to a patient receiving an essentially lethal dose of irradiation (treatment of leukaemic diseases) followed by sufficiently large stem cell transplantation (stem cell transplantation plus all essential supportive measures). If this is a reasonable chance of an essentially reversible damage to the stem cell pool, an onset of recovery of blood cells can be expected after 30–35 days after exposure. In these cases a transient haematopoietic failure will develop to be treated by platelet transfusions and specifically selected antibiotics and a prudent use of haematopoietic growth factors.

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Annex

PHOTOS AND FIGURES

Photos to Chapter 4 – The accident in Peru

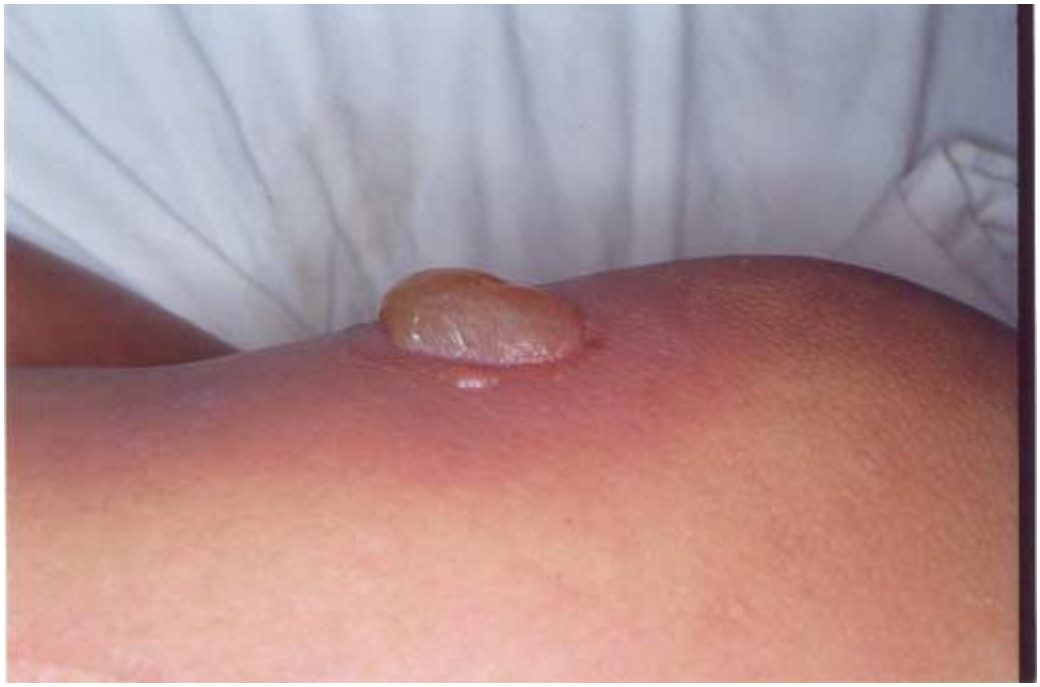


PHOTO 4-1. Blistering lesion surrounded with large inflammatory halo on the mid-upper line of the rear surface of the right thigh on Day 2 (22 February 1999).

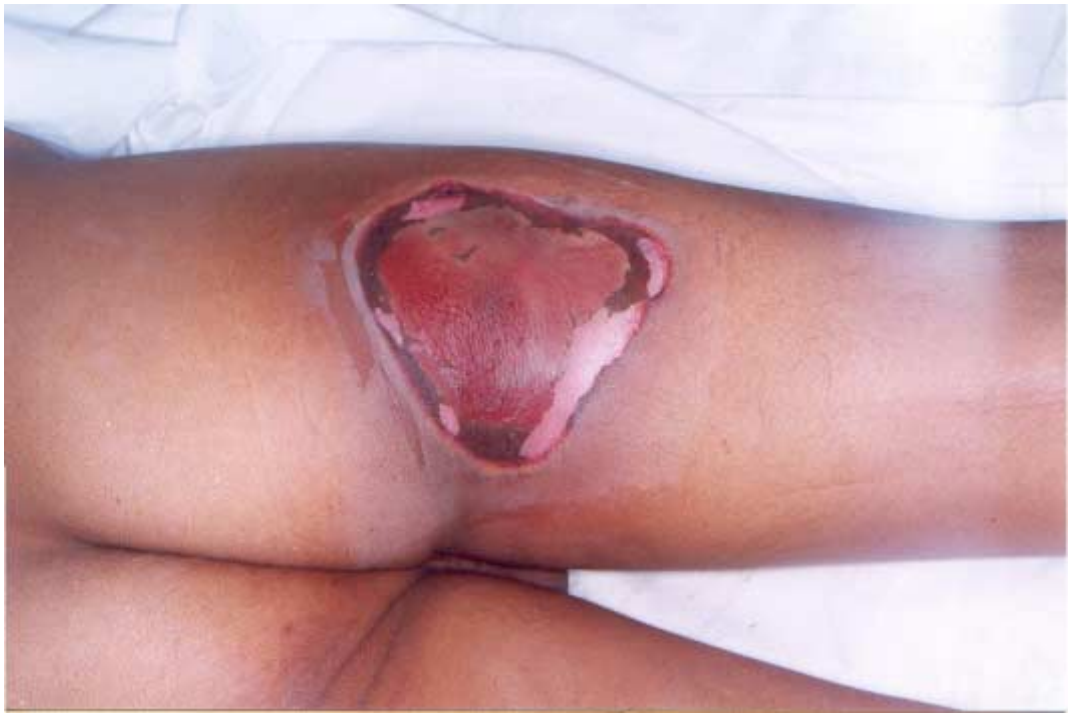


PHOTO 4-2. Extended superficial erosion surrounded by a large dusky (hyperpigmented) inflammatory area in the rear surface of the right thigh on Day 9 (1 March 1999).

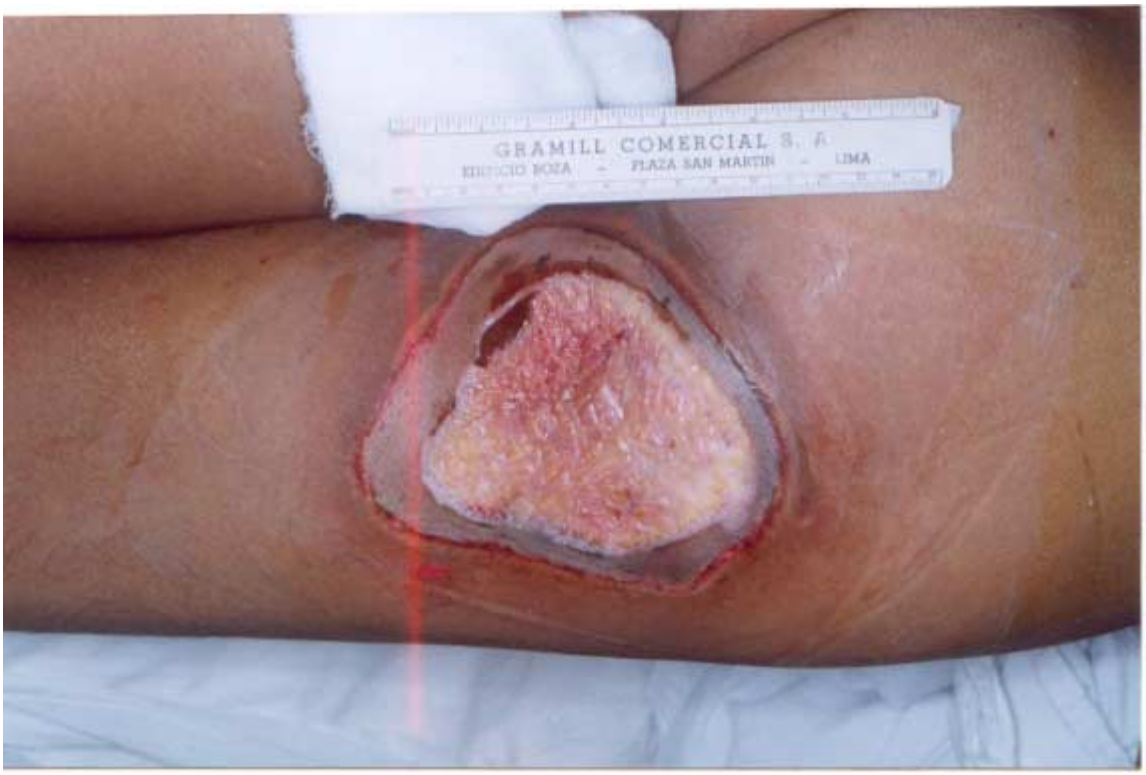


PHOTO 4-3. Superinfected ulcer on the right thigh. The bottom of the lesion is covered by a fibrin crust on Day 27 (19 March 1999).

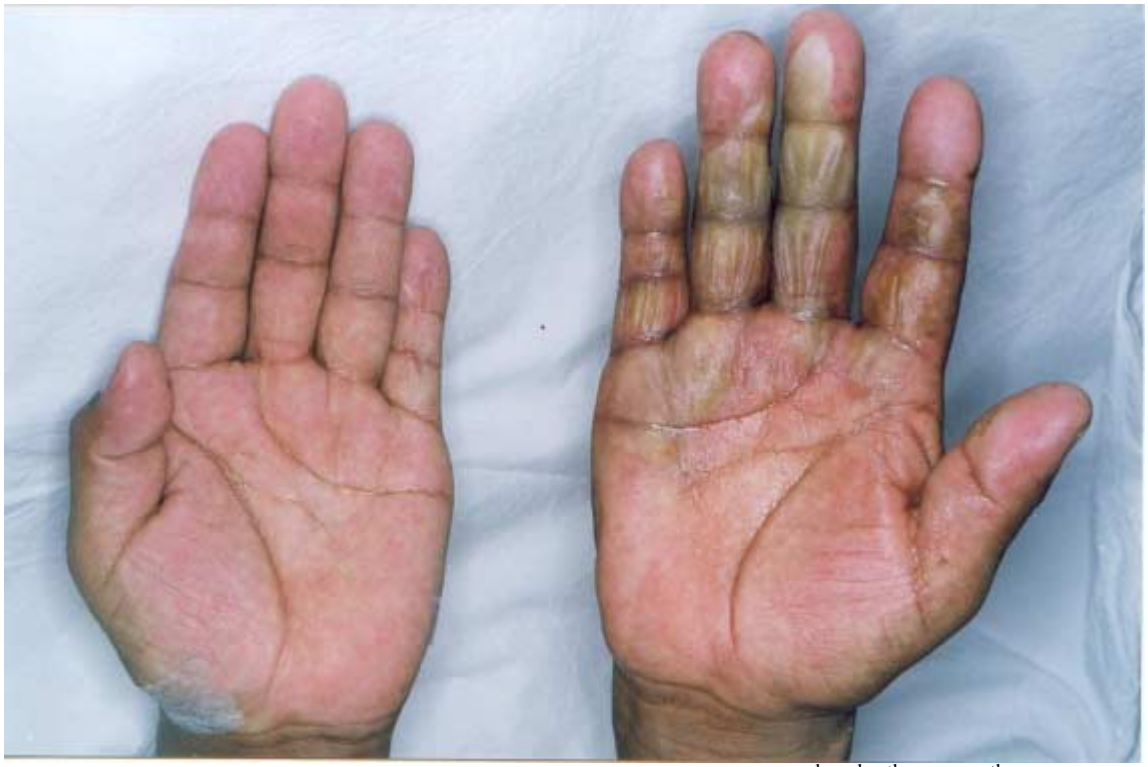


PHOTO 4-4. Blistering of the right hand palmar surface of the 2nd,3rd,4th, and 5th fingers. (Day 50, 13 April 1999).

