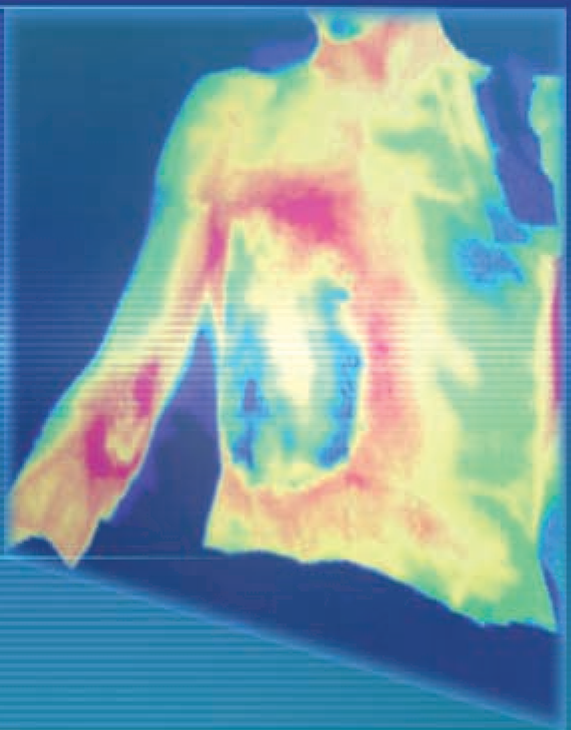
The Radiological Accident in Gilan



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THE RADIOLOGICAL ACCIDENT IN GILAN

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FOREWORD

The use of radioactive materials continues to offer a wide range of benefits throughout the world in medicine, research and industry. Precautions are, however, necessary in order to protect people from the detrimental effects of the radiation. Where the amount of radioactive material is substantial, e.g. with sources used in radiotherapy or industrial radiography, extreme care is necessary to prevent accidents that may have severe consequences for the individuals affected. Nevertheless, in spite of all precautions, accidents with radiation sources continue to occur. As part of its activities dealing with the safety of radiation sources, the IAEA follows up severe accidents in order to provide an account of their circumstances and medical aspects from which those organizations with responsibilities for radiation protection and the safety of radiation sources may learn.

On 24 July 1996 a serious accident occurred at the Gilan combined cycle fossil fuel power plant in the Islamic Republic of Iran, when a worker who was moving thermal insulation materials around the plant noticed a shiny, pencil sized metal object lying in a trench and put it in his pocket. He was unaware that the metal object was an unshielded 185 GBq ^{192}Ir source used for industrial radiography. This report compiles information about the medical and other aspects of the accident.

As a result of exposure to the iridium source, the worker suffered from severe haematopoietic syndrome (bone marrow depression) and an unusually extended localized radiation injury requiring plastic surgery.

The IAEA is grateful for the assistance of the Atomic Energy Organization of Iran, and in particular its Medical, Radiation Protection and Biodosimetry Sections, in preparing this report and thereby sharing its experience with other Member States. The IAEA is also grateful for the assistance of staff and experts from the Institut de Protection et de Sûreté Nucléaire (IPSN) and the Institut Curie, France, and from the UK National Radiological Protection Board.

The Scientific Secretary responsible for preparation of this publication was I. Turai of the Division of Radiation and Waste Safety.

EDITORIAL NOTE

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1. INTRODUCTION

1.1. BACKGROUND

Industrial radiography is used throughout the world to examine the structural integrity of materials non-destructively, and in most cases this is done in a safe and controlled manner. However, on 24 July 1996 a serious radiological accident occurred at the combined cycle fossil fuel power plant in Gilan, Islamic Republic of Iran, when a worker picked up a ^{192}Ir industrial radiography source and put it in his chest pocket, where it remained for approximately 1.5 h, resulting in his receiving a high radiation dose.

The IAEA is authorized to establish standards for radiation protection and for the safety of radiation sources, and to assist in their application. The International Basic Safety Standards for Protection against Ionizing Radiation and for the Safety of Radiation Sources (BSS) [1] establish the requirements for protection and safety. The BSS presume that States have an adequate legal and regulatory infrastructure within which the requirements can effectively be applied. Requirements and guidance relating to the establishment of an appropriate infrastructure and to occupational radiation protection have been published in Refs [2, 3].

1.2. OBJECTIVE

For a number of years, the IAEA has provided support and assistance, and has conducted follow-up investigations upon request, in the event of serious accidents involving radiation sources. Reports have been published on follow-up investigations of radiological accidents, for example, in San Salvador, El Salvador [4], Soreq, Israel [5], Hanoi, Viet Nam [6], Tammiku, Estonia [7] and Goiânia, Brazil [8, 9]. The findings and conclusions of these reports have provided a basis for lessons to be learned on safety improvements [10–12].

The objective of the present report is to compile information about medical and other aspects of the radiological accident in Gilan, Islamic Republic of Iran, in 1996. The information is intended primarily for medical specialists but may also be of interest to national authorities, regulatory organizations and a broad range of radiation protection specialists.

1.3. SCOPE

The accident was reportedly caused by a radioactive source which temporarily was not under control. Radiological aspects of the accident have not, however, been considered in depth in this report, as little substantive information was made available to the IAEA. The report discusses the medical aspects of the accident and the estimation of doses, and includes a brief description of the circumstances of the accident.

At the time of writing this report, the victim of the accident has been followed up for 4.5 years. His health status is satisfactory, despite severe restriction of movement in his right elbow, which appeared early on, and fibrosis in the left palm, which developed unusually late (4 years after the accident). He survived the acute radiation disease without very severe complications, and fortunately he has a good prognosis for survival. Nevertheless, his ability to work remains considerably limited. Even though there might be further (stochastic) health effects in the future for the exposed person, sufficient information is already available for a report to be written.

1.4. STRUCTURE

An account of the circumstances and events of the accident is given in Section 2. The health consequences for the accident victim and the medical treatment he received are described in Section 3. The lesion on his chest was reportedly not consistent with exposure to a point source, and an explanation of this phenomenon by physical reconstruction is attempted in Section 4. Doses estimated from clinical observations and laboratory investigations are given in Section 5. Conclusions and recommendations are presented in Section 6, followed by bibliographical references and an annex containing a set of photos clearly demonstrating the development of extended radiation induced skin injuries. A list of the contributors to drafting and review completes the report. Here, mention should also be made of the medical and technical professionals employed by the relevant technical divisions of the Atomic Energy Organization of Iran (AEOI).

2. CIRCUMSTANCES OF THE ACCIDENT

2.1. GENERAL OVERVIEW

During the night of 23–24 July 1996, industrial radiography was undertaken at the Gilan combined cycle fossil fuel power plant, situated 600 km north of Tehran.

Welds on a boiler and pipes located at a height of 6 m above the plant floor were radiographed with a 185 GBq ^{192}Ir source. At the end of the shift, at around 03:00 on 24 July 1996, the iridium source became detached from its drive cable, reportedly due to failure of the lock on the radiography container. This resulted in the source falling

6 m into a trench which was surrounded by a 1 m high wall made of concrete blocks. As the source was shielded by the concrete, its loss was not detected by the radiography team when they finished work and they assumed that it had been safely returned to its container, as usual.

K.Z., then 33 years of age, worked at the plant; his job included moving insulation materials for the lagging of boilers and pipes. He came from a rural village in the north of the Islamic Republic of Iran and was unable to read. Soon after starting work at 08:00 on 24 July 1996 (Day 1), K.Z. was climbing up a ladder carrying heat insulation material when he noticed a shiny metallic object (the ^{192}Ir source) lying in the trench. Once down the ladder, he picked up the source and put it in the right breast pocket of his coveralls. Over the next 1.5 h, K.Z. reportedly removed the source from his pocket to inspect it and then returned it to the pocket on a number of occasions. At around 09:30 he started to experience dizziness, nausea, lethargy and a burning feeling in his chest. Believing that the object was a possible cause of his symptoms, he put it back in the trench and then went to the workers' rest room.

Shortly before K.Z. returned the object to the trench, at around 09:00, the radiographers discovered that the iridium source was not in its container when they observed that the end of the 'pigtail' was not visible in the channel of its holder. A search was immediately initiated and the source was found in the trench at approximately 10:00. It was recovered and placed in a shielded container, and the Site Manager and the Radiation Protection Officer were informed.

Soon after 13:00, K.Z. reportedly told his colleagues that he was feeling weak and lethargic and he mentioned the strange shiny object that he had found and then put back in the trench. The Site Manager was informed, and after consulting the Radiation Protection Officer he notified the Atomic Energy Organization of Iran (AEOI), who advised him to send K.Z. to a doctor to have blood samples taken.

Management at the plant also arranged medical examinations of all personnel suspected of having been exposed, as required by the Radiation Protection Act of the Islamic Republic of Iran [13].

A team of AEOI inspectors was assembled and travelled to Gilan to investigate the accident. On arrival at the plant, the inspection team reviewed the circumstances of the accident and recommended repeat blood checks of all 600 personnel. The team sent 55 workers and blood samples of all the plant employees to the AEOI's Medical Service in Tehran for detailed medical and haematological examination.

The blood test results (of about 3000 samples altogether in the month after the accident) were reviewed by the AEOI's medical adviser, who reported that all samples were normal except K.Z.'s. The 55 workers examined in Tehran showed no pathological symptoms or signs that could be associated with exposure to ionizing radiation.

