DOI: 10.1259/bjr/77700378

Multi-organ involvement as a pathogenetic principle of the radiation syndromes: a study involving 110 case histories documented in SEARCH and classified as the bases of haematopoietic indicators of effect

T M FLIEDNER, MD, H D DÖRR, MD and V MEINEKE, MD

Radiation Medicine Research Group, Faculty of Medicine, University of Ulm, Germany

Abstract. The purpose of this contribution is to analyse the extent and severity of radiation-induced multi-organ involvement (MOI) and multi-organ failure (MOF) following whole body exposure to ionising radiation in 110 patients who were involved in different radiation accidents that occurred between 1945 and 2000. The clinical case histories were documented systematically in SEARCH (System for Evaluation and Archiving of Radiation Accidents based on Case Histories), which was established by our group in collaboration with international experts. The consequences of radiation-induced MOI in these patients were examined for two severity-of-response categories. On the basis of early (days 1–10 following exposure) haematological signs and symptoms, 45 of the patients could be assigned to response category (RC) 4; 65 patients presented early haematological changes characteristic for RC 3. All patients assigned to RC 4 died within 60 days, whilst the patients in RC 3 survived the first 100 days owing to an autologous haematopoietic recovery as well as necessary recovery of other organ systems. All of the 45 patients assigned to RC 4 suffered from the consequences of haematological, gastrointestinal, skin and neurovascular involvement. Regarding other organ systems in these 45 patients in RC 4, 20 patients showed evidence of cardiovascular involvement, 32 showed respiratory involvement, 25 showed liver involvement and 32 showed urogenital involvement. The patients assigned to RC 3 also displayed MOI, but at a significantly lower level. All of them showed signs and symptoms of involvement of haematopoiesis, the gastrointestinal system, skin and the neurovascular system. However, in contrast to the RC 4 patients, the RC 3 patients were reported to have less severe impairments of the cardiovascular, respiratory, metabolic and urogenital systems. It also became clear that the symptomatology of organ system involvement could be traced not only to the pathophysiology of the rapidly turning over cell renewal systems but — of equal or more importance — to the vascular system and specifically, to the endothelial components. Thus, it will be a challenge of further research to consider the cellular and molecular mechanisms involved in radiation-induced MOI and MOF. Necessary therapeutic measures should be determined on an improved pathophysiological basis.

Introduction

The purpose of this exploratory research project was to evaluate 110 case histories of accidentally whole body irradiated humans identified in the SEARCH (System for Evaluation and Archiving of Radiation Accidents based on Case Histories) database developed by our group [1] and to characterise the incidence and type of response with respect to the extent of involvement of different organ systems in the pathogenesis of acute radiation syndrome. It will be shown that study of the pathophysiology of acute radiation syndromes in man requires a multi-organ involvement (MOI) approach. In the case of multi-organ trauma due to radiation exposure, the pathogenesis and recovery of a patient must consider the complexity caused by the multi-organ trauma *per se* as well as the impairment of recovery potential associated with radiation effects on slowly regenerating cells and tissues such as endothelial and connective tissue cells, thus potentially resulting in multi-organ failure (MOF).

Present affiliation for H D Dörr and V Meineke: Bundeswehr Institute of Radiobiology, Munich, Germany.

Material and methods

Materials

In the SEARCH database, a total of 824 case histories was collected from 81 accidents in 19 countries between 1945 and 2001 [1]. Of these case histories, 110 were selected in order to study MOI.

An initial group of 45 patients was assigned to response category (RC) 4. RC 4 has been described in detail in the "*Medical Management of Radiation Accidents: manual on the acute radiation syndrome*" [2] (see Methods section). None of these patients survived beyond 60 days.

100 cases in the SEARCH database could be assigned to RC 3, all of whom survived the first 100 days following exposure. Of these 100 cases, 65 had a sufficient amount of detailed clinical data and were selected for detailed analysis.

Methods

The key point in investigation of the pathophysiology of radiation-induced MOI or MOF is the assignment of patients to an appropriate response category. Since it is the first time in such a study that the clinical response of a

person to whole body radiation exposure is categorised according to "indicators of response and repair", and not to indicators of exposure (measured in Gy or cGy), the approach used is described in some detail.