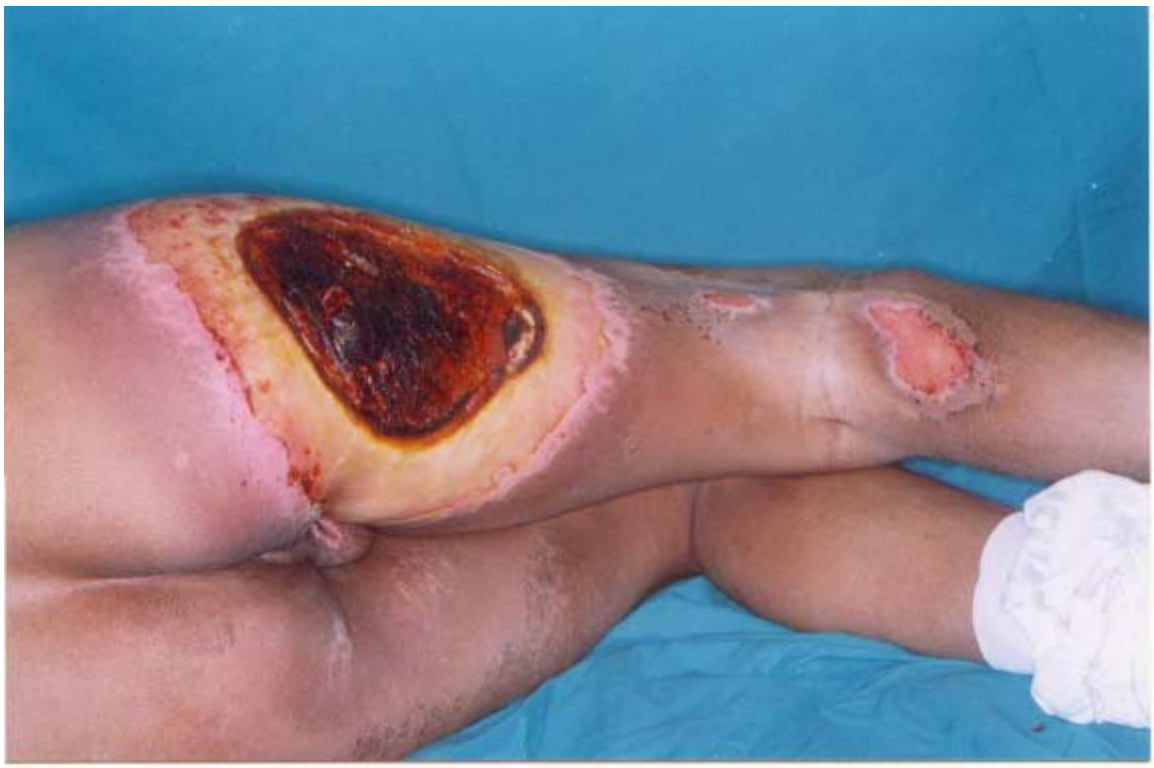


PHOTO 4-5. Very large (20 × 30 cm) necrotic lesion extended in the upper third of the right thigh. The depth of the defect is significant. The bottom is covered by a superinfected crust. The lesion edges are well defined, blistered and are above the surface of the surrounding tissue. They are surrounded by a depigmented halo (on Day 70, 3 May 1999).

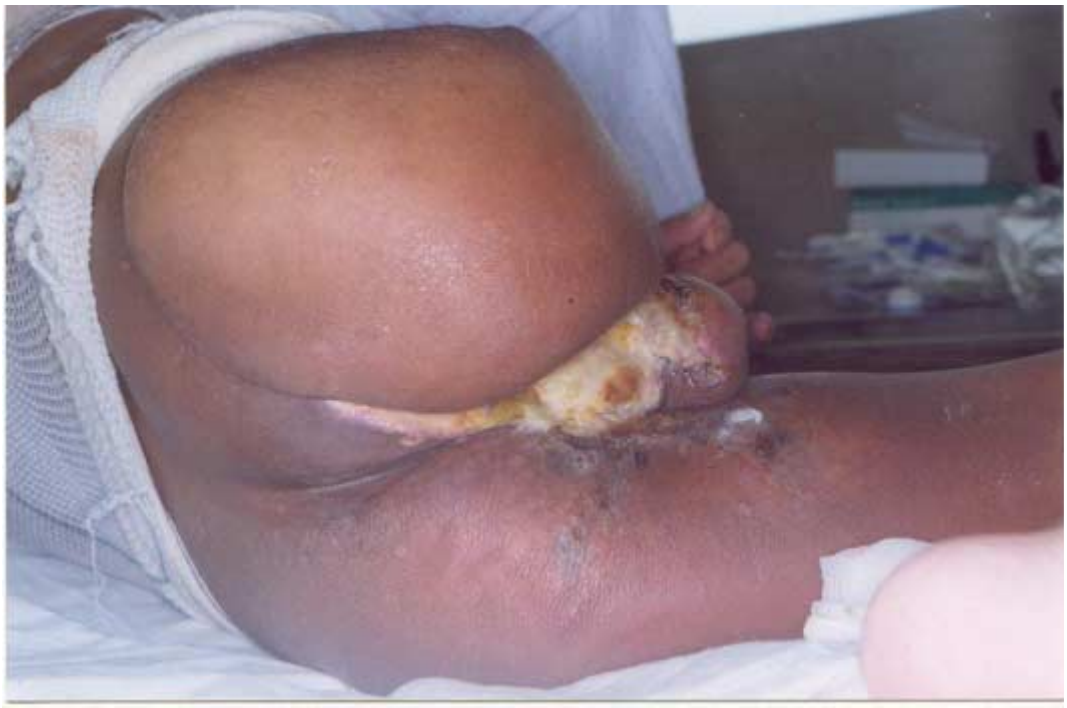


PHOTO 4-6. Colostomy and severe superinfected large ulceronecrotic lesions of the perineum (14 December 1999).

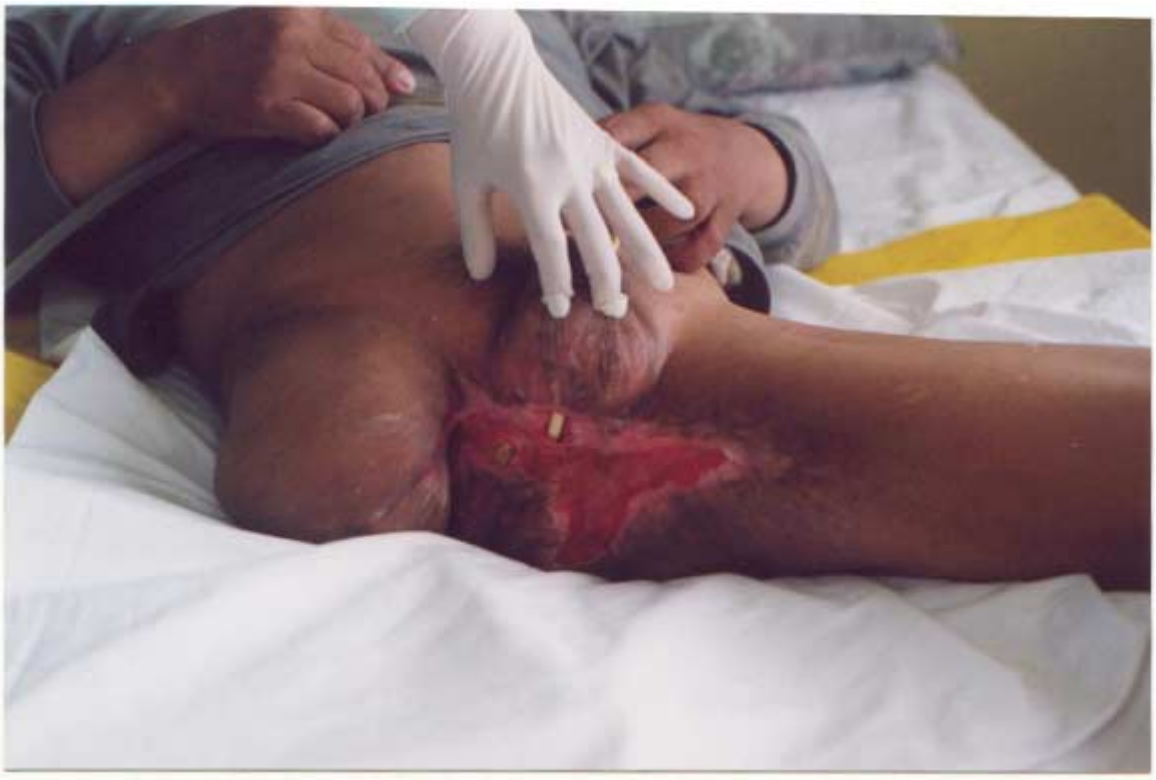


PHOTO 4-7. The urethral fistula is visible following clean up of the wound (Aug.2001).