2.2. RADIOGRAPHY EQUIPMENT

The equipment involved in the accident was a Gammamat projector manufactured by Isotopen-Technik Dr. Sauerwein GmbH, Haan, Germany (Fig. 1(a)[1]). The radioactive source was a ^{192}Ir pellet of 2 mm diameter, enclosed in an X540 type stainless steel cylindrical capsule 7.5 mm long and 5.0 mm in diameter (Fig. 1(b)). The capsule was attached to a Gammamat link TI series source holder (Fig. 1(c)), which was connected to a flexible drive cable. The radiography company assessed the activity of the source to be 185 GBq (1.85×10^{11} Bq, or 5 Ci) at the time of the accident.

3. MEDICAL ASPECTS OF THE ACCIDENT

3.1. INITIAL MEDICAL MANAGEMENT IN THE ISLAMIC REPUBLIC OF IRAN (24 July – 15 August 1996)

After spending two days at home, during which time his nausea and dizziness improved but the burning feeling in the chest area and decrease in lymphocyte counts (Fig. 2) continued, K.Z. was transferred to Tehran on 27 July 1996 (Day 4). He was placed in a single ward of the Medical Division at the AEOI's Headquarters, where he was examined. The patient was reportedly very anxious, and on examination he had erythema on the right side of his chest extending to the upper abdomen. Blood was taken for haematology and cytogenetic dosimetry. These examinations were performed by the Medical Division and the Biodosimetry Laboratory of the AEOI. K.Z. remained at the AEOI under 24 h medical observation until he was admitted to an isolation room at the Imam Hossein Hospital, Nezamabad, Tehran, on 29 July 1996 (Day 6). Over the next 16 days, the chest lesion continued to expand with ever deepening erythema (Photo 1, Day 6), which progressed to dry desquamation starting at the nipple (Photo 2, Day 12) and eventually to moist desquamation extending over an area of 30 cm × 15 cm (Photo 3, Day 15) with early epidermal necrotic change.

By 29 July 1996 (Day 6), erythema had also developed on the medial side of his elbow (right antecubital fossa), and by 2 August 1996 (Day 10) erythema with early blistering had appeared on the palm of his left hand. In addition, the patient was by now also complaining of a burning feeling on the anterior surface of his right thigh, an area that was showing early erythema. By 10 August 1996 (Day 18), the area of erythema on the left palm had developed into a tense bulla (Photo 4, Day 19).

[1] All figures and photos are shown in a separate section at the end of the report.

After progressive falls in both white blood cell (leucocyte) and platelet counts (see Figs 3 and 4), a left iliac crest bone marrow trephine was taken on 12 August 1996 (Day 20) and was reported as aplastic, with almost complete absence of cellular elements (Photo 5). Results of blood samples taken on 27 July 1996 for cytogenetic dosimetry were reported by the Biodosimetry Laboratory of the AEOI as being consistent with a whole body dose of about 4.5 Gy (see Section 5.2).

Serious consideration was given in the Islamic Republic of Iran to the possibility of performing a bone marrow transplant to treat the severe haematopoietic syndrome predicted by biological dosimetry and manifest by the continuing decline in the haematological parameters. However, HLA typing (a measure of tissue compatibility) of the patient's half-brother, his only living close relative, showed him to be incompatible with K.Z., and non-related donor grafting is not possible in the Islamic Republic of Iran.

The patient had been treated with prophylactic antibiotics and provided with analgesia since admission, and the skin lesions on the chest had been treated with topical silver sulphadiazine. Transfusion of 7 units of platelets on Day 20 produced a transient rise in platelet count, but by 16 August 1996 (Day 22) it was clear that further therapy was required, so the patient was put on granulocyte-colony stimulating factor (G-CSF): 400 μg Leucomax twice daily, subcutaneously.

The Iranian physicians reportedly still thought that bone marrow transplantation might be the only treatment that could save the patient, and therefore contacted the Radiopathology Unit of the Institut Curie in Paris to request further treatment of the patient and consideration of bone marrow transplantation. The patient was transferred to Paris on the morning of 16 August 1996 (Day 24).

3.2. FURTHER TREATMENT AT INSTITUT CURIE, PARIS (16 August – 25 October 1996)

The medical staff at the Institut Curie were confronted not only with the problem of a patient near the nadir of the haematological syndrome but, as no medical attendant had travelled with him, also with only brief medical details and a language barrier — the patient spoke some Farsi, but his native tongue was a regional language. Additionally, the patient was in severe pain from his skin lesions, unco-operative and also frightened, never having left the Islamic Republic of Iran before (his hospitalization in Tehran was the first time he had visited the country's capital).

On initial examination at the Institut Curie on 17 August 1996 (Day 25), K.Z.'s skin lesions were diagnosed as:

— Total loss of epidermis on the right anterior chest/upper abdominal wall — 30 cm × 15 cm — with necrotic epidermis around the edge (Photo 6),

— An area of moist desquamation on the medial side of the right antecubital fossa — 6 cm × 7 cm (Photo 7),
— A large bulla on the palm of the left hand — 5 cm × 5 cm (Photo 8), and
— A small area of increased pigmentation and erythema on the anterior surface of the right thigh — 2 cm × 2 cm (Photo 9).

The rest of the clinical results were normal. The patient was slightly pyrexial but the rest of his vital parameters were normal. His chest X ray was normal, as were all other biological indicators except for haematology. A contamination survey of the skin for radioactivity was negative.

He was treated in an isolation room using reverse barrier nursing techniques. Intravenous fluids, platelet transfusions and intravenous antibiotics were administered. He required intravenous morphine for nearly two months to treat the considerable pain of his skin lesions, especially during the daily local treatments. G-CSF (300 μg) was continued to be given subcutaneously daily for a further 10 days until his white blood cell population showed marked improvement.

Thermography of the area of affected skin on 20 August 1996 (Day 28) suggested that both the chest and elbow lesions (Photo 10) had a viable dermis, as no cold areas were present, and consequently spontaneous re-epithelialization of both lesions was possible. Similarly, thermography of the hand lesion (Photo 11) was compatible with spontaneous healing, but with some reservations about the likely functional outcome from scarring. The small size of the thigh lesion suggested that healing might be possible without grafting.

A marrow sample taken from the right iliac crest on 27 August 1996 (Day 35) showed marrow with essentially normal appearance, with all cellular elements present and without abnormal forms (Photo 12); this finding was surprising as the previous marrow sample, taken on 12 August 1996 (Day 20) from the opposite iliac crest, had been acellular.

By 27 August 1996 (Day 35), re-epithelialization from the edges had decreased the chest lesion to 23 cm × 15 cm (Photo 13). However, there was no evidence of epidermal repopulation of hair follicles within the lesion. For the next month re-epithelialization continued, but based on this rate and pattern of skin growth it was estimated that it would take 12–18 months for full cover to be achieved. Conversely, the elbow lesion had shown both peripheral and intra-lesional re-epithelialization and was close to being fully covered (Photo 14). The left palm presented moist desquamation (Photo 15), and a 2 cm × 2 cm blister developed on the right anterior thigh (Photo 16).

Clearly, an extended stay to allow full recovery of the chest lesion in a hospital in a foreign country was neither desirable nor practical for the patient physically or, more importantly, psychologically. The dermis appeared viable, with no obvious necrosis. It was therefore decided to graft the chest lesion with a free graft from the thigh and to graft the thigh lesion at the same time; grafting was undertaken on 24 September 1996 (Day 63). The short term outcomes of this procedure by 16 September 1996 (Day 85) were that the chest graft had ‘taken’ without problems (Photo 17) while the thigh graft had developed some early partial necrosis (Photo 18). Concurrently, the hand lesion had healed spontaneously, with some slight scarring but without functional impairment (Photo 19), and the elbow lesion had become covered with healthy new skin (Photo 20).

During the first two months in Paris, the patient had shown a poor appetite, had been profoundly depressed and had required very large doses of morphine to control his pain. The grafting transformed his condition: he became animated and his mood improved significantly. By 15 October 1996 (Day 84) he appeared to have recovered completely, and he was therefore transferred back to his physician in Tehran on 26 October 1966 (Day 95).

3.3. SUBSEQUENT EVENTS IN THE ISLAMIC REPUBLIC OF IRAN (October 1996 – October 1997)

The patient remained in Tehran for five days before returning to his village. He was seen again two months later and had no physical problems, with all his skin lesions well healed and no restriction of function in the hand or at the elbow. His chest X ray was normal, but he did have a marginally raised alkaline phosphatase. A further check-up six weeks later was similarly unremarkable, but within 10 days (in February 1997, seven months after the accident) he developed severe epigastric pain. Endoscopic visualization of the upper gastrointestinal tract showed severe gastritis and duodenitis, but barium studies of the oesophagus, stomach and small bowel demonstrated no pathology. The symptoms responded quickly to normal anti-inflammatory therapy.

In early April 1997 (8.5 months after the accident), he visited a doctor after having suffered for five days from pain, redness and induration (hardness) at the site of his right elbow lesion. An X ray of the area was inconclusive, but an isotope scan ($^{99}Tc^{m}$ MDP) showed higher uptake at the right elbow (consistent with inflammation), not suggestive of osteitis. The elbow settled after 10 days of anti-inflammatory treatment. Imaging of the right anterior chest wall also showed increased uptake, which was considered not to be in the ribs but probably more superficial, underlying the skin graft near the nipple. Isotope imaging of the lungs ($^{99}Tc^{m}$ MAA) showed an apical deficit, but given the prevalence of pulmonary tuberculosis in rural areas of the Islamic Republic of Iran this was probably consistent with old disease. Similar imaging of the liver ($^{99}Tc^{m}$ sulphur colloid) was normal. However, the alkaline phosphatase had risen to 50% above normal.

During September 1997, a fissure opened below the lower end of the fully vitalized chest graft and discharged a clear exudate (Photo 21). By November this lesion had healed with the application of local skin care.