The data show that the severity and complexity of the radiation syndromes can be best correlated with the pattern of blood cell changes within the first 10 days after exposure as a direct result of the extent of damage to the haematopoietic stem cell system distributed throughout all sites of haematopoietic cell renewal [3, 4].

In assigning a patient to RC 4, one can observe a characteristic blood cell response; examples are given in Figures 1 and 2.

Crucial for the assignment of a patient to RC 4 on the basis of haematological grade H4 are the following response patterns. In all cases one can observe an extensive initial granulocytosis within the first 24–48 h after exposure. This is followed by a rapid disappearance of granulocytes from the blood between days 4 and 6. This pattern is due to a (unspecific) mobilisation of granulocytes from intravascular as well as vascular reserve pools and is related to the maturation time of granulocytes in the bone marrow (approximately 4 days) in combination with the radiation-induced cell death of granulocyte precursor cells [5, 6].

In all the cases in RC 4, the platelet count decreases progressively to minimal values of less then 10 000 mm^{-3} within 10 days. Such a pattern is seen if the megakaryocyte precursors in the bone marrow are essentially "wiped out". The disappearance of platelets from the blood must then be seen in relation to the survival time of platelets (10 days) under the assumption of a nearly complete destruction of bone marrow megakaryocytes. It is most likely that the early disappearance of platelets from the blood in these severely affected patients is related to the attempt to maintain vascular integrity.

Furthermore, in these patients a very rapid fall of lymphocytes can be seen within the first 24 h after exposure as a result of impairment of lymphocyte recirculation rather than the radiation sensitivity of an individual cell. Exposure of a large volume of the organism always results in lymphocytopenia. However, the degree of this phenomenon is not necessarily correlated with the extent of damage to the bone marrow stem cell pool, which is widely distributed throughout the skeleton. Thus, in principle, a severe initial lymphopenia can also be seen if the distribution of radiation is inhomogeneous, sparing some bone marrow units.

A software system is under development utilising neuronal networks to assess the predictive power of these blood cell changes [7].

As far as assigning patients to RC 3 rather than RC 4 is concerned, Figure 2 demonstrates the essential differences in the haematological responses during the first 10–20 days that result in haematological grade H3.

The granulocyte pattern following radiation exposure is characterised by an initial granulocytosis, although this is not as extensive as in H4. The crucial difference from H4 can be seen in the fact that the granulocytes decrease progressively towards day 10 after exposure, rather than abruptly between days 4 and 6. In particular, the granulocytes levels on days 5, 6 and 7 do not reach "zero" but remain at 200–500 mm^{-3}. The values remain at this level on subsequent days, or even show an "abortive" rise lasting for several days (as described earlier, supporting the concept of the "injured stem cell hypothesis" [3, 8]). Such a response pattern indicates that there must be some pluripotent stem cells remaining in any one of the active haematopoiesis-producing bone areas. This is likely to be associated with the principal potential of stem cells to repopulate the entire marrow. Therefore, the grading of a patient into H3 can be correlated with "an autologous