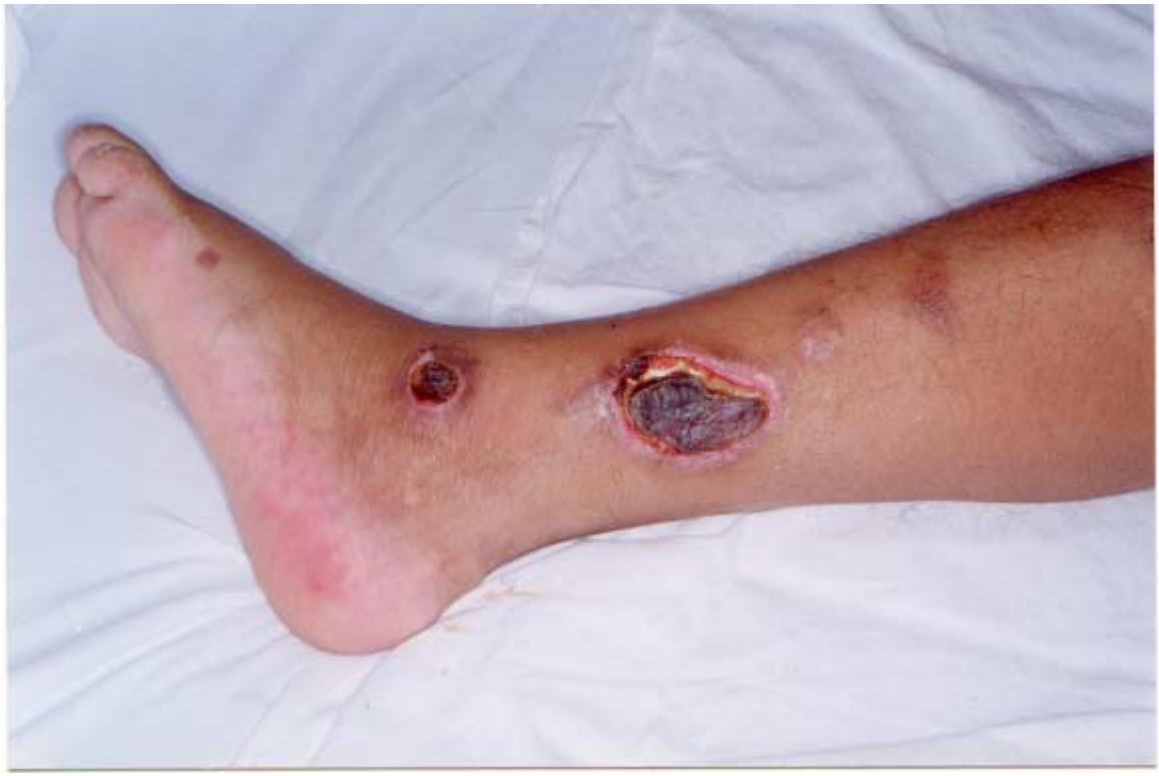


PHOTO 4-8. Infected ulceronecrotic lesions in the external surface of the lower third of the left leg and at the external portion of the ankle (14 December 1999).

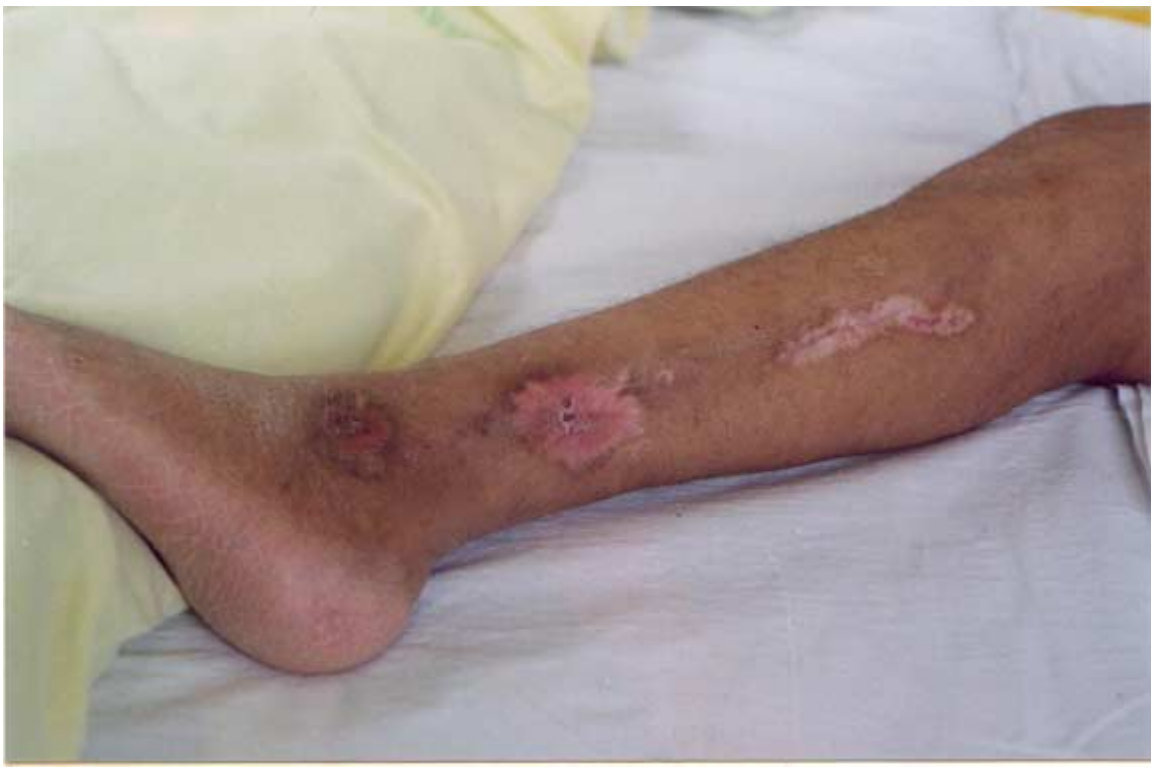


PHOTO 4-9. Reopening of the ulceronecrotic lesions in the external surface of the lower third of the left leg (28 April 2000).

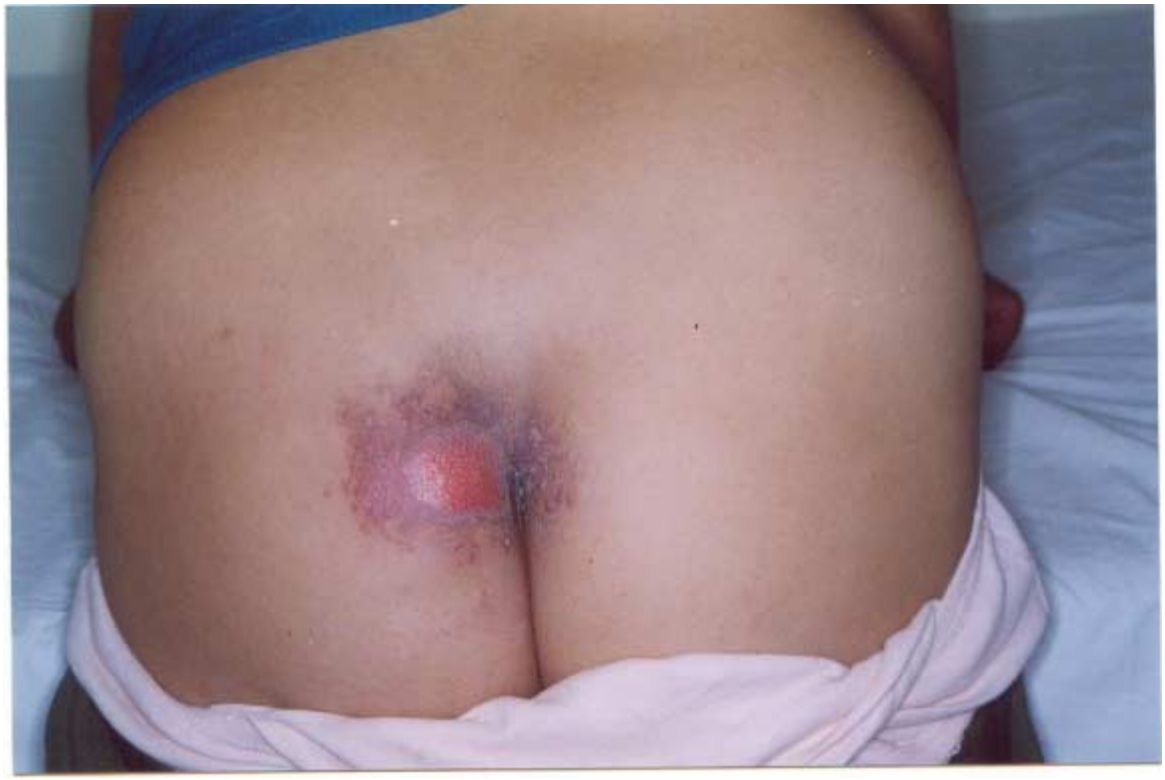


PHOTO 4-10. Small infected circular lesion following moist desquamation surrounded by a colourless halo with punctual haemorrhages on the lower back of the patient´s wife (18 March 1999).

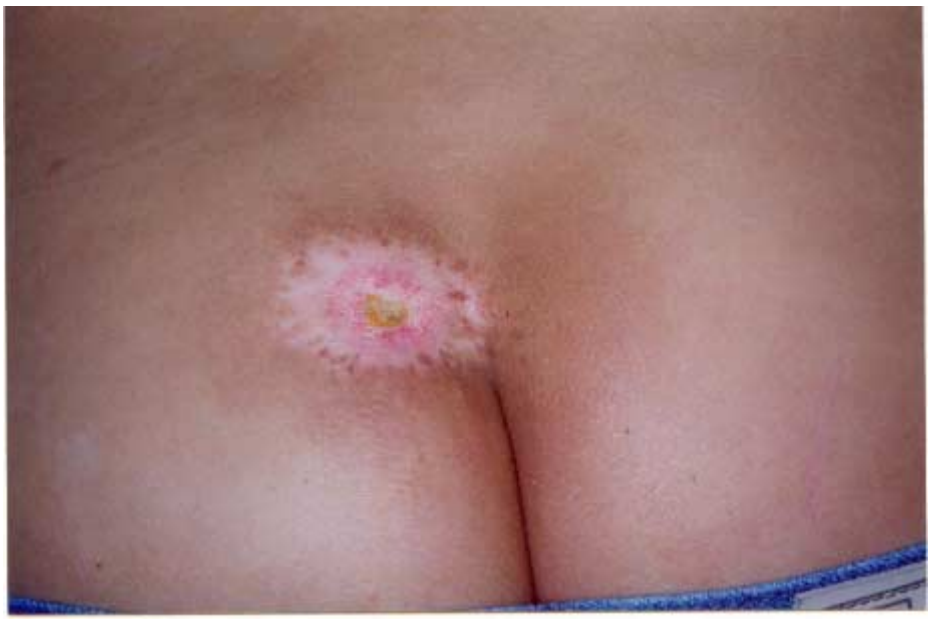


PHOTO 4-11. Ulcerative lesion on the lower back of the patient´s wife (in Oct.1999).

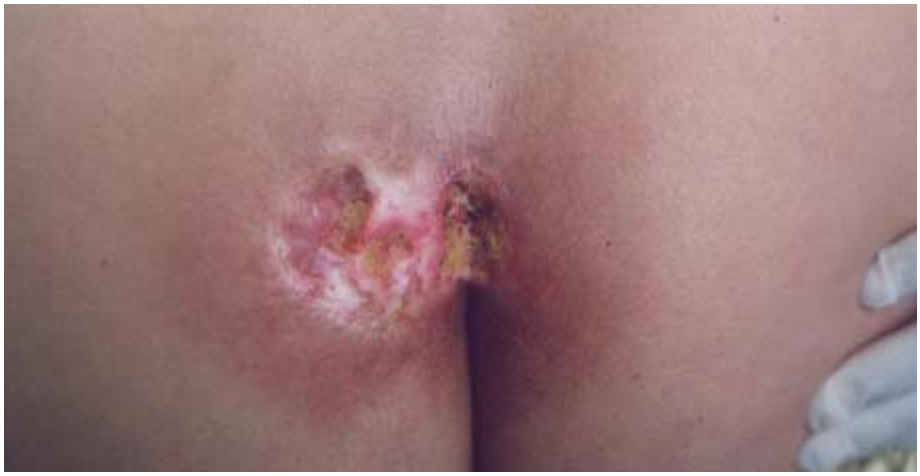


PHOTO 4-12. Ulcerative lesion on the anal area of the patient´s wife (May 2001).