At the request of the AEOI, in November 1997 an IAEA team (consisting of two staff members — a radiation protection specialist and a radiation medicine specialist — being responsible for data collection and preparation of this report) visited the Islamic Republic of Iran and was able to consult with technical and medical specialists of the AEOI and to examine the patient (15 months after the accident), with the following results:

— The chest lesion measured 25 cm × 10 cm, which included the graft and the surrounding depigmented area (Photo 22). The fissure below it was closed, self-healed. The graft was warm and dry, and there were no necrotic areas. The skin and underlying tissues were rigid and fixed to the chest wall, preventing all movement. Fibrosis in the chest lesion had led to a moderate degree of retraction, which had adversely affected posture (Photo 23).
— The surface appearance of the elbow lesion was unchanged compared with that at discharge from the Institut Curie, but movement had become significantly restricted in both flexion (80º) and extension (135º) (Photos 23 and 24).
— The patient had full function of the left hand, despite some thickening of the palmar skin (Photo 25).
— The right thigh lesion felt hard to the touch, was surrounded with a narrow depigmented halo, and was well healed and non-painful (Photo 26).

The patient had discomfort in the elbow on extremes of functional movement, but no symptoms from the other lesions and no constitutional symptoms.

3.4. IMMUNOLOGICAL INVESTIGATION (31 July 1996 – early 1999)

3.4.1. Introduction

Experimental and clinical materials that have been accumulated to date give evidence of the influence that irradiation has on lymphocyte subpopulations and on different aspects of the protein metabolism or on the concentration of immunoglobulins. Thus, careful monitoring of humoral factor alterations and changes in cell population can provide a reliable indication of exposure [14–25]. On this basis, a detailed immunological follow-up study of patient K.Z. was performed in the Islamic Republic of Iran, as described in this section.

3.4.2. Materials and methods

The following materials and methods were used:

- Blood sampling took place on 3 August 1996 (Day 11), 16 February 1997 and 4 January 1999 (6 months and 2.5 years after the accident, respectively).
- Controls: 20 persons without any occupational or recent medical radiation exposure were examined.
- Determination of lymphocytic subpopulations was carried out using monoclonal antibodies and flow cytometry.
- The serum levels of immunoglobulins (IgM, IgG and IgA) and C3, C4 were determined by Mancini's method of radial immunodiffusion.

3.4.3. Results and discussion

Table I shows the distribution of T and B lymphocytes and killer cells in three samples of peripheral blood of the exposed patient and in the control range.

This table shows that total T cells ($CD3^+$) were normal in the first sample but remarkably decreased in the second sample, in spite of treatment. Although growth factors may not be the only factors that play a role in enhancing residual stem cells, the treatment with G-CSF in August 1996 in the Islamic Republic of Iran could have resulted in stimulation or normalization of K.Z.'s neutrophil counts.

In the third sample, $CD3^+$ cells were in the normal range. $CD4^+$ T cells were normal in the first but significantly decreased in the second sample, and then became normal again in the third sample. However, $CD8^+$ T cells were in the normal range in all three samples. Thus $CD4^+/CD8^+$ ratios were normal in the first and decreased in the second sample, and were still not normal in the third sample. Total B cells were highly decreased in the first sample and became normal in the other two samples.

TABLE I. DISTRIBUTION OF T AND B LYMPHOCYTES AND KILLER CELLS

Sample	$CD3^+$ (total T cells) (%)	$CD4^+$ (%)	$CD8^+$ (%)	$CD4^+/CD8^+$ ratio	$CD19^+$ (total B cells) (%)	$CD56^+$ (%) (killer cells) (%)
3 Aug. 1996	85	55	27	2	2	10
16 Feb. 1997	43	12	31	0.5	25	10
4 Jan. 1999	64	43	37	1.2	30	10
Control range	60–85	29–59	19–42	1.8–2.2	7–23	10–20

Killer cells did not show any difference in any of the three samples because they were relatively radioresistant as compared to B or T lymphocytes.

In other investigations, Tuschl and Kovac [17] demonstrated that in persons occupationally exposed to very low doses of ionizing radiation (within the annual dose limits), $CD4^+$ cells and NK cells did not show any dose related difference and $CD8^+$ cells were slightly (not significantly) increased. There was a relative increase of $CD2^+$ cells, which may have been due to the ability of low doses of ionizing radiation to induce an augmentation of DNA repair processes [17]. B cells have been reported to be more radiosensitive than T cells [18].

Assessment of the immune status of more than 300 persons who worked in the 30 km zone of the Chernobyl nuclear power plant was carried out four years after the 1986 accident by Oradovskaya and Ruzybakiyev [19]. Clinical features of immune deficiency were detected in 6.7% of persons. A decrease in T and B cells was observed in 25 and 75%, respectively. No changes in serum immunoglobulin levels were observed.

A comparative analysis of NK cell activity in children from areas with and without high ^{137}Cs levels after the Chernobyl accident revealed a high frequency of abnormal NK cell activity only in children from the area contaminated by radioactive fallout. In addition, there was no correlation between NK cell activity and NK cell number in the children from the area with high ^{137}Cs levels [20].

In another investigation, alterations in the numbers of T cell subpopulations, $CD19^+$ B cells and $CD16^+$ NK cells of atomic bomb survivors in Hiroshima were studied. Overall, with increasing age significant decreasing trends in the numbers of some lymphocytes in T cell subpopulations and of B cells were observed. Consequently the $CD4^+/CD8^+$ ratio tended to decrease, while $CD16^+$ cells tended to increase with age [21].

Table II presents the results of comparing the serum concentrations of immunoglobulins and of complement systems (C3, C4) in the first and second blood samples of the exposed patient (K.Z.) with the control range. The serum immunoglobulins IgM, IgG and IgA and the C3, C4 components of K.Z.'s complementary system are at or

TABLE II. CONCENTRATION (mg/100 mL) OF SERUM IMMUNOGLOBULINS AND OF COMPLEMENTS IN TWO SAMPLES OF THE EXPOSED PATIENT COMPARED WITH THE CONTROL RANGE VALUES

Sample	IgM	IgG	IgA	C3	C4
First	135	900	130	70	49
Second	140	1400	197	140	55
Control range	80–310	600–2000	90–540	50–120	20–50

very close to the normal values. It has been shown that immunoglobulin producing cells which are functional end cells are highly radioresistant. The IgM response is more radioresistant than the IgA and IgG responses [15].

It is known that radiation can cause some changes in the concentration of serum proteins. Different immunoglobulin classes respond differently to radiation [22]. The following data support these findings. Telnov examined workers of the "Mayak" nuclear facility (in the Urals) exposed to chronic irradiation with total doses of external gamma irradiation in the range of 0.01–7.6 Gy. Levels of IgG increased but levels of IgA and IgM in the groups compared did not differ significantly [23].

Long term immunological follow-up of survivors of the Oak Ridge Y-12 accident in 1958 showed abnormality of serum immunoglobulins with fluctuating values. Immunological tests of the patients from the 1963 accident in China (2 Gy) [24] showed a normal rate of lymphocyte transformation. Serum contents of IgA, IgG, IgE and IgM were within the range of normal variation, except in one patient whose IgG level was subnormal.

Conrad carried out immunological studies on Marshall Islanders sixteen years after radiation exposure from fallout. Their results indicate that a 1.75 Gy gamma radiation dose had not changed the serum levels of IgM; however, IgA and IgG had slightly decreased [25].

3.4.4. Conclusions of immunological studies

Some of K.Z.'s immunological parameters were investigated three times: on 3 August 1996 (Day 8 after exposure), on 16 February 1997 and on 4 January 1999. Lymphocytic subpopulations in peripheral blood as well as different immunoglobulin classes and the C3, C4 components of the complementary system in serum were determined. $CD3^+$ cells (T cells) were normal in the first sample but showed a remarkable decrease in the second sample, and then became about normal in the third sample. $CD4^+/CD8^+$ cells (T helper/suppressor cells) were normal in the first sample, remarkably decreased in the second sample and not yet normal in the third sample. This decrease was due to an absolute decrease in $CD4^+$ cells and subnormal T cell values in the second sample.

The most significant effect of radiation exposure was observed in the first sample in $CD19^+$ cells (B cells), which became normal in the later samples. Killer cells did not show any variation in the three samples. The serum immunoglobulins IgM, IgG and IgA and the C3, C4 components of the complementary system were normal in the first and second samples. All results were compared with those of the 20 persons in the control group.

The present data show that some immune parameters are affected by radiation exposure. Comparing immunological findings at three time points (before and after medical treatment), an attempt of the immune system to regain its homeostasis is seen. However, the risk of late effects of radiation cannot be ignored.

3.4.5. Status at the end of the year 2000

K.Z.'s general status was satisfactory 4.5 years after the accident. He had moderate oedema and pain in the right elbow, where movement had been limited since early 1997. Severe fibrosis of his left palm (from repeatedly handling the source during the 1.5 h exposure time) appeared unusually late — 4 years after the accident — and has not reacted well to conservative dermatological treatment.

4. PHYSICAL RECONSTRUCTION OF EXPOSURES

The lesions on the hand and thigh were consistent with exposure to a point source but the chest and — to some extent — elbow lesions did not seem to be consistent with such a source. Consequently, a theoretical estimation of the activity of the ^{192}Ir source and a proposed mechanism for the generation of a large superficial burn on the body was simulated.

This section presents the simulations performed at the Institut de Protection et de Sûreté Nucléaire (IPSN), Paris, to reconstruct the exposure and dose distribution in order to explain the unusually large superficial injury to K.Z.'s chest area.