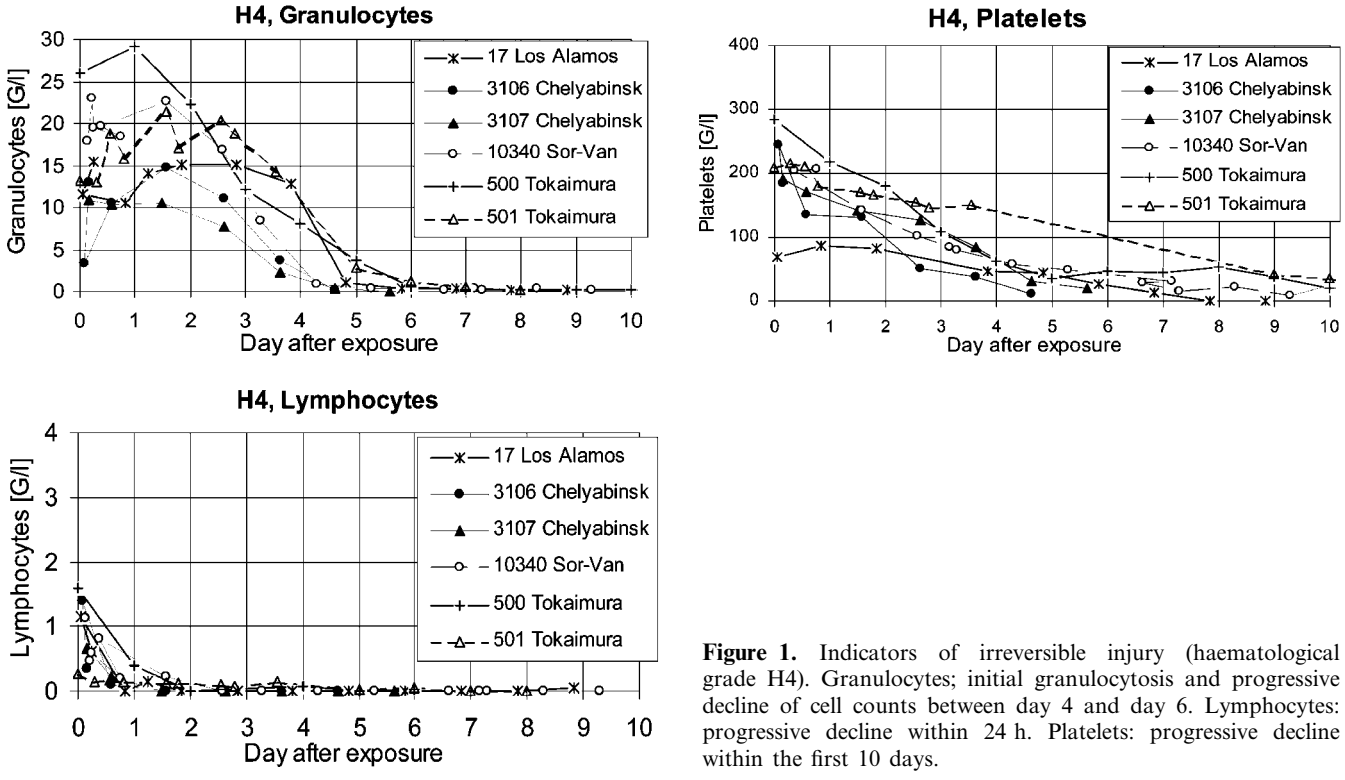
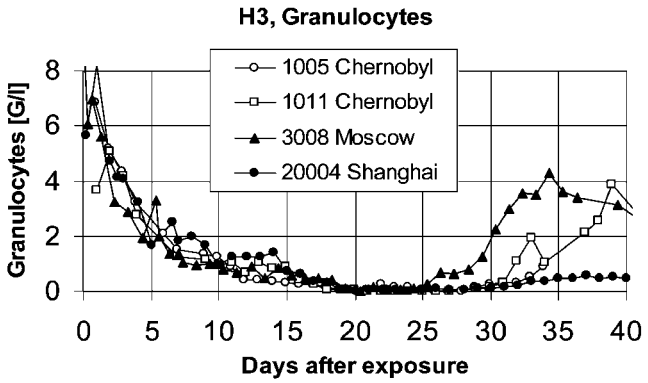
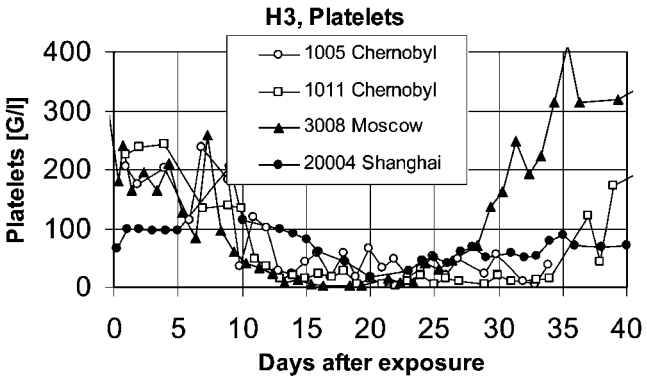


Figure 1. Indicators of irreversible injury (haematological grade H4). Granulocytes; initial granulocytosis and progressive decline of cell counts between day 4 and day 6. Lymphocytes: progressive decline within 24 h. Platelets: progressive decline within the first 10 days.