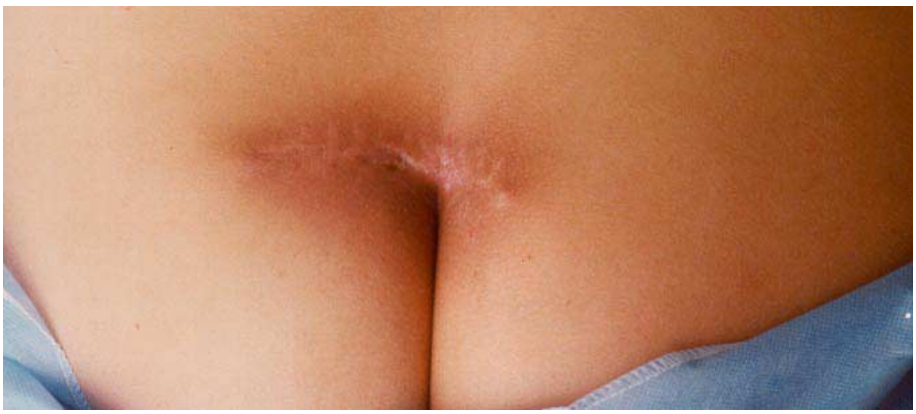


PHOTO 4-13. Ulcerative lesion on the anal area of the patient´s wife operated in June 2001 (Aug. 2001).

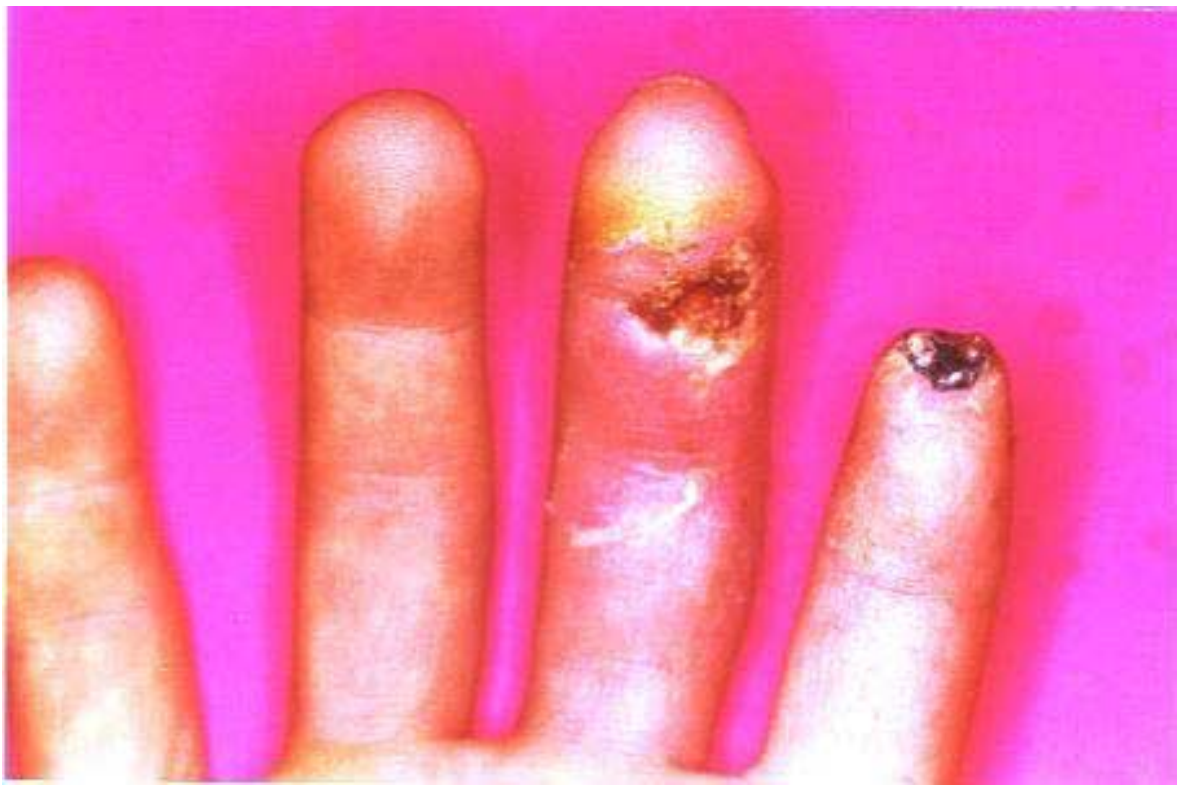


Photo 5-1. A deep ulcer on 2nd IPJ of the 3rd finger and scab on amputation line of the 2nd finger14 months after the accident.

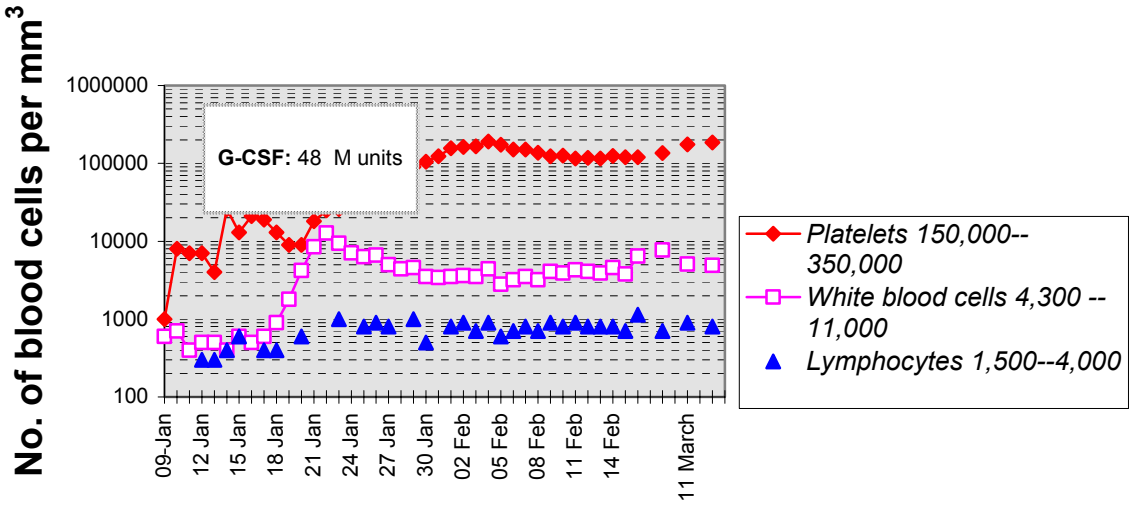


FIG. 5-1. Haematological chart of Patient 1-(MI) during his hospitalization from 9 January to 24 February 1999.

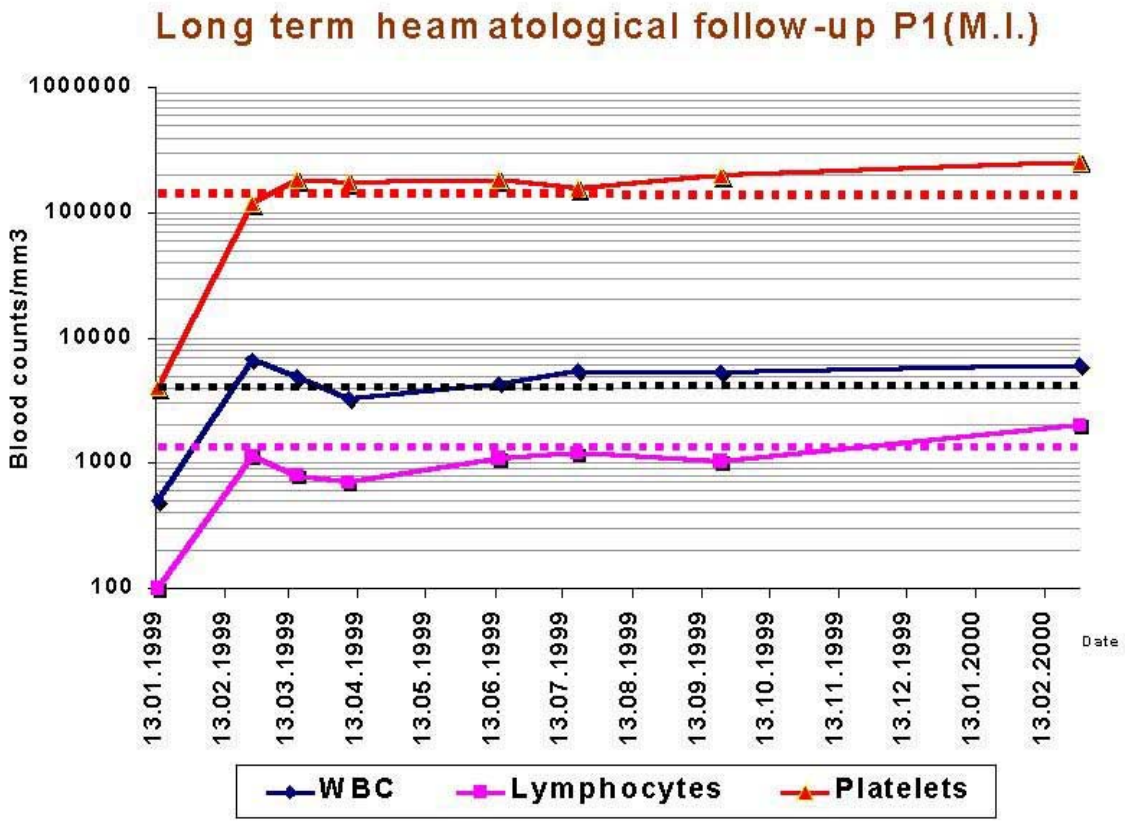


FIG. 5-2. Haematological chart of Patient 1-(MI) during a one-year follow-up.