4.1. ESTIMATION OF ACTIVITY OF THE ^{192}Ir SOURCE

The simulations were based on the following data:

Source:	^{192}Ir, 185 GBq (5 Ci)
Exposure time:	1.5 h
Estimated average whole body dose:	2 Gy

Estimates were made of the whole body dose per unit activity. The important assumptions were related to the influence of the exposure geometry.

4.2. SCENARIO A: SOURCE IN A POCKET, IN CONTACT WITH SKIN

From a source in a pocket, radiation from one side (2π) does not strike the body. From the other side (2π total), some radiation may not strike the body, especially if the source is not in contact with it and a considerable fraction will pass through the body. In addition, a significant proportion is backscattered (~20%). On that basis, it was estimated that a maximum of 30% of the source energy would be deposited in the body. The total energy emitted per decay of ^{192}Ir is 0.811 MeV [26], and hence deposition of 0.24 MeV per decay was assumed. Calculations were then undertaken assuming a 1.5 h exposure to a 1 GBq source, with the following results.

Energy deposited:	$0.24 \times 5400 \times 10^9$ MeV
	1.3×10^{12} MeV
	$1.3 \times 10^{12} \times 1.6 \times 10^{-13}$ J
	0.21 J

Assuming K.Z. weighed 60 kg: Dose = $0.21/60 = 3.5 \times 10^{-3}$ Gy

Using this value, and taking the average dose as 2 Gy, gives a source activity of 580 GBq (16 Ci). Hence, it was concluded at the IPSN, Paris, that the source activity was about three times higher than the 185 GBq quoted by the Iranian authorities for this geometry.

However, during the long investigation and procedure of verification of the source and the type of exposure, the German company performing the radiography work confirmed that the source activity had indeed been 185 GBq.

4.3. SCENARIO B: SOURCE AT A DISTANCE OF 20 cm FROM THE SKIN

This geometry could be produced if someone were wearing loose coveralls and were bending over while, for example, sweeping. This would make it easier to explain the uniformity of the burn. The dimensions of the burn were approximately 30 cm × 15 cm. For a source on the axis of the burn this gives a maximum displacement from the centre of $[(15)^2 + (7.5)^2]^{1/2}$ cm. If it is assumed that this gives a dose which is equivalent to 60% of the centre dose, the resulting distance from the source to the surface is approximately 20 cm. A source at this distance is just about credible if, for example, it had been put in the pocket of loose coveralls. Recalculating the source activity to give an average whole body dose of 2 Gy gives a value of 2 TBq, or 53 Ci, which is a credible activity. This would lead to a subsurface dose with a maximum of about 10 Gy.

However, this scenario was rejected by both the victim of the accident and the Head of the AEOI's Radiation Protection Service during the IAEA site visit to the Islamic Republic of Iran in November 1997.

4.4. SCENARIO C: MOVING SOURCE IN A LOOSE POCKET

An alternative scenario would be that the source was placed in a pocket which was only 10 cm from the body, but that the source moved around in the pocket with respect to the body as a consequence of being taken out to be looked at and then being replaced in a different position, or perhaps also while the individual was working (moving up and down the ladder, etc.). This could help generate a larger, apparently uniform area of exposure.

This was the scenario confirmed by the victim of the accident and supported also by the Head of the AEOI's Radiation Protection Service during the IAEA site visit to the Islamic Republic of Iran in November 1997.

4.5. COMMENT ON DOSE RECONSTRUCTION

Exposure scenarios A and B seem to be rather unlikely. The most feasible scenario is that given in Section 4.4. However, even accepting scenario C, the nature of the consequences cannot be fully explained.

5. DOSE ESTIMATION FROM CLINICAL OBSERVATIONS AND LABORATORY INVESTIGATIONS

5.1. PRODROMAL SYMPTOMS

The onset of nausea and fatigue 1.0–1.5 h after exposure and their disappearance within 48 h suggests a whole body dose of 3.0–4.0 Gy [27]. However, the reported absence of vomiting and diarrhoea and the mild to moderate nature of the symptoms suggest a dose at the lower end of this range or possibly just below it.

5.2. HAEMATOLOGICAL DATA

The first blood sample was taken about 8 h after the exposure began, facilitating an almost complete haematological picture of the effects of the exposure. The total white blood cell count (Fig. 3) demonstrates the previously described 'pulse' of cells released into peripheral circulation in response to radiation injury, before the subsequent fall in all types of white blood cells. The profile of the fall, the abortive second rise, the nadir and the absolute granulocyte counts suggest an average whole body dose greater than 2.0 Gy but less than 5.0 Gy [27, 28]. The lymphocyte count between 27 and 30 July 1996 (Days 4–7) supports this assessment, but with a dose near the middle of the range (utilizing Chernobyl data) of 3.0–3.5 Gy. Similarly, the platelet count (Fig. 4) suggests a dose in the range of 2.0–5.0 Gy [27, 28]. The aplastic marrow picture on 12 August 1996 (Day 20) also supports this dose estimate. G-CSF therapy was not commenced until 14 August 1996 (Day 22), when the total white cell count fell below 1000, and was continued until 26 August 1996 (Day 34). A marrow aspirate from the right iliac crest showed an essentially normal appearance on Day 35.

Cytokine therapy is unlikely to have made a major contribution to marrow recovery by Day 35, because of its relatively late initiation, although it would have assisted the process. Marrow recovery was clearly under way already, most probably related to the heterogeneous nature of the irradiation of the bone marrow, but this picture may also indicate an average whole body dose of less than 3.5 Gy.

Despite platelet transfusions on Days 20, 24, 27 and 31 only minor improvement in platelet count occurred on each occasion. There were no episodes of spontaneous haemorrhage. After G-CSF therapy was discontinued on Day 34, the platelet count rapidly rose. This is consistent with reports of G-CSF inhibiting budding, despite the presence of normal megakaryocytes [29]. At no time did serious wound or systemic infections supervene, but there was an episode of pyrexia, associated with a significantly raised white cell count, between 15 and 25 September (Days 54–64). No infection site or infecting organism was identified. Haematologically, the dose to the bone marrow was assessed to have been 2.5–3.5 Gy, but with highly non-uniform exposure.

5.3. BIOLOGICAL DOSIMETRY FINDINGS

Biological dosimetry, using a cytogenetic technique, was requested for K.Z. at various periods after his accidental overexposure. The samples taken on Days 6, 11, 239 and 562 were analysed in the Islamic Republic of Iran and those taken on 19 August and 23 September 1996 (Days 27 and 62) at the IPSN at Fontenay-aux-Roses, France. The sample taken on Day 27 contained few lymphocytes, making an assessment particularly difficult. The techniques used by the two laboratories for the lymphocyte cultures are similar and are described in IAEA Technical Reports Series No. 260 [30].

No calibration curves for ^{192}Ir are available; consequently, IPSN used a dose–effect relationship constructed from in vitro irradiation of blood samples by gamma radiation from a ^{60}Co source with a dose rate of 0.5 Gy/min.

The dose estimates were obtained after scoring 97–530 metaphases, according to the richness of the examined cultures. The different unstable aberration yields

TABLE III. ESTIMATE OF THE DOSE TO K.Z.

Day of sampling	Scored metaphases	Dicentrics	Centric rings	Excess acentrics	Dicentrics yield	Mean dose ± 95% confidence interval (Gy)	U test
6	128	80	7	138	0.68	3.3 ± 0.4	3.7
11	138	65	5	94	0.51	2.8 ± 0.4	4.9
27	119	37	0	57	0.31	2.1 ± 0.4	5.7
62	97	21	0	64	0.22	1.7 ± 0.5	10.1
239	288	41	9	46	0.17	1.4 ± 0.3	7.2
562	530	34	4	60	0.07	0.8 ± 0.2	13.6

observed and the related dose estimates are presented in Table III, which shows estimates of the dose to K.Z. based on the frequency of dicentric chromosomes in blood lymphocytes taken 6–562 days after his exposure.

A reduction in the frequency of dicentrics over time can be easily observed. This reduction, initially fast during the first two months after the accident, subsequently becomes slower. It clearly represents the partial replacement of the circulating heavily damaged lymphocytes by new lymphocytes coming from the bone marrow. This renewal was undoubtedly accelerated by the lymphopenia that began when the patient was in the Islamic Republic of Iran and continued during his early stay in France.

The aberration distribution allows evaluation of the heterogeneity of the irradiation to some extent. When irradiation is homogeneous, the distribution of chromosome aberrations follows Poisson's law and the two most numerous classes of cells are those with no and one aberration per cell. In the case of heterogeneous irradiation, the distribution moves towards the classes of cells containing several anomalies. Papworth's extended 'U' test, based on the mean to variance ratio of the aberration distribution, quantifies the deviation from Poisson's law. When the U test value exceeds 2, the radiation exposure may be considered to have been heterogeneous. Applied to the results of Table III, the exposure of K.Z. was clearly heterogeneous.

For cases of heterogeneous irradiation, few currently published methods exist that allow retrospective analysis of the initial dose absorbed by the irradiated area. Two mathematical models have been described in Ref. [30].

The first model, proposed by Dolphin [31], considers that the distribution observed in blood samples is the sum of two subpopulations: a homogeneous fraction representing the irradiated part of the body and a fraction representing the non-irradiated remainder. The great advantage of this model is that it gives, in addition to the absorbed dose, the irradiated fraction of the body. Its disadvantage is that it needs

TABLE IV. CORRECTED DOSE ESTIMATES

Days after irradiation	Mean dose ± 95% confidence interval (Gy)	Dolphin [30] corrected dose (Gy)	Dolphin [30] irradiated body fraction (%)	Qdr [32] corrected dose (Gy)
6	3.3 ± 0.4	4.1	≈50	4.14
27	2.1 ± 0.4	4.6	≈50	3.5
62	1.7 ± 0.5	4.7	≈50	4.7
239	1.45 ± 0.3	2.8	≈50	3.13

relatively high radiation exposure to indicate some classes of aberrations. Moreover, it is sensitive to lymphocyte renewal by the bone marrow.