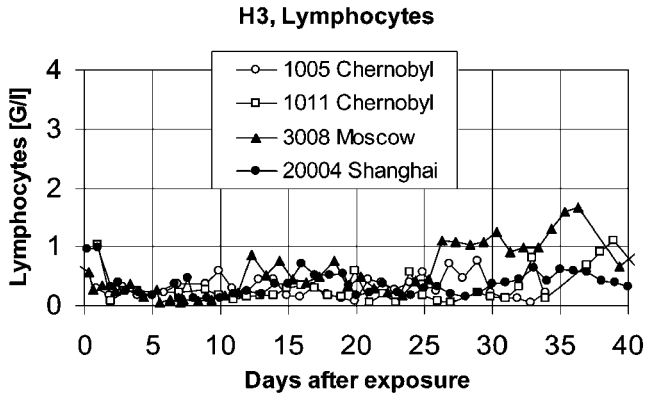


Figure 2. Indicators of reversible injury (haematological grade H3). Granulocytes: moderate granulocytosis, decline between day 4 and day 10, abortive recovery followed by nadir days 20–30. Lymphocytes: decline to nadir levels within 2 days, slow recovery thereafter. Platelets: initial 10-day shoulder followed by decline towards day 20, nadir days 20–30.

recovery possible" if systematic therapy is used to enhance recovery and to "bridge" the consequences of a temporary pancytopenia.

The platelet pattern in patients assigned to H3 leads to similar conclusions. In these patients, the platelet concentration in the first 10 days after exposure remains at "clinically comfortable" levels, *i.e.* above 50 000–100 000 mm^{-3}. A thrombocytopenia develops within 10–20 days, reaching a nadir between days 15 and 25. This initial pattern can be explained by some platelet production somewhere in the bone marrow. This pattern is also in agreement with the assumption of some replication and proliferation of pluripotent cells in the stem cell pool.

The pattern of lymphocyte changes is similar to that seen in H4 patients, but levels of these cells do not approach zero but remain "countable" and eventually recover slowly.

Thus, the crucial distinction between H4 and H3 is whether or not the blood cell changes are compatible with essentially irreversible damage to the stem cell pool (H4) or whether there is evidence for continued proliferation and maturation of some haematopoietic cells somewhere in the bone marrow (H3) [3] and hence evidence of a possible autologous recovery of haematopoietic cell production.

Indicators for the assignment of patients to RC 4 and RC 3 with regard to MOI

In the patients evaluated in this study assigned to either RC 4 or RC 3 mainly on the basis of their haematological grading code (H4 and H3, respectively) (as described *in extenso* in [2]), the following criteria of organ involvement were used.

- Haematopoietic system: aberration of peripheral blood cell count.
- Skin: epilation, erythema, ulceration.
- Gastrointestinal tract (GIT): mucositis, vomiting, diarrhoea.
- Central nervous system (CNS): headache, fatigue, dizziness, coma.
- Kidney: biochemical parameters (creatinine, urea), anuria.
- Liver: biochemical parameters (alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (γGT), bilirubin), jaundice.
- Respiratory system: pneumonia, respiratory failure.
- Cardiovascular system: hypotension, heart failure.

To identify organ involvement, all available data for each patient stored in the SEARCH database were analysed. The rating (Table 1) is based on the clinical significance of symptoms and on the results from examinations such as biochemical parameters. No rating was given if no involvement of the organ system occurred or when no information about this was available in the cohort of patients under examination.

The rating "+" was given for mild involvement of the particular organ system, *i.e.* there were indications of involvement but with little or no clinical consequences. For example, marginal deviation of biochemical parameters such as ALT, AST or γ-GT indicates involvement of the liver/hepatic system but would not affect the patient at all. The rating "+" also indicates that no or only minor therapeutic measures were necessary.