Figures to Chapter 6

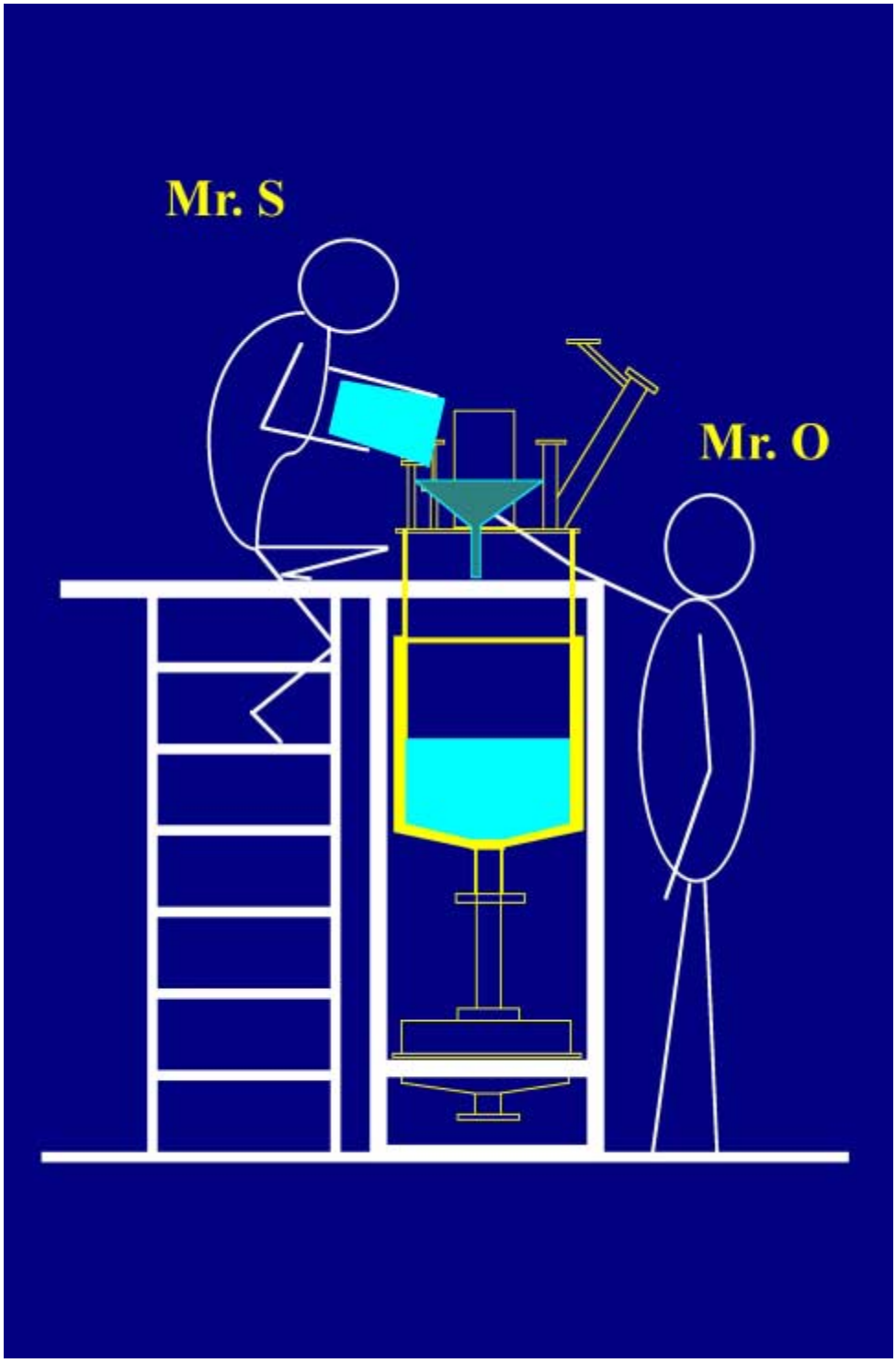


Figure 6-1. Position of workers 'O' and 'S' to the precipitation tank at the Tokaimura criticality accident on 30 Sept. 1999.

Case O was irradiated when he held a funnel by his right hand standing beside the tank at right oblique position. Case S was irradiated when he pour an 18.8%-enriched uranyl nitrate solution by stainless steel bucket bending his knees on a ladder. Case Y was irradiated in the next room.

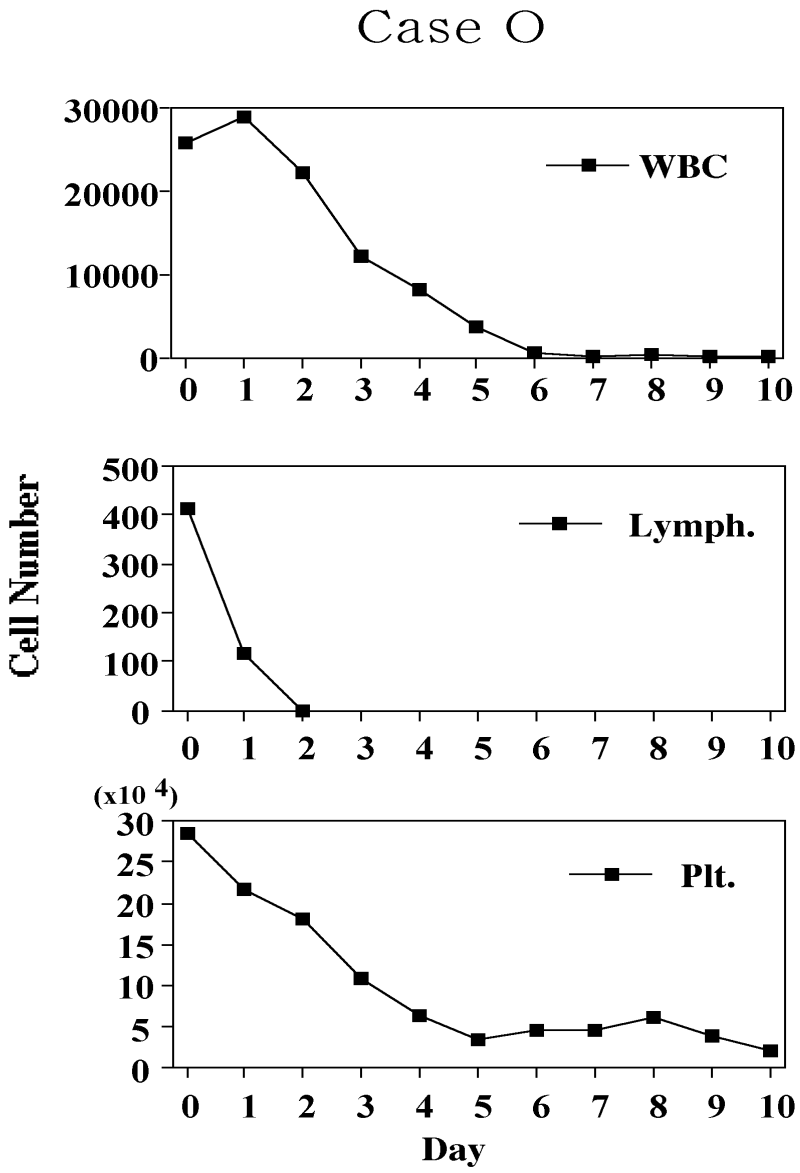


Figure 6-2.a Kinetics of blood cells after exposure of patient 'O' in the Tokaimura accident.

Counting of neutrophil granulocytes, lymphocytes and platelets in the peripheral blood was repeated at least twice a day.

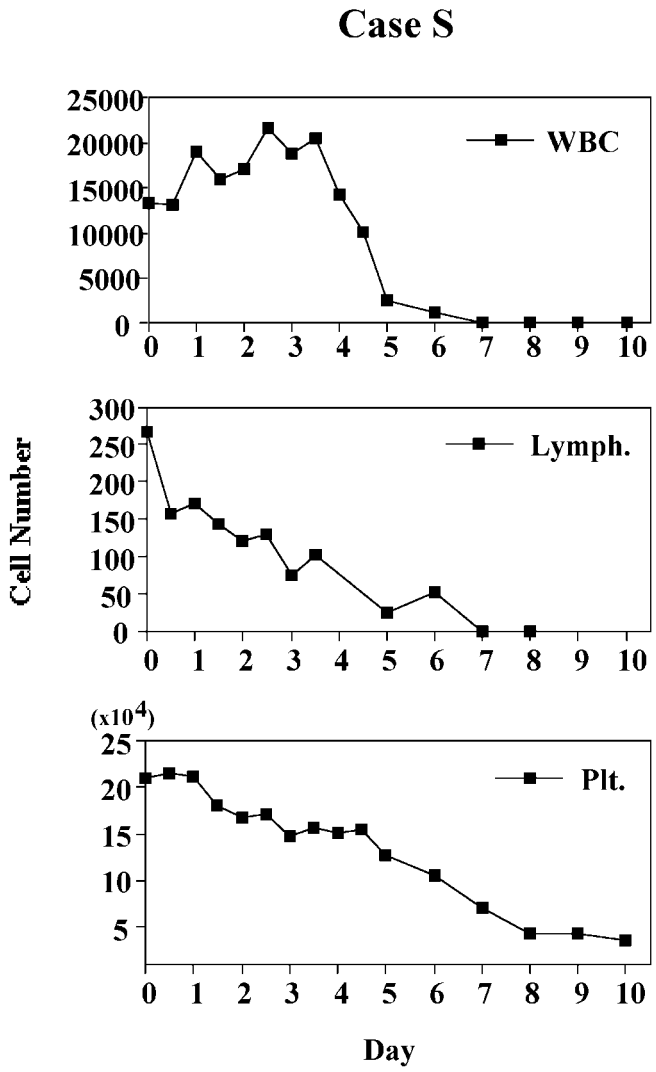


Figure 6-2.b Kinetics of blood cells after exposure of patient 'S' in the Tokaimura accident.