The second model, proposed by Sasaki and Miyata [32], uses the well known 'Qdr' terminology. Briefly, it considers the frequency of dicentrics only among cells presenting any unstable chromosome aberrations at the time of the accident. Consequently, blood dilution by newly produced cells may not intervene in the calculation. Moreover, it is not necessary to have heavily damaged cells. On the other hand, this method of computation gives no information on the irradiated fraction of the body.

Table IV shows the corrected dose estimates accounting for the irradiated fraction of the body.

It appears that there is good agreement in the results of the two mathematical models used, whatever the sampling time after irradiation. However, it is not possible to confirm the irradiated body fraction, which therefore remains speculative.

It is important to note that the assumptions used to support these models are sometimes debatable in their application to accident situations. Moreover, they assume a homogeneous exposure of the irradiated fraction of the body, which is rarely the case.

5.4. SKIN LESIONS

5.4.1. Chest

The chest lesion demonstrated a rapid progression. The patient reported that a feeling of burning started within 1 h of the beginning of exposure, which progressed to a surprisingly large area of erythema (redness of skin) by 26 July 1996 (Day 3). Moist desquamation had started lateral to the nipple by 4 August 1996 (Day 12) and progressed until the epidermis over the majority of the initially erythematous area was necrotic by 11 August 1996 (Day 19). The area healed slowly from the edges without superinfection. At no time before grafting was epithelial growth observed within the lesion, suggesting that the keratinocytes lining the bottom of the hair follicles in the lesion had been killed.

However, thermography suggested that damage was homogenous throughout the area with a mostly intact dermis. Survival of the deeper dermis was confirmed by the uncomplicated ‘take’ of a free graft taken from the left thigh. The histology of tissues excised at operation showed non-specific necrotic and inflammatory change. Such early and complete epidermal destruction would require over 30 Gy to the epidermis, but less than 15 Gy to the dermis. This decrease in dose with depth would be over a distance of about 50 mm. This suggests that the source was an electron emitter of some type. The superficial nature of the extended lesion is difficult to explain by irradiation from a point source that generates radiation of the energy spectrum typical of ^{192}Ir. It is possible that the extent of the lesion could be explained by considerable movement (repeated removal and return in different positions) of a point source within a confined area, e.g. a large pocket (see Section 4.4).

5.4.2. Right elbow

Erythema first appeared on 29 July 1996 (Day 6) and progressed in a similar way to that on the chest. Thermography suggested an essentially intact dermis. The lesion healed rapidly by re-epithelialization from the periphery and from islands within the lesion, leaving a large hypopigmented area without initial functional problems. However, movement of the right elbow has become significantly limited since early 1997, and the contracture has remained after 4.5 years.

5.4.3. Left palm

Erythema on the palm developed on 2 August 1996 (Day 10) with some early blistering, which by 10 August 1996 (Day 18) had developed into a tense bulla. Surgical removal of the roof of the bulla was undertaken on 27 August 1996 (Day 35) (Photo 20). This revealed a necrotic area at the centre measuring 3 cm × 1 cm, which was consistent with the putative ^{192}Ir point source. The lesion was left to heal spontaneously. The end result was a slightly contracted fibrotic scar without obvious functional problems. The estimate of dose would lie in the range of 40–80 Gy [27, 28, 33, 34]. However, the full functional recovery and lack of significant atrophy 15 months later suggests a dose at the lower end of this range. Severe fibrosis of the left palm appeared unusually late — four years after the accident.

5.4.4. Right anterior thigh

The patient first complained of pain on the anterior surface of the right thigh on 2 August 1996 (Day 10). On admission to the Institut Curie on 16 August 1996 (Day 24) he had a hyperpigmented area of 2 cm × 2 cm, which developed into an area of moist desquamation of 3 cm × 3 cm with a surrounding area of depigmentation by 23 August 1996 (Day 35) (Photo 21). Initially this lesion healed only slowly, and therefore the opportunity to graft was taken when the chest lesion was grafted. A small part of the graft became necrotic, but subsequently the lesion healed. The evolution and nature of the lesion again suggests contact with a point source with an estimated dose of about 40 Gy.

6. CONCLUSIONS AND RECOMMENDATIONS

6.1. LESSONS LEARNED

The only source of well established data on this accident is the clinical course of the patient's radiation induced haematological changes and skin lesions. Consequently, lessons can only be learned from the treatment of these lesions.

6.1.1. Whole body exposure

In effect, intervention with cytokines probably made little contribution to the eventual recovery, as treatment was initiated at a stage where bone marrow recovery was likely to be already under way. However, the use of G-CSF probably accelerated the process, thereby reducing to some degree the risk of intercurrent infection. Administration of G-CSF, as reported previously, appeared to inhibit the recovery of platelet numbers; this is suggested by the almost immediate rise in platelet count after the therapy was discontinued. The future availability of effective platelet growth factors could make a significant contribution to resolving this problem, reducing the haemorrhage risk of such patients.

Yet again, this case demonstrates that bone marrow transplantation is inadvisable for patients who have received whole body doses of 2–4 Gy, particularly when the pattern of exposure is likely to be non-homogeneous — a common feature in accident situations.

6.1.2. Local (skin) exposures

For the skin lesions, thermography proved reliable in predicting the viability of the underlying dermis to support spontaneous re-epithelialization or split-skin grafting. Of considerable significance was the fact that grafting reduced morbidity, pain and psychological distress in a patient significantly disadvantaged by language and cultural differences.

The longer term outcome of these injuries remains uncertain, particularly as retraction in the chest lesion has led to postural problems and the function of the right elbow has been compromised, suggesting deeper damage in the elbow joint.

Despite investigation, repeated simulations, deliberation and the full scale assistance of the Iranian professionals involved in this case, the nature of the exposure of the chest wall and right elbow has not been clearly established and is increasingly unlikely to be further clarified with the passage of time.

6.2. RECOMMENDATIONS

(1) In the case of non-homogeneous whole body irradiation (i.e. the situation in most accidents), bone marrow stimulating cytokine treatment should be initiated at the earliest opportunity. G-CSF may be the drug of first choice, but if this drug is used, particular attention should be given to the monitoring of platelet counts.

(2) Allogeneic bone marrow transplantation is not indicated when doses in the range of 2–4 Gy have been received.

(3) Thermography, where available, should be used to assess the potential of radiation induced skin injuries for spontaneous recovery or their suitability for grafting.

(4) Where dermal tissues are viable after radiation induced skin injury, and spontaneous re-epithelialization is likely to be prolonged, consideration should be given to early skin grafting to reduce physical and psychological morbidity.

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FIGURES
AND
PHOTOS

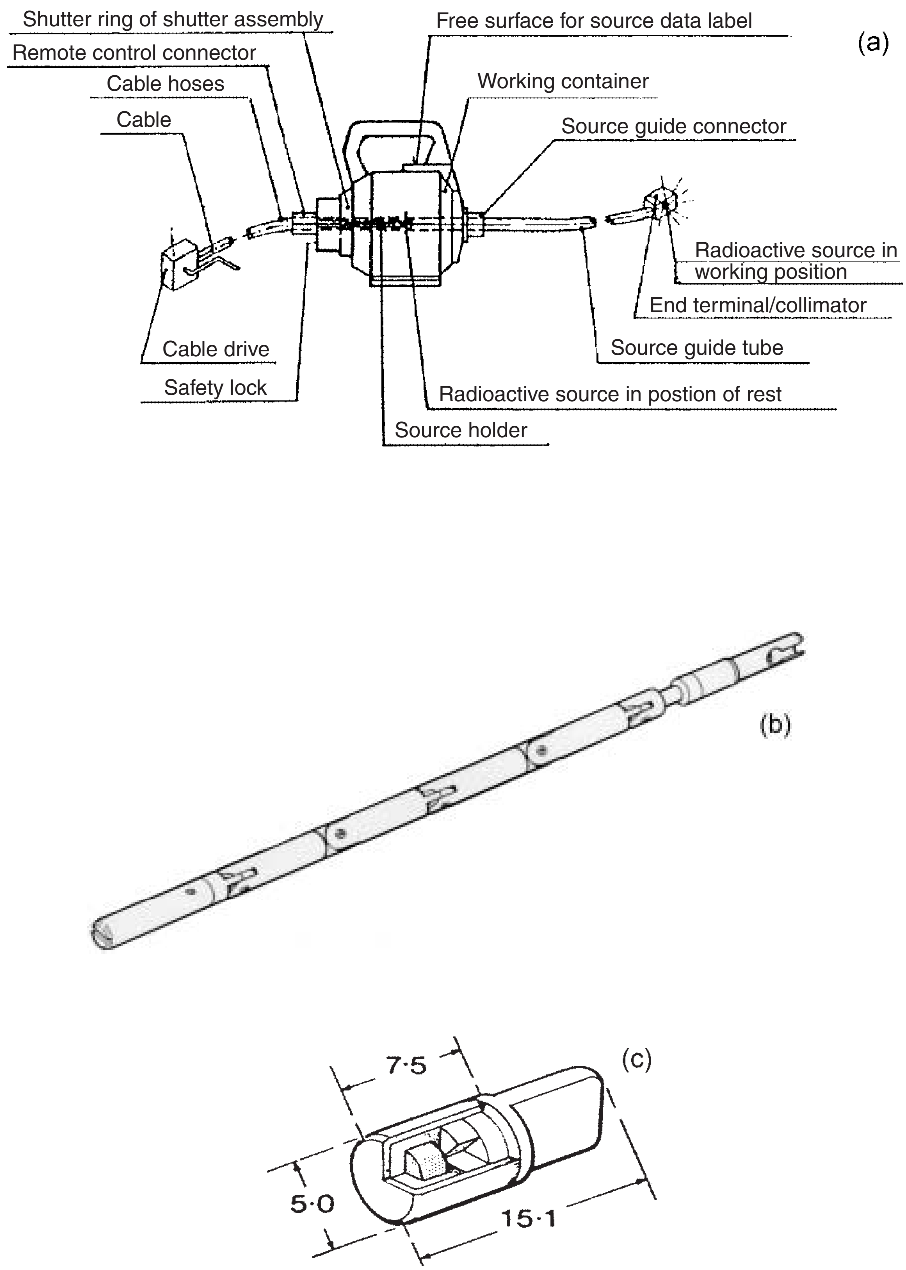

FIG. 1. (a) Gamma projector, (b) source holder, and (c) source. The size of the source is given in mm.