If involvement of the organ system was more extensive but still "moderate", the rating "++" was used. For example, if the degree of radiation-induced "skin burns"

Table 1. Clinical significance of symptoms and results from examinations such as biochemical parameters

Case No.	Survival time (days)	Haematopoietic system	Skin	GIT	Liver	Kidney	CNS	Respiratory system	Cardiovascular system
24	2	++	++	+++		++	++++	++	++++
3039	2	+	++	++			++++		++++
3110	3	+	+	+		++++	+	++	++++
3106	5	++++	++	++	+	++	++++		++++
3105	5	++	++	++		++++	+		++++
3107	8	++++	++	+++	++		+	+	++++
17	9	++++	++	+++		++++	++++	+++	
36	10	++++		+			++++	++	++++
40004	12	++	+++	++		++++	+++	++	
1015	14	++++	+++	+++		++	++		
3032	14	++++	++	++++	++		++		++
1023	15	++++	+++	++		++++	++	+++	
1002	15	++++	++	+++		++++	++	++++	
1010	15	++++	+++	++	+		++++	++	+
1025	16	++++	+++	+		++	++++	++	++
1003	17	++++	+++	+++	+++	++	++	++	
1020	17	++++	+++	++	++	++	++	++	
3035	18	++++	++	+++			+		
1004	18	++++	+++	+++	++	++	+++	++	
1007	18	++++	+++	+	++		++++		++++
1014	18	++++	+++	++	+++	+++	++	++	++
1017	18	++++	+++	++		++++	++	++	
3034	19	++++	+++	+		+++	+		
1030	21	++++	++	+			+		
1062	21	++++	+++	+	++	++	+		++++
1024	23	++++	++++	+	++	++	++++	++	
1009	23	++++	+++	++	++	+++	++++	++	
1012	24	++++	+++	+++	++++	++++	++	+++	
15	24	++++	+++	+++			+		++++
1026	24	++++	++	++	++	++	++	+++	+
1027	24	++++	++	+	++++	++	++	+++	
1001	25	++++	+++	+	++++	++++	++	++	++++
20001	25	++++	++	++			+	+++	
3033	26	++++	+++	+	+	++	++	++	++++
1008	30	++++	+++	++		++++	++		
1031	32	++++	+++	++	+	++	++++	+++	
9	32	++++	++	++++	++++	++++	++	++	
1005	34	++++	+++	++	++++	++++	++	+++	
45	35	++++	+++	+++			++++	++	
10340	36	+++	++	+++	++++	++++	++	++	
3046	36	++++	+++	+	++		++++	++	
1028	48	++++	++	++	++++	++	++	+++	++
1034	48	++++	+++	+	++	++	++++	++	++++
3047	54	+++	++++	+	++	+	++	+	
46	55	++++		+			++++		++++

GIT, gastrointestinal tract; CNS, central nervous system.
+, mild; ++, moderate; +++, severe; ++++, very severe.

described in the SEARCH database was between 0.5 and 1.5 (erythema), then the rating "++" (skin) was given.

The rating "+++" was given for "severe" involvement of a particular organ system. For example, if biochemical parameters indicated a severe affect on an organ system requiring therapeutic interventions but without evidence for development into organ system failure, then the rating "+++" was given.

Very severe organ system involvement was rated as "++++". This rating was given particularly when failure or very severe malfunction of the particular organ system occurred. Here, the rating "+++++" as used in the SEARCH database was reassigned to "++++", as the meaning of the rating "+++++" as "fatal" was of no interest here because of the yet unknown pathophysiological mechanisms of MOF following exposure to ionising radiation.

In Table 1, the degree of organ involvement is shown for the 45 patients assigned to RC 4 (H4). An identical approach was used (not shown here) to determine the extent of organ involvement in the 65 patients assigned to RC 3 (H3).

Results

Overview

Table 2 shows the clinical involvement of different organ systems in the patients assigned to RC 4 (death within 60 days). The mean survival time was

approximately 22 days (range 2–55 days). Table 2 shows the involvement of the haematopoietic system, skin, GIT, CNS, kidney, liver, respiratory system and cardiovascular system in correlation with the survival time of the patients. It is clear that all patients in this cohort had severe signs and symptoms of radiation-induced responses in the four key organ systems (haematopoiesis, skin, gastrointestinal system and CNS), but also to some extent in the respiratory system, cardiovascular system, kidney and liver (at least 20 of the 45 patients).

In Table 3, results of MOI are shown for the 65 patients assigned to RC 3. It can be seen that there was evidence for significant injury to haematopoiesis, the skin and the GIT in nearly all patients. Furthermore, there is evidence for health consequences related to the CNS in more then 70% of the patients. However, involvement of the respiratory and cardiovascular systems was less prominent, as were effects observed in the liver and kidney (less then 30% of the cases showed involvement).