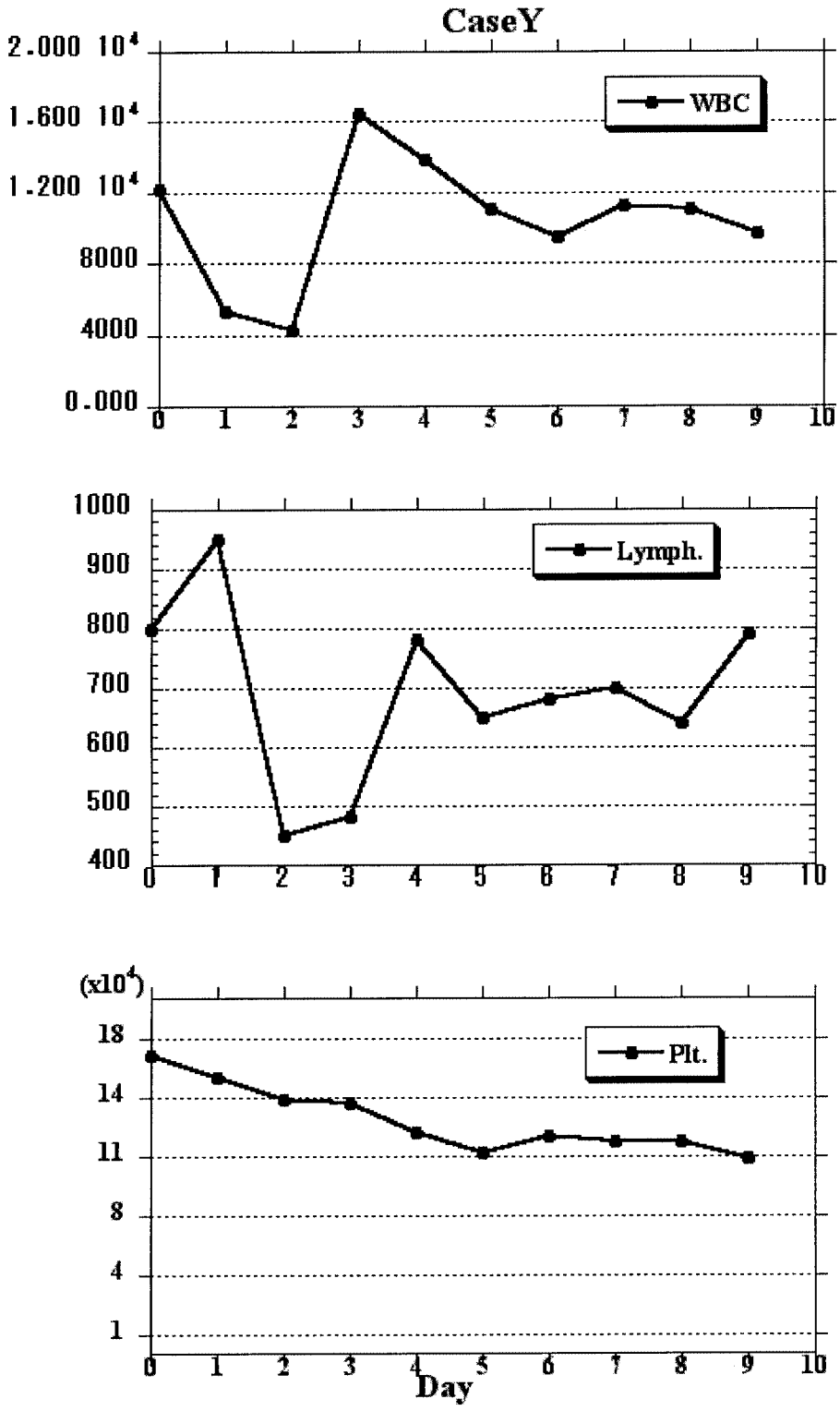


Figure 6-2.c Kinetics of blood cells after exposure of patient 'Y' in the Tokaimura accident.

Figures to Chapter 7

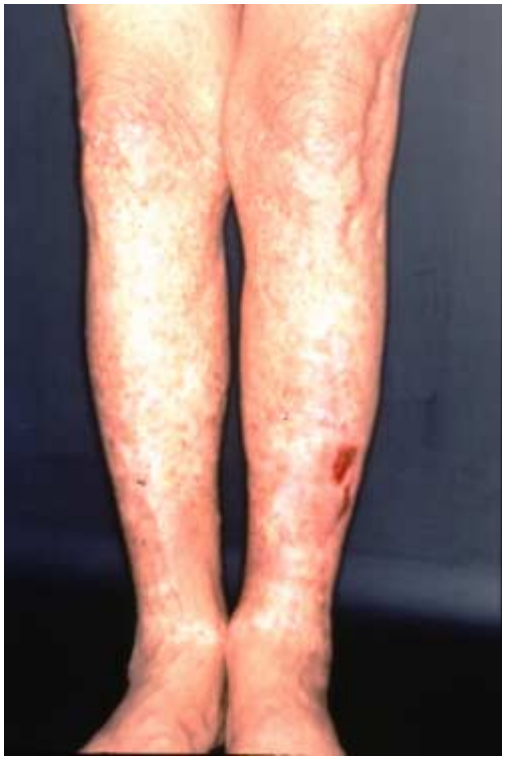


FIG. 7-1. Survivor of the radiation accident in Chernobyl, late stage of the Cutaneous Radiation Syndrome with hypo- and hyperpigmentation, telangiectasias and radiation ulcer.

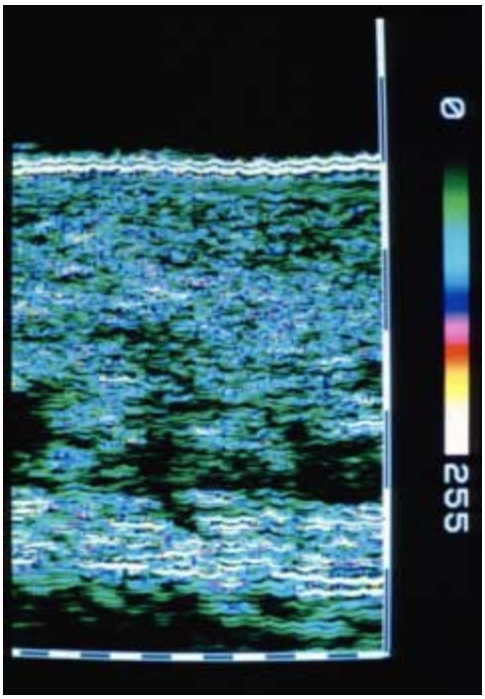


FIG. 7-2. Survivor of the radiation accident in Chernobyl, 20 MHz-sonography (DUB 20, tpm, Germany): The thickness of the corium is increased, very echorich and reaches to the muscle fascia. The differentiation between corium and fatty tissue is difficult. The skin thickness is 4 mm. E-entry echo, c-corium, f-fatty tissue, m-muscle fascia.

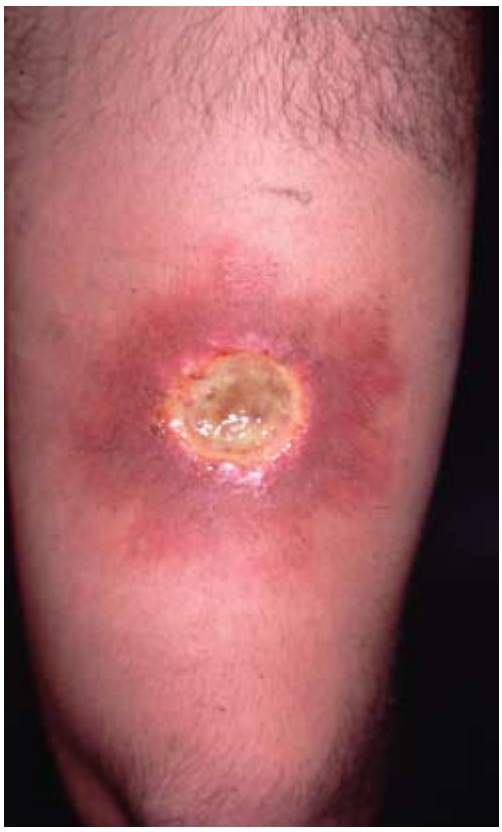


FIG. 7-3. Patient from the radiation accident in Lilo (Georgia): radiation ulcer on the thigh.

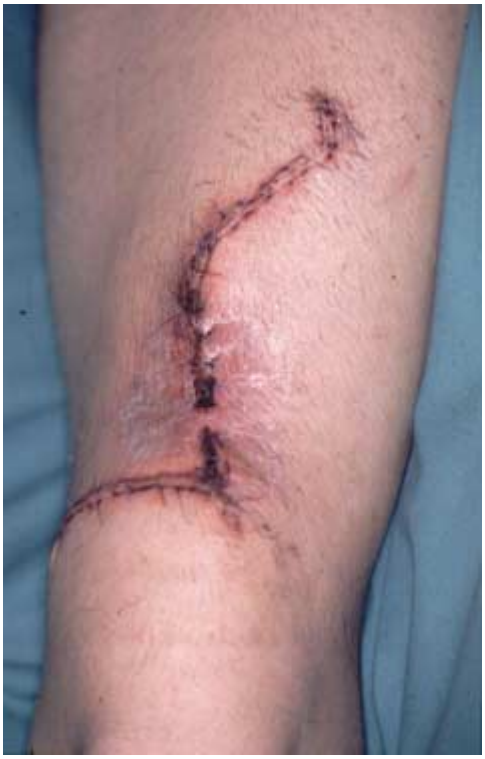


FIG. 7-4. Patient from the radiation accident in Lilo (Georgia): Radiation ulcer was excised and primary closed.

Figures to Chapter 8

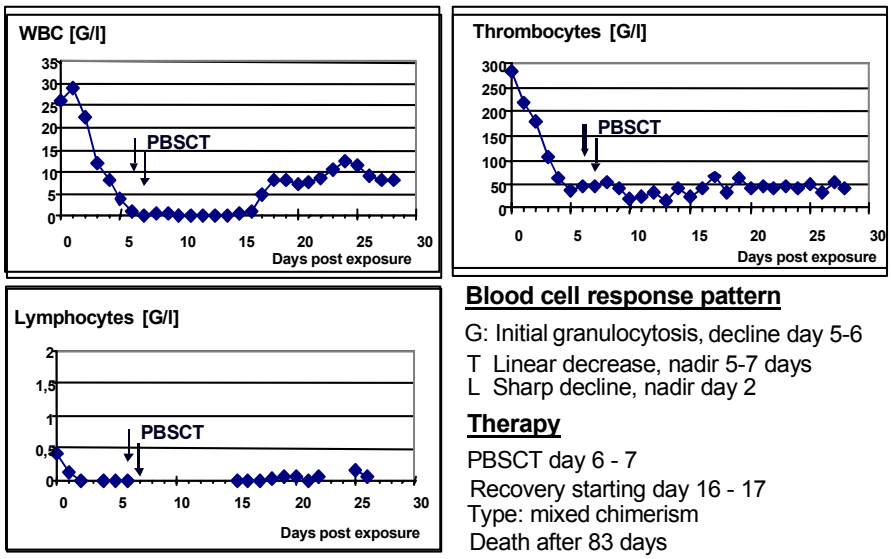


FIG. 8-1a. Clinical course of Patient A (Tokaimura accident in 1999).

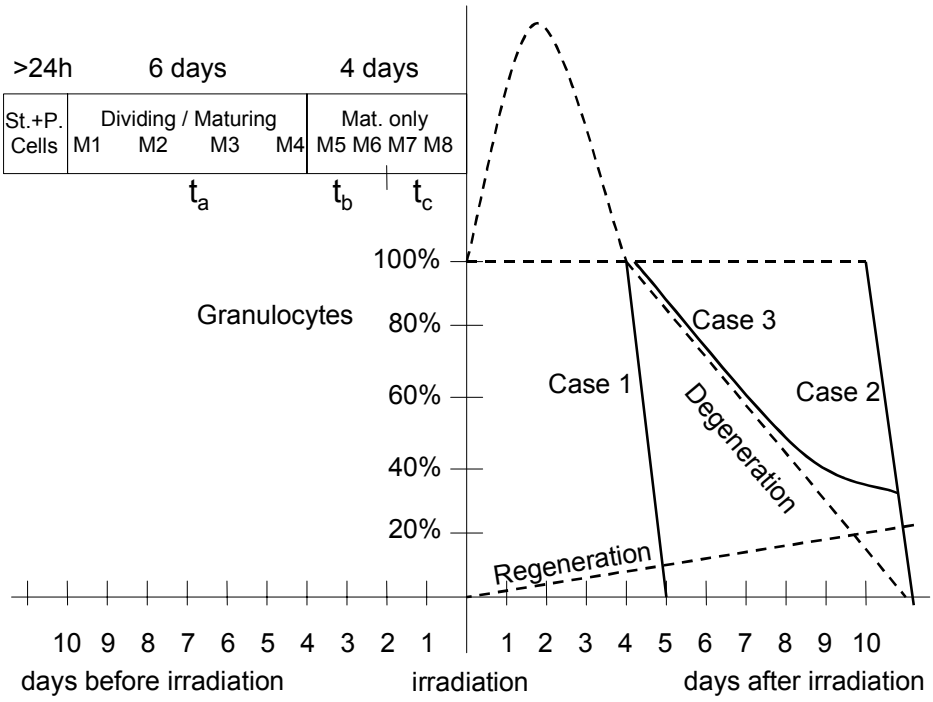


FIG. 8-1b. Schematic representation of the pathophysiological mechanisms resulting in "early" granulocyte changes after acute whole body radiation exposure (for explanation see text).