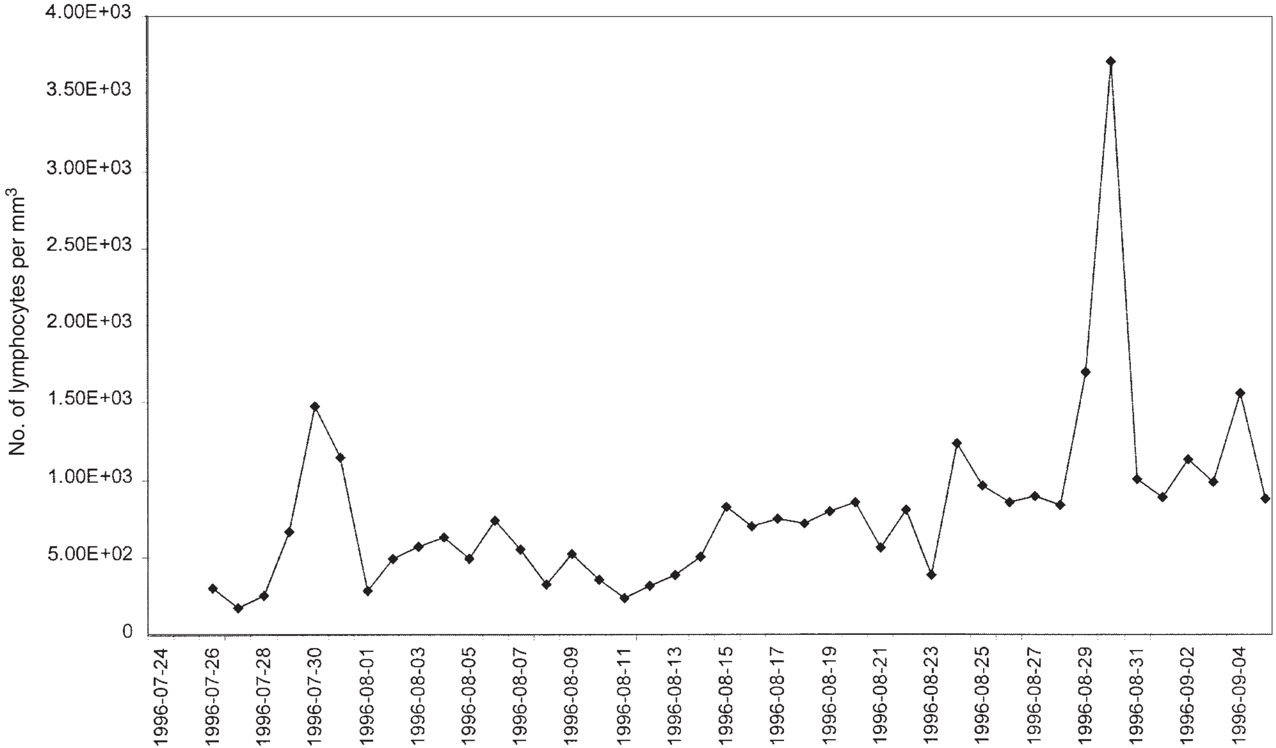

FIG. 2. Evolution of lymphocytes in July–August 1996.

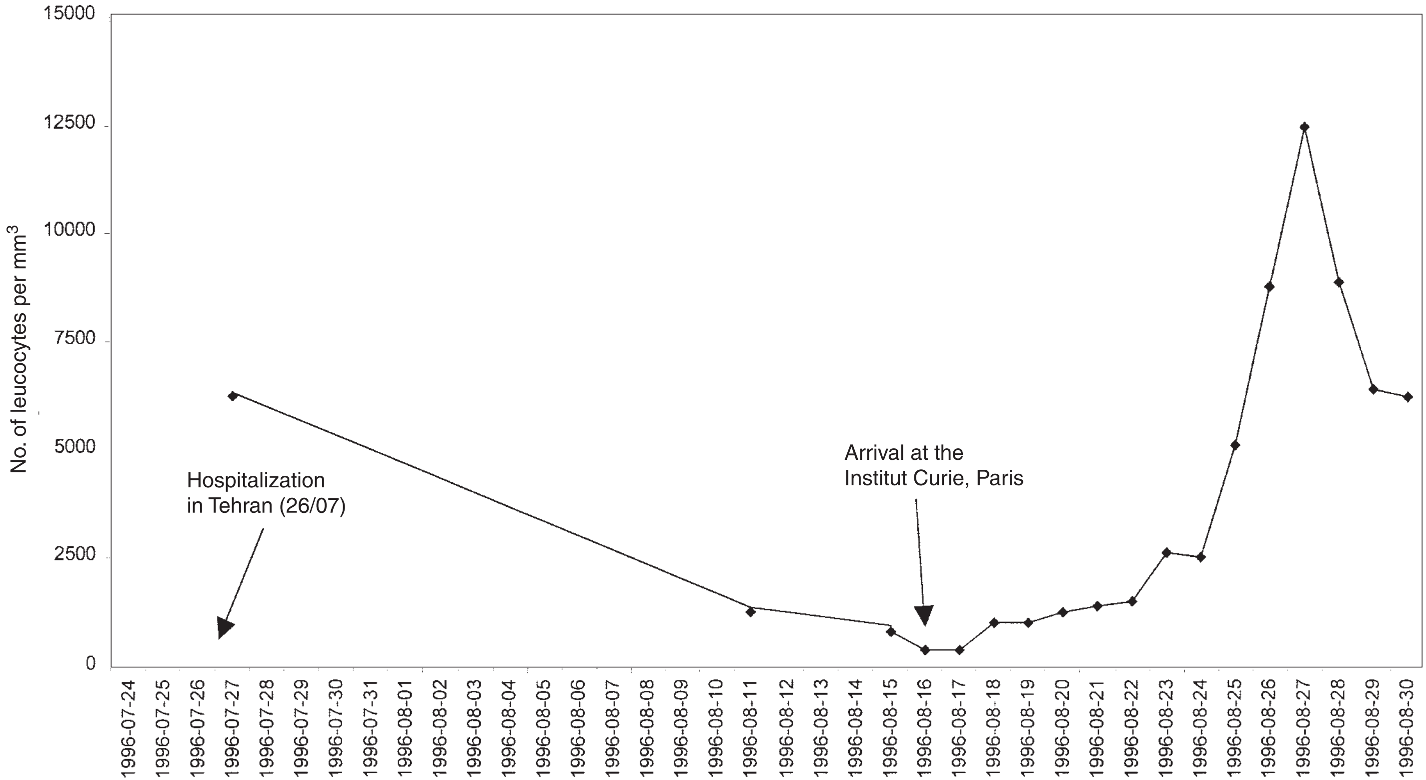

FIG. 3. Evolution of leucocytes in July–August 1996.