It was of considerable interest to analyse the MOI data regarding the quality and quantity of changes as a function of time after exposure in the two response categories. Such an analysis will eventually help to determine the pattern of interorgan relationships with respect to their functional potentialities and pathophysiological mechanisms.

Signs and symptoms of organ involvement in patients assigned to RC 4

43 of the 45 patients assigned to RC 4 showed involvement of the skin, GIT and CNS in addition to developing very severe pancytopenia as mentioned above. In particular, the changes observed were as follows.

Skin

Nearly all the patients developed an initial erythema (within hours). There was a lack of information in the database about the development of erythema for only five patients. Most of the patients in RC 4 showed erythema on the day of the radiation exposure. In 12 patients the erythema was reported to be present on the day after exposure. In three patients the erythema was noted and reported on the second day or later post radiation.

In 19 patients, epilation occurred between days 11 and 20 (average approximately day 15) after exposure. Seven patients did not show epilation, but these patients died before day 15; epilation in these patients would probably have developed later. No information about epilation was recorded in the database for 19 patients.

Other symptoms of skin involvement were radiation-induced "skin burns". Frequently, dermatological experts did not perform the descriptions of such changes and hence the descriptions in the database records are incomplete.

Gastrointestinal tract

Most of the patients developed symptoms such as diarrhoea and vomiting, as well as mucositis and bloody diarrhoea. The pathogenetic mechanisms behind these symptoms differ depending on their primary or secondary origin, *e.g.* denudation of the mucosa (primary) compared with diarrhoea or haemorrhage (secondary). From the viewpoint of clinical judgement, these symptoms affect the functions of the GIT.

CNS

Most of the patients exhibited headache, fatigue, dizziness, somnolent state and even coma. Coma occurred mainly in conjunction with the consequences of involvement of other organ systems. The more unspecific symptoms such as headache, fatigue and dizziness occurred in most patients during the first day after exposure.

Other organs

32 of the 45 patients developed significant symptoms of renal impairment. 25 of the 45 patients showed changes in the liver, 32 showed impairments of the respiratory system and 20 of them of the cardiovascular system.

Renal impairment was identified as serious changes in biochemical parameters and of course, if organ failure/anuria became apparent. 32 of the 45 patients showed involvement of the renal system, which occurred on

Table 2. Participation of different organ systems in the morbidity and mortality of the acute radiation syndrome observed in 45 patients classified as haematological grade H4 severity of effect: death <60 days

Survival time (days)	*n* (total)	Haematopoietic system	Skin	GIT	CNS	Kidney	Liver	Respiratory system	Cardiovascular system
0–10	8	8	7	8	8	5	2	5	7
11–20	15	15	15	15	15	11	7	10	5
21–30	12	12	12	12	12	9	8	8	5
31–40	6	6	6	6	6	4	5	6	0
Total	45	45	43	45	45	32	25	32	20

GIT, gastrointestinal tract; CNS, central nervous system.

Table 3. Participation of different organ systems in the morbidity and mortality of the acute radiation syndrome observed in 65 patients classified as haematological grade H3 severity of effect (clinical course in the first 90 days after exposure)

n (total)	Haematopoietic system	Skin	GIT	CNS	Kidney	Liver	Respiratory system	Cardiovascular system
65	65	58	61	50	9	18	5	14

GIT, gastrointestinal tract; CNS, central nervous system.

average 14.6 days post irradiation. 13 patients either did not show renal impairment or no data regarding renal impairment were available.

Liver involvement was identified as serious changes in biochemical parameters or as jaundice and if organ failure occurred. Involvement could be seen in 25 of the 45 patients and occurred after approximately 15 days. 20 patients either did not show liver involvement or no data regarding liver involvement were available.

Of all the patients who survived 17 days or longer (n=40), 36 showed signs of mild to very severe liver involvement. Liver failure occurred only if the patient's survival time was between 24 days and 48 days. During this particular time span, 7 of 15 patients showed signs of liver failure.

Involvement of the respiratory system could be seen in 32 of the 45 patients. Involvement ranged from dyspnoea only (7 patients), through adult respiratory distress syndrome (ARDS) (6 patients) and interstitial pneumonitis (7 patients) to pneumonia (11 patients). Pneumothorax due to subclavian vein puncture occurred in one case.