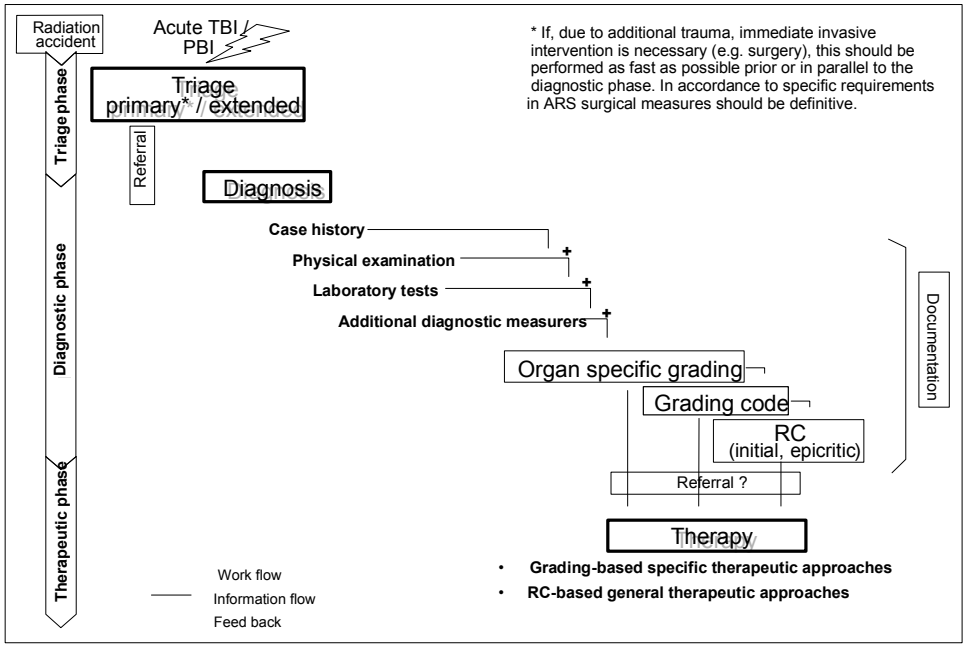


FIG. 8-2. Medical radiation accident management — the METREPOL approach.

Organ system	Grading number and severity of damage **1** **Mild damage**	Grading number and severity of damage **2** **Moderate damage**	Grading number and severity of damage **3** **Severe damage**	Grading number and severity of damage **4** **Serious/fatal damage**
N	Recovery certain	Recovery with possible deficit	Recovery with severe deficit	Recovery most unlikely
H	**Autologous recovery certain**	**Autologous recovery likely**	**Autologous recovery possible**	**Autologous recovery most unlikely**
C	Recovery certain	Recovery without deficit likely	Recovery with deficit likely	Recovery most unlikely or with serious deficit
G	Recovery certain	Recovery with possible deficit	Recovery may be possible	Recovery most unlikely

FIG. 8-3. Grading code in the METREPOL approach

Haematopoietic System

Symptom	Degree 1	Degree 2	Degree 3	Degree 4
		H		
Lymphocyte changes[1]	≥1.5 x 10^9/l	<1.5–1 x 10^9/l	<1–0.5 x 10^9/l	<0.5 x 10^9/l
Granulocyte changes[2]	≥2 x 10^9/l	<2–1 x 10^9/l	0,5–1 x 10^9/l	<0.5 x 10^9/l or initial granulocytosis
Thrombocyte changes[3]	≥100 x 10^9/l	<100–50 x 10^9/l	<50–20 x 10^9/l	<20 x 10^9/l
Infection	local; no antibiotic therapy required	local; only local antibiotic therapy required	systemic; p.o. antibiotic treatment sufficient	sepsis; i.v. antibiotics necessary
Blood loss	petechiae; easy bruising; normal Hb	mild blood loss with <10 % decrease in Hb	gross blood loss with 10–20 % decrease in Hb	spontaneous bleeding or blood loss with >20 % decrease in Hb

[1] Reference value: 1.5–4 x 10^9/l

[2] Reference value: 4–9 x 10^9/l

[3] Reference value: 140–400 x 10^9/l

Cutaneous System

Symptom	Degree 1	Degree 2	Degree 3	Degree 4
		C		
Erythema[1]	minimal and transient	moderate; isolated patches <10cm^2; not more than 10 % of body surface (BS)	marked; isolated patches or confluent; 10–40 % of BS	Severe[2]; isolated patches or confluent; >40 % of BS; erythroderma
Sensation/Itching	pruritus	slight and intermit. Pain	moderate and persist. pain	severe and persistent pain
Swelling/Oedema	present; asymptomatic	symptomatic; tension	secondary dysfunction	total dysfunction
Blistering	rare, with sterile fluid	rare, with haemorrhage	bullae with sterile fluid	bullae with haemorrhage
Desquamation	absent	patchy dry	patchy moist	confluent moist
Ulcer/Necrosis	epidermal only	dermal	subcutaneous	Muscle/bone involvement
Hair loss	thinning, not striking	patchy, visible	complete and most likely reversible	complete and most likely irreversible
Onycholysis	absent	partial	Ø	complete

[1] With respect to assessing the CS the extent of the skin area affected is decisive and should be documented for all skin changes.

[2] Only for penetrating irradiation

Changes in the skin pigmentation may also occur. However, given the lack of reference data describing de- or hyperpigmentation, this symptom is not included in the grading. Nevertheless it should be recorded systematically, as it may be helpful in future radiation accidents.

Gastrointestinal System

Symptom	Degree 1	Degree 2	Degree 3	Degree 4
		G		
Diarrhoea				
Frequency	2–3 stools/d	4–6 stools/d	7–9 stools/d	≥10 stools/d; refractory diarrhoea
Consistency	bulky	loose	sloppy	watery
Mucosal Loss/d	intermittent	intermittent with large amount	persistent	persistent with large amount
Bleeding/d	occult	Intermittent	persistent	gross haemorrhage
Abdominal Cramps / Pain	minimal	tolerable	intense	excruciating

Neurovascular System

Symptom	Degree 1	Degree 2	Degree 3	Degree 4
		N		
Nausea	mild	Tolerable	intense	excruciating
Vomiting	occasional, 1/d	intermittent, 2–5/d	persistent, 6–10/d	refractory >10/dor parenteral nutrition
Anorexia	able to eat, reasonable intake	significantly decreased intake but able to eat	no significant intake	parenteral nutrition
Fatigue syndrome[1]	able to work or per-form normal activity	interferes with work or normal activity	needs some assistance for self-care	prevents daily activity
Fever	<38°C	38–40°C	>40°C for less than 24 h	>40°C for more than 24 h or accompanied with hypotension
Headache	minimal	Tolerable	intense	excruciating
Hypotension	HR>100 / BP>100/70	BP<100/70	BP<90/60; transient	BP<80/?; persistent
Neurological deficits[2]	barely detectable neurological deficit; able to perform normal activity	easily detectable neurological deficit, no significant interference with normal activity	prominent neurological deficit, significant inter-ference with normal activity	life threatening neurological signs, loss of consciousness
Cognitive deficits	minor loss of memory, reasoning and / or judgement	moderate loss of memory, reasoning and / or judgement	major intellectual impairment since accident	complete memory loss and / or incapable of rational thought

[1] Fatigue: Self-recognised state of overwhelming, sustained exhaustion and decreased capacity for physical and mental work – not relieved by rest. Typical descriptions are drained, finished off, lethargic, beaten, exhausted, or worn out, Prostration, Drowsiness. Components are physical, cognitive, emotional / affective.
[2] Neurological deficits: Reflex-status incl. Reflexes of the eye, ophthalmoscopy (oedema of papilla), fainting, dizziness, ataxia and other motor signs, sensory signs

FIG. 8-4. Organ-specific checklists in the METREPOL approach [1].

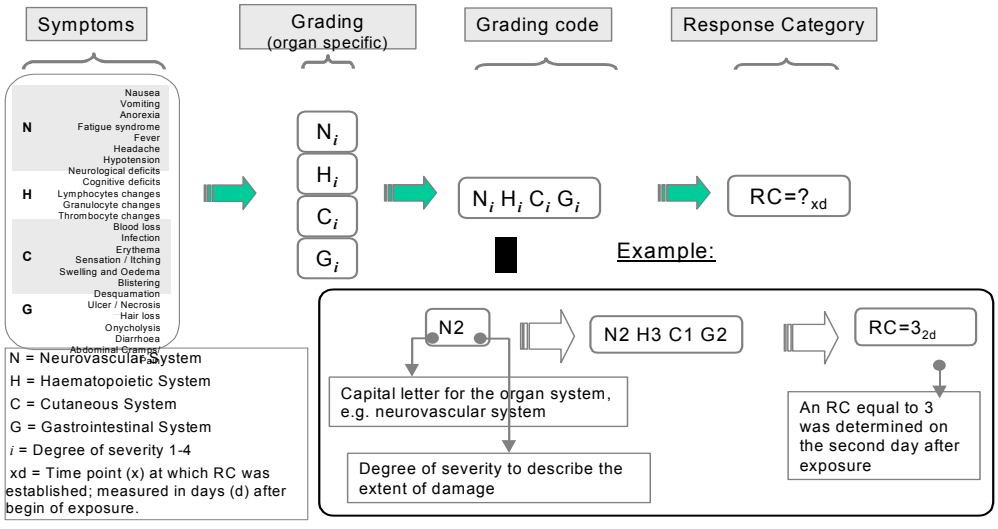
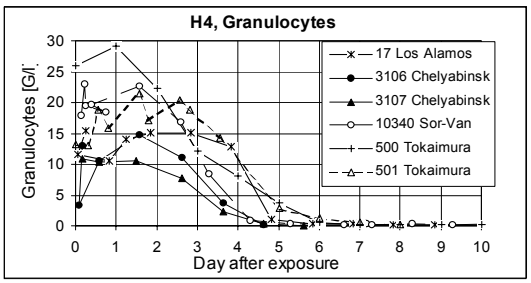
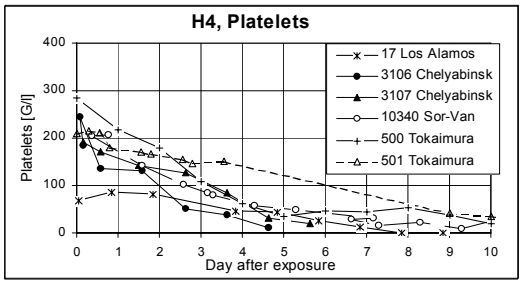
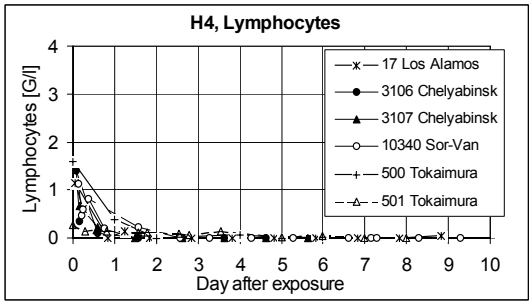


FIG. 8-5. The response category (RC) concept.