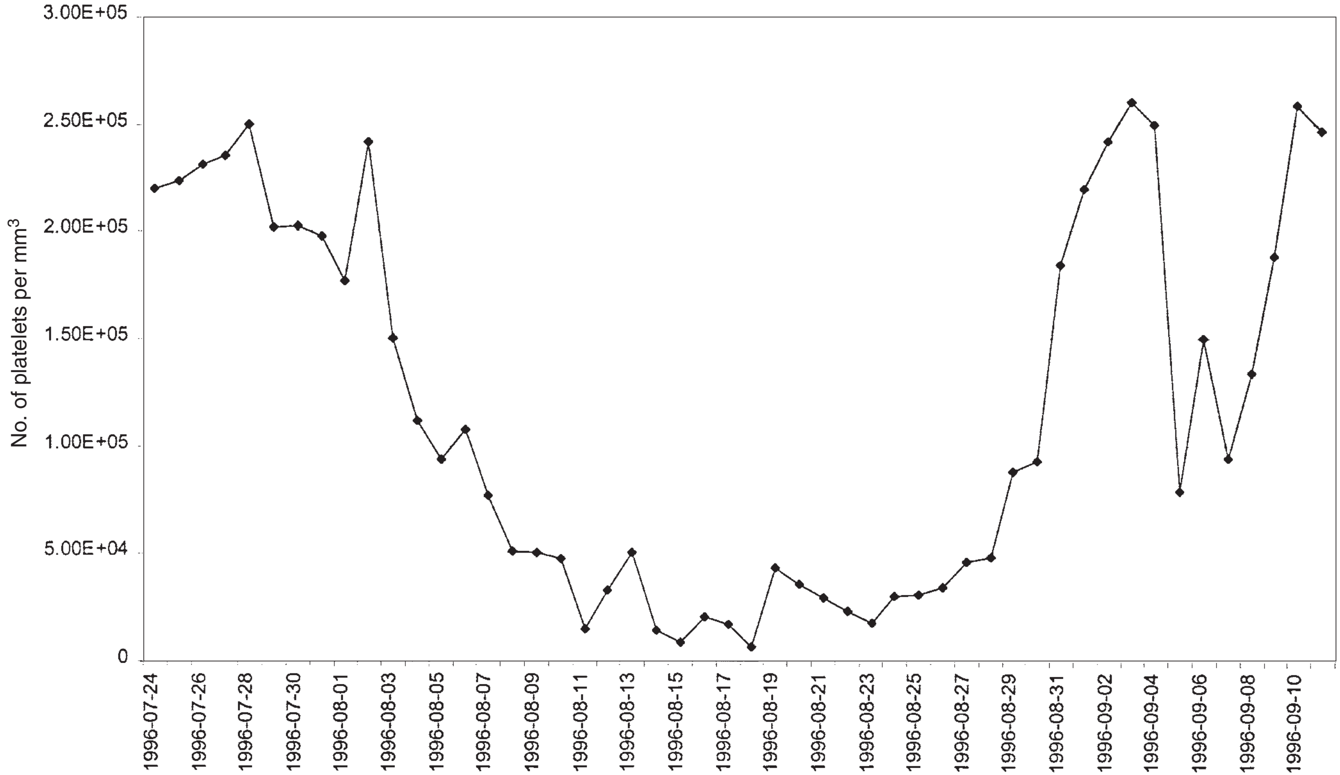

FIG. 4. Evolution of platelets in July–August 1996.

PHOTO 1. Start of reddening of the right side of the chest and upper abdomen on Day 6.

PHOTO 2. Dark erythema with dry desquamation starting at the nipple on Day 12.

PHOTO 3. Necrosis of the epidermis on Day 15 (the white spots refer to silver ointment).

PHOTO 4. Erythema and tense bulla in the left palm on Day 19.

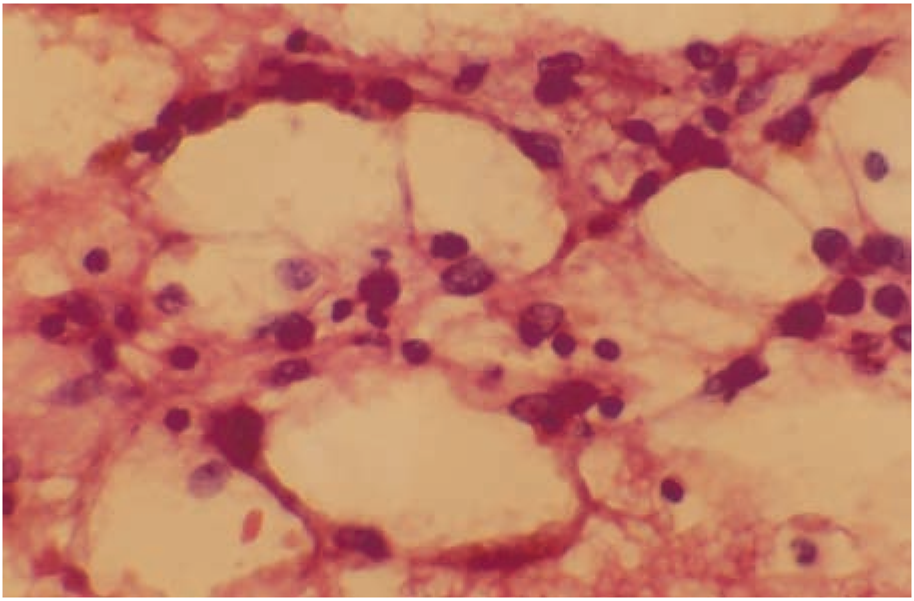

PHOTO 5. Aplastic bone marrow on Day 20.

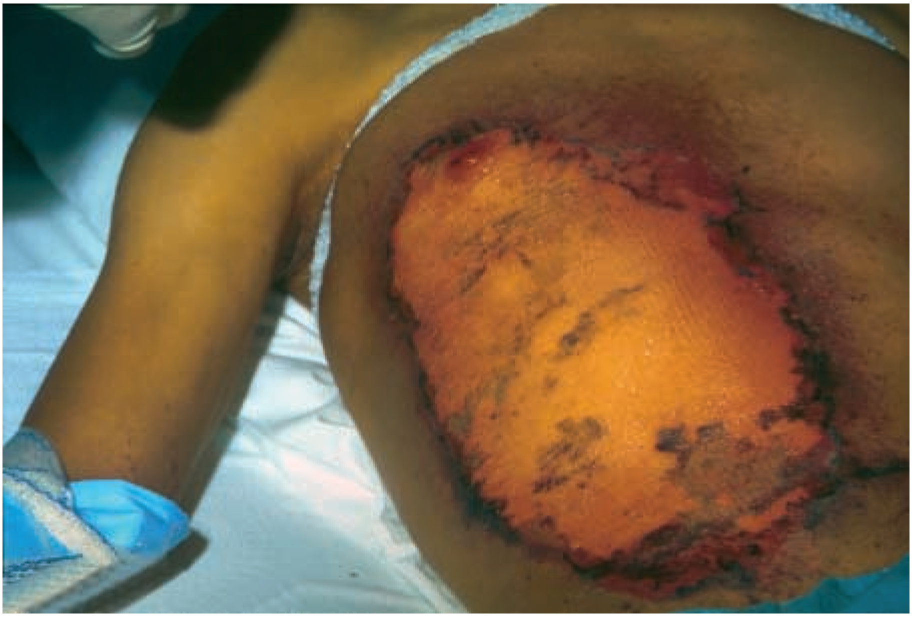

PHOTO 6. Loss of epidermis on the right side of the chest on Day 25.

PHOTO 7. Moist desquamation on the medial side of the right antecubital fossa on Day 25.

PHOTO 8. Large (5 cm × 5 cm) bulla on the left palm on Day 25.

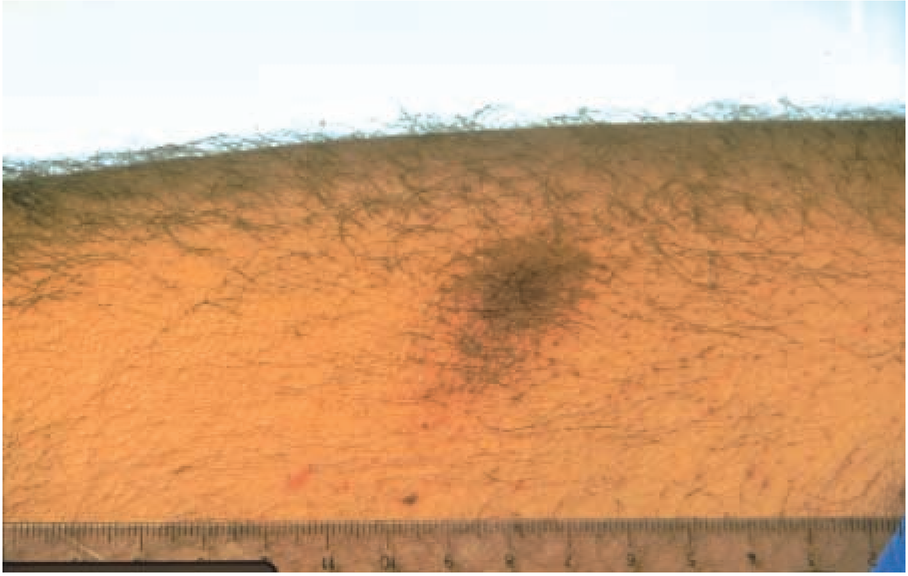

PHOTO 9. Erythema (2 cm × 2 cm) on the anterior upper surface of the right thigh on Day 25.