Involvement of the cardiovascular system occurred in most cases as heart failure. Seven of eight patients with a survival time of 10 days or less showed signs of failure of the cardiovascular system. For a survival time of 12 days or longer, only 7 of 37 patients showed signs of failure of the cardiovascular system, and 5 more showed mild or moderate symptoms of cardiovascular involvement.

Signs and symptoms of organ involvement in patients assigned to RC 3

The type of blood cell changes that occur as a consequence of exposure of the haematopoietic system has been described above as a transient but often severe pancytopenia with potentially serious clinical consequences in the 3rd and 4th week after exposure, resulting in infectious complications or thrombocytopenic purpura (see Figure 2).

Skin

58 of the 65 patients assigned to RC 3 had signs of involvement of the skin in terms of erythema and ulceration as well as epilation. In most of the 58 cases, erythema was reported starting on days 1–2 after exposure. Epilation occurred in only 5 of the 58 patients with skin involvement.

Gastrointestinal tract

61 of the 65 patients developed signs and symptoms related to the GIT. The most common clinically relevant symptoms were nausea, vomiting and diarrhoea. Apart from these symptoms as a consequence of the radiation exposure (which from the pathophysiological viewpoint can also be seen as an affect on the neurovascular system), other affects such as mucositis, oesophagitis and parotitis were seen in 23 of the 61 patients with involvement of the GIT.

CNS

50 of the 65 patients showed involvement of the CNS in terms of headache, fatigue, dizziness and coma.

Other organs

As far as the kidney, liver, respiratory system and cardiovascular system are concerned, the frequency of signs and symptoms of response are much less prominent than in RC 4 patients. The following general observations are pertinent.

The frequency and the time when an affect on one of the listed organ systems occurred was much more variable than in the RC 4 group. Involvement of the liver or the renal system was identified by pathological biochemical data. In some cases there was suspicion that hepatitis was caused by transfusion. Only one patient showed jaundice, and in this case hepatitis was verified serologically. A detailed description of signs and symptoms as they evolve as a function of time after irradiation is under preparation.

Summary of the results from the RC 4 and RC 3 groups

The available information indicated a distinct difference between the two groups (RC 4 and RC 3) with regard to the frequency, severity and quality of signs and symptoms of involvement of different organ systems.

In the first group of patients assigned to RC 4 and who survived less than 60 days, 43 of 45 showed involvement of the skin. All 45 patients showed affects to the GIT. The renal system was involved in 32 of the 45 patients and the liver in 25 of the 45 patients. The respiratory system showed involvement in 32 patients and the cardiovascular system in 20 of the 45 cases. MOI with affects on the haematopoietic system, skin, kidney and liver could be seen in 19 of the 45 patients.

In the RC 3 group, MOI was not as frequent or consistent compared with the RC 4 group. Involvement of the organ systems was also less severe than in the RC 4 group. None of the patients developed radiation-induced MOF, and all patients survived more than 100 days. Most of the signs and symptoms, such as erythema and oedema, could be interpreted as a disturbance of endothelial function. However, the massive cell loss and cell turnover that is expected in the RC 4 group would not occur. Moreover, in this context the generally slight aberrations of the biochemical data for the kidney and liver could be interpreted as a consequence of a functional deficit of the endothelium.

Assessments and perspectives

In the context of the "Proceedings of the Advanced Research Workshop on Multi-Organ Involvement and Failure" published in this special volume of the British Journal of Radiology, two areas appear of importance: the pathophysiological mechanisms resulting in the radiation syndromes observed; and the consequences for the medical management of such patients, including the logistics of dealing with accidentally radiation-exposed persons at a national and international level.

As far as the pathophysiological mechanisms that are operative in the development of an acute radiation syndrome are concerned, a new look is required. In an earlier publication [8], emphasis was placed on the disturbance of cellular kinetics. It is an undisputed fact that the effects of whole body exposure to ionising

radiation manifest themselves in a perturbation of rapidly turning-over cell renewal systems, such as haematopoiesis, skin, gastrointestinal mucosa and gonads. In these systems, there is an immediate injury to the population of cells capable of DNA synthesis, cell proliferation and differentiation, with the stem cell pool being the most sensitive target among these systems. There is also consensus that whether an autochthonous system recovery may occur or whether therapeutic interventions are needed, such as stem cell transplantation or skin engraftment, depends on the number and quality of remaining stem cells. It was taken for granted for years that the distinction of a ''haematological form'' from a ''gastrointestinal form'' of the acute radiation syndrome is a clinically useful categorisation [9–13].