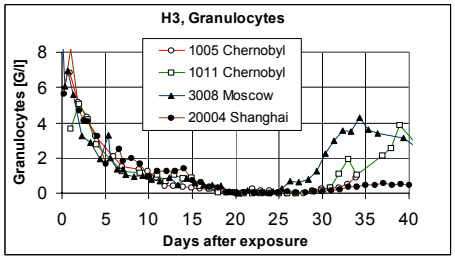


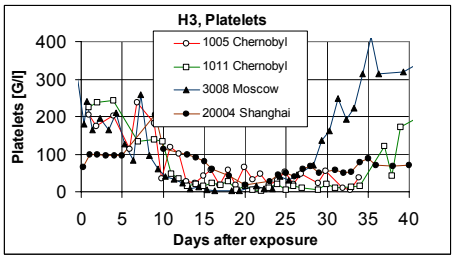


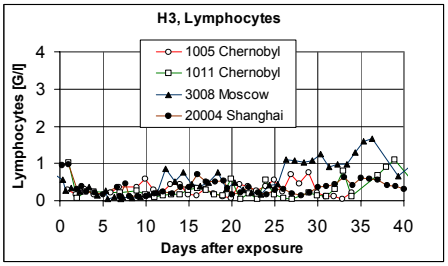


❑Irreversible Injury: Indicators
↗Granulocytes: initial granulocytosis and progressive decline of cell counts between day 4. and 6.
↗Lymphocytes: progressive decline within 24 h
↗Platelets: progressive decline within the first 10 days

FIG. 8-6. Examples of irreversible damage (grading code H4) in different accidents.







❑Reversible Injury: Indicators
↗Granulocytes: moderate granulocytosis, decline between day 4. and 10., abortive recovery followed by nadir: days 20.-30.
↗Lymphocytes: decline to nadir-levels within 2 days, thereafter slow recovery.
↗Platelets: initial 10-day-shoulder followed by decline towards day 20., nadir: days 20.-30.

FIG. 8-7. Examples of reversible damage (grading code H3) in different accidents.

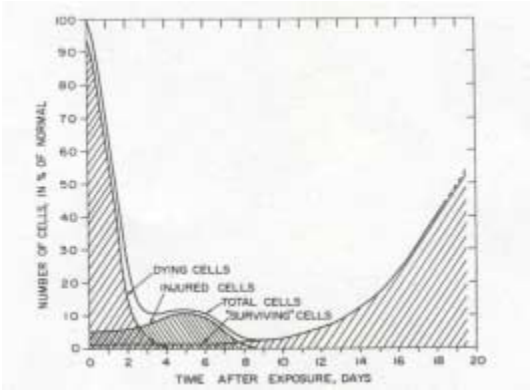


FIG. 8-8. "Injured cell hypothesis" in radiation pathophysiology: Schematic representation of the abortive rise, oriented about one plausible explanation for the phenomenon. "Dying cells" are grossly damaged and disappear rapidly from the system. "Injured" cells proliferate for a time, but these cells and all progeny die after a few divisions. Surviving cells are those capable of proliferation indefinitely.

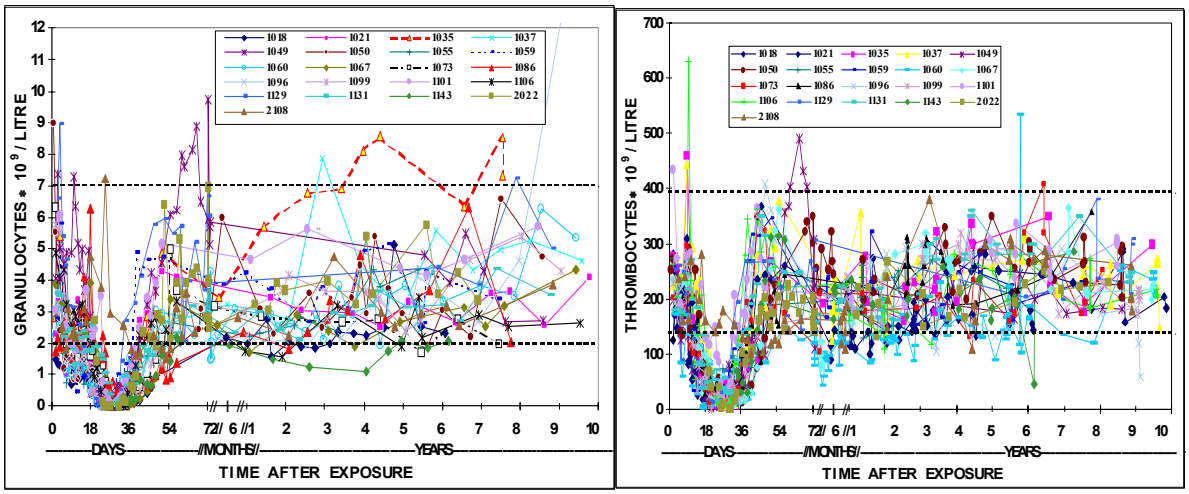


FIG. 8-9. Patterns of granulocytes and thrombocytes of Chernobyl patients (grading code H3) in the course of time.

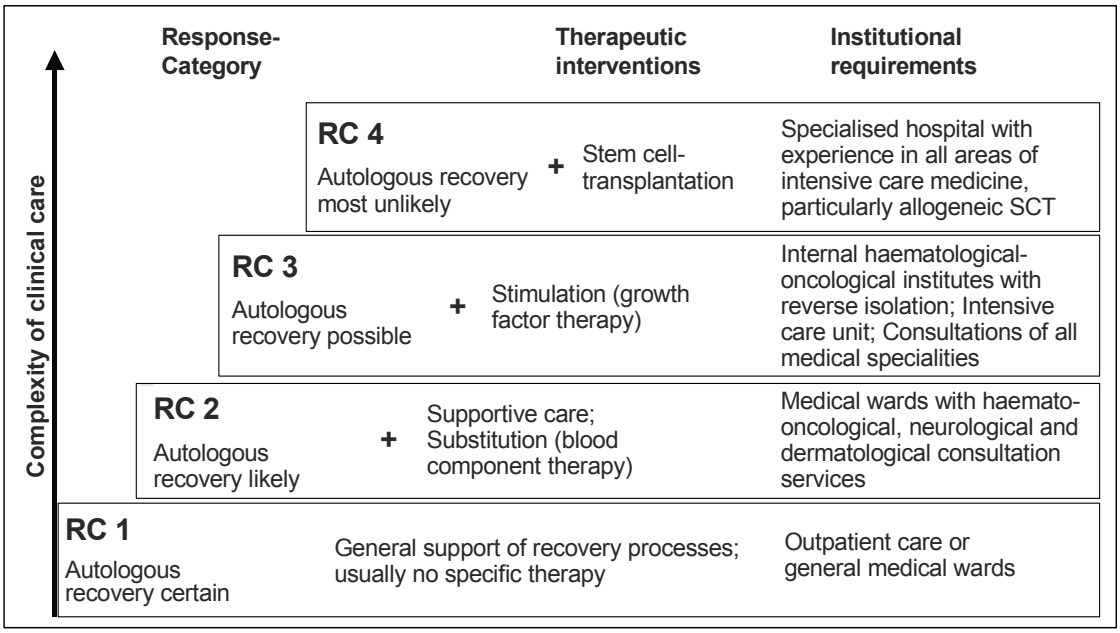


FIG. 8-10. Response category (RC) based levels of care.

CONTRIBUTORS TO DRAFTING AND REVIEW

Bebeshko, V.	Research Centre for Radiation Medicine, Kiev, Ukraine
Belyi, D.	Research Centre for Radiation Medicine, Kiev, Ukraine
Berger, M.E.	Radiation Emergency Assistance Centre and Training Site, Oak Ridge, United States of America
Cosset, J.M.	Institut Curie, Paris, France
Ergen, K.	Haseki Hospital, Istanbul, Turkey
Fliedner, T.M.	WHO Collaborating Centre for Radiation Accident Management, University of Ulm, Ulm, Germany
Gergel O.	Research Centre for Radiation Medicine, Kiev, Ukraine
Goans, R.E.	Radiation Emergency Assistance Center and Training Site, Oak Ridge, United States of America
Gottlöber, P.	Department of Dermatology, University of Ulm, Germany
Graessle, D.H.	WHO Collaborating Centre for Radiation Accident Management, University of Ulm, Ulm, Germany
Günalp, B.	Gülhane Medical Academy, Ankara, Turkey
Heredia, A.	Instituto de Enfermedades Neoplasicas, Lima, Peru
Hirama, T.	National Institute of Radiological Sciences, Chiba, Japan
Jikia, D.	University Hospital, Tbilisi, Georgia
Kovalenko A.	Research Centre for Radiation Medicine, Kiev, Ukraine
Loganovsky, K.N.	Research Centre for Radiation Medicine, Kiev, Ukraine
Nyagu, A.I.	Research Centre for Radiation Medicine, Kiev, Ukraine
Paulsen, C.	WHO Collaborating Centre for Radiation Accident Management, University of Ulm, Ulm, Germany
Peter, R.U.	Department of Dermatology, University of Ulm, Germany
Picon, C.,	Instituto de Enfermedades Neoplasticas, Lima, Peru
Pinillos-Ashton, L.	Instituto de Enfermedades Neoplasticas, Lima, Peru
Reimers, K.	WHO Collaborating Centre for Radiation Accident Management, University of Ulm, Ulm, Germany
Ricks, R.C.	Radiation Emergency Assistance Center and Training Site, Oak Ridge, United States of America
Souchkevitch, G.	World Health Organization
Steinert, M.	Department of Dermatology, University of Ulm, Ulm, Germany
Suzuki, G.	Radiation Effect Research Foundation, Hiroshima, Japan
Turai, I.	International Atomic Energy Agency
Yuryev, K.L.	Research Centre for Radiation Medicine, Kiev, Ukraine
Zaharia, M.	Instituto de Enfermedades Neoplasticas, Lima, Peru

IAEA-WHO Joint Expert Advisory Group Meeting,
Geneva, Switzerland: 1–3 October 2001

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