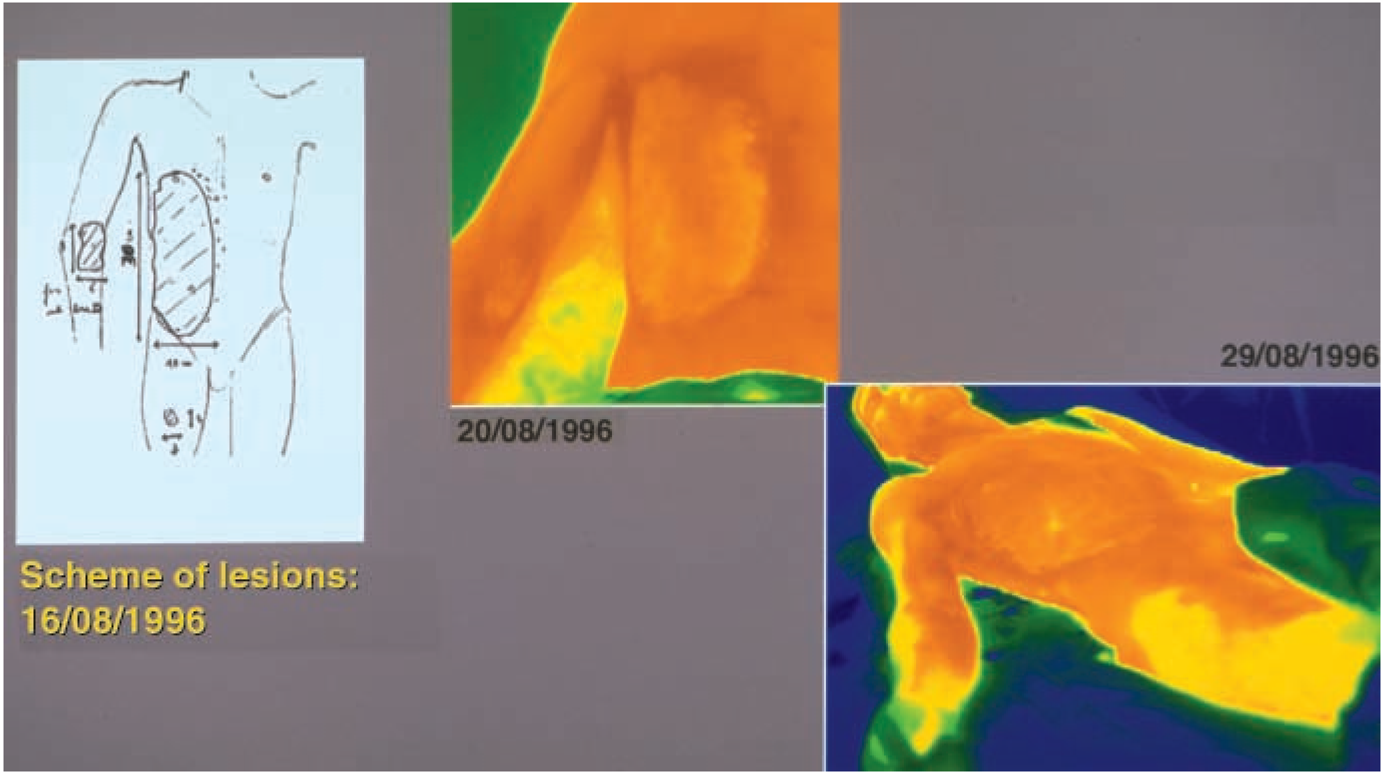

PHOTO 10. Thermography of the chest and right elbow on Day 28.

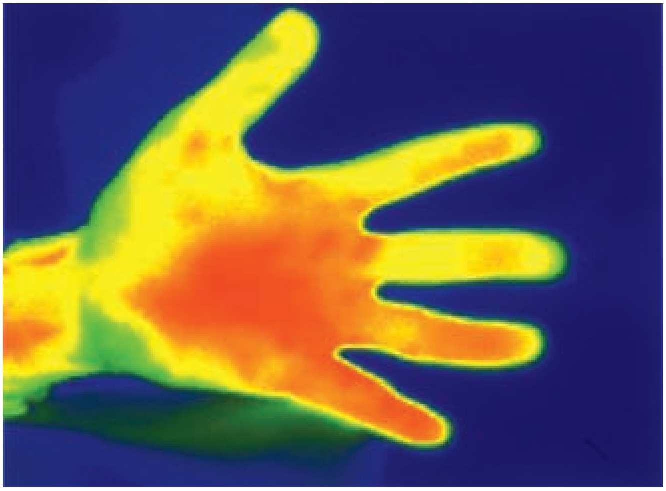

PHOTO 11. Thermography of the left hand on Day 28.

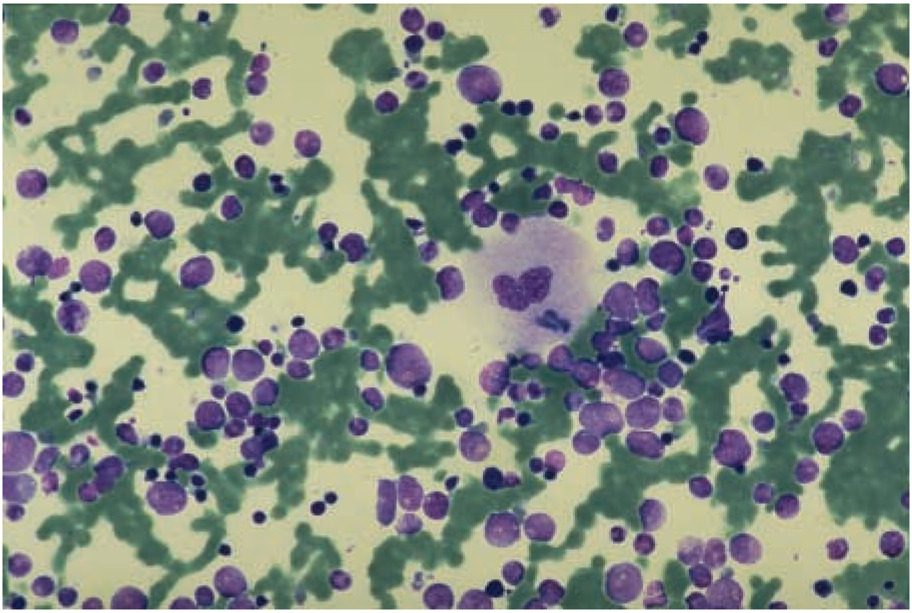

PHOTO 12. Normocellular bone marrow on Day 35.

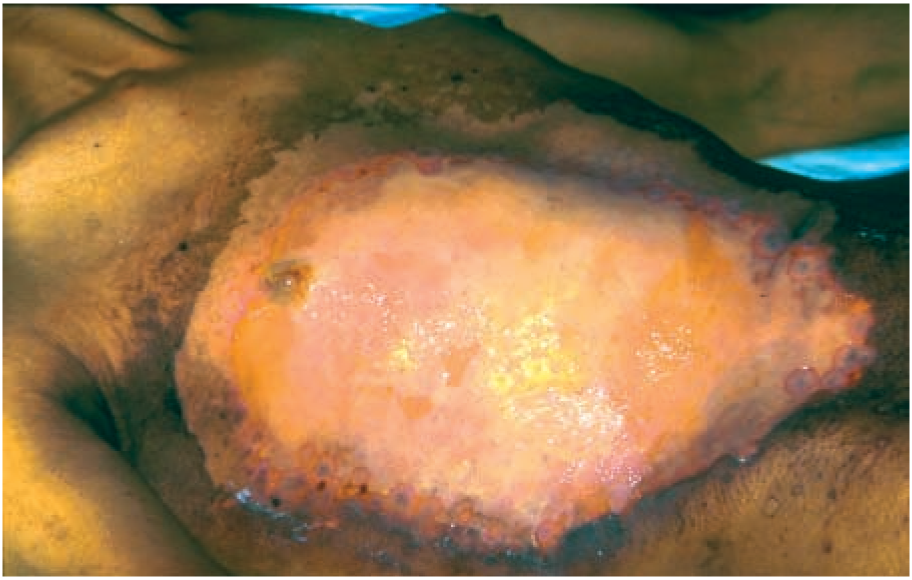

PHOTO 13. Re-epithelialization from the edges of the chest lesion on Day 35.

PHOTO 14. Peripheral and intralesional re-epithelialization in the elbow region on Day 35.

PHOTO 15. Moist desquamation on the left palm on Day 35.

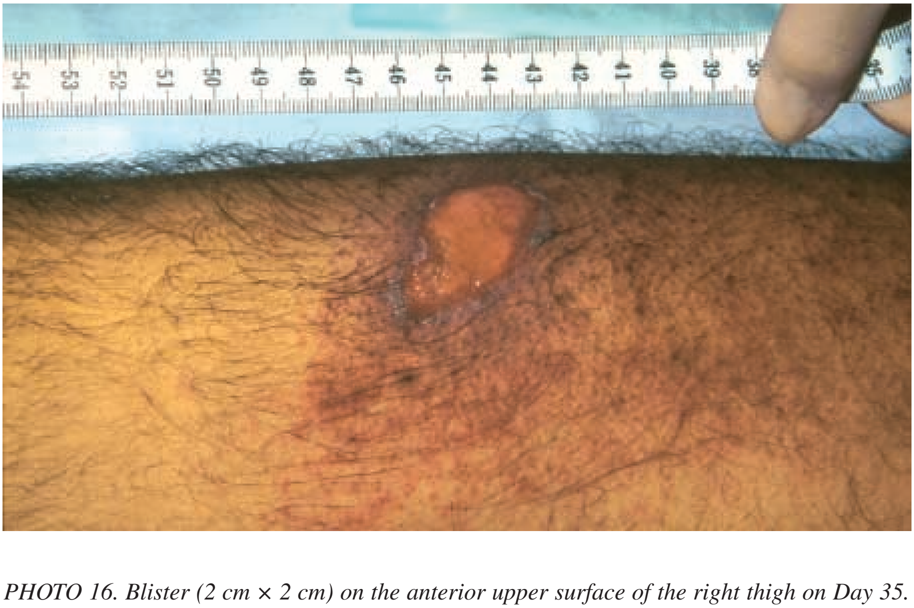

PHOTO 16. Blister (2 cm × 2 cm) on the anterior upper surface of the right thigh on Day 35.

PHOTO 17. Chest graft (made on Day 63) well taken on Day 85.

PHOTO 18. The thigh graft (made on Day 63) developed some necrosis on Day 85.

PHOTO 19. Self-healed hand lesion without functional impairment on Day 85.

PHOTO 20. Self-healed elbow lesion on Day 85.

PHOTO 21. Fully vitalized graft on the chest and a small fissure below it in September 1997.

PHOTO 22. Fully vitalized fibrotic chest graft surrounded with a depigmented halo with the self-healed fissure below it in November 1997.

PHOTO 23. Slight retraction of the body to the right side due to the fibrotic chest graft in November 1997.

PHOTO 24. Contracture of the right elbow in November 1997.

PHOTO 25. Thickened skin in the left palm with no functional disorder in November 1997.

PHOTO 26. Small scar with a depigmented halo on the right thigh in November 1997.

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Consultants Meetings

Vienna, Austria: 21–26 April 1997, 11–12 January 1999