However, the observations of two patients treated in Tokyo after the Tokai-mura accident [14] have led to a more differentiated view. It was realised that, in all accidentally whole body radiation exposed persons, the medical doctor in charge is confronted with a patient characterised by MOI possibly resulting in MOF. It became evident that one is able to ''bridge'' the acute phase of the radiation syndrome affecting all cells, cell systems and organs (characterised by haematopoietic or gastrointestinal failure) by appropriate therapeutic interventions (stem cell transplantation, cytokine therapy, antibiotics, appropriate fluid replacement, platelet transfusion). However, during the subsequent clinical course of events, the medical doctors have to deal with perturbations in the ''latently resting'' cell systems (endothelial cells, cells of the liver, lung, kidney, etc.) and their metabolic function. Thus, the doors are wide open to a new era of pathophysiological research: to examine the interplay between ''cellular kinetics'' and ''neurovascular responses'' following irradiation.

In this context, it is of interest to note the historical observations on the early effects of whole body irradiation on experimental mammals as well as human reported many years ago [15–19] and reviewed by several authors [20–23]. They already alluded to a very initial response of the vascular endothelium resulting in an increase in capillary fragility and permeability as an important event initiating the ''chain of events'' that one observes in irradiated patients as a function of time after exposure to ionising radiation. The vascular system of the bone marrow and its dramatic response to radiation exposure leading to its breakdown within 3 days deserves special attention [24, 25].

In these proceedings, Gaugler [26] addresses the relevant problems by asking the question: ''Does the vascular endothelium have a role to play in multi-organ failure following radiation exposure?'' Furthermore, Gourmelon et al [27] point to ''the involvement of the central nervous system in radiation-induced multi-organ dysfunction and/or failure''. These authors suggest that in some of the severely injured accident victims, a radiation-induced systemic inflammatory response syndrome (SIRS) occurs in radiation sickness, mediated by ''endogenous regulators'' and being observed either following local irradiation of the CNS or whole body irradiation.

As far as the consequences for medical management and logistics of these pathophysiological considerations is concerned, it is important to point out the medical complexity involved in the handling of severely affected accident victims.

In the Tokai-mura accident, the two severely affected patients remained alive for 83 days and 211 days, respectively. Primary responsibility for their care was in the hands of the intensive care specialists. They in turn consulted the ''organ specialists'' — haematologists, dermatologists, neurologists, gastroenterologists, etc. — to give specific recommendations regarding the organ system of their competence. Thus, one upshot is that any medical facility that is called upon to care for severely affected radiation accident victims needs to be a major hospital with all the appropriate specialties available 7 days a week, 24 h a day. Another consequence is that a large hospital prepared to participate in the medical management of severely injured accident patients will not be able to take care of more than a very few such patients (two to five at the most) because of the manpower needed ''around the clock''. This means that in any ''industrialised country'' of the world, one may need significantly more than one major hospital that would be prepared to handle such patients. One should be aware of the treatment cost for any one of such patients and make sure that the financial aspects of radiation accident medical management are considered well in advance.

Finally, such accident cases are rare. The need to handle several dozens of patients such as in Chernobyl (1986) will remain the exception, although in some terrorist scenarios one may have to consider how medically to handle the care of large numbers of victims. Nevertheless, professional ''know how'' on treating radiation accident patients will be concentrated more and more in a very few professional centres in the world. It is therefore suggested that a computerised and continuously updated guidance system (on CD-ROM) be developed and made available to all appropriate major national medical centres to support the professional medical management of radiation accident victims in spite of the fact that these hospitals are lacking medical staff to attend radiation injured persons but have a lot of experience handling multi-trauma patients or patients undergoing extensive chemotherapy or radiation therapy (analogue health impairments).

Acknowledgments

The scientific work was supported by a grant of the Federal Ministry of Defence, the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety and from the European Communities. This scientific work would not have been possible without the continuous support and cooperation in the relevant radiation medicine centres participating in the WHO–REMPAN Network.

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