RC-7a
The Medical Diagnosis and Treatment of Radiation Overexposed People

J.M. Bertho, N.M. Griffiths and P. Gourmelon
Institut de Radioprotection et de Sûreté Nucléaire,
Fontenay aux Roses, France
Abstract:

Although rare, accidental irradiation overexposures remain difficult to treat, mainly because of a complex physiopathology, known as the acute radiation syndrome (ARS). As a consequence, the issue remains fatal for most of high dose radiation accident victims. This is due in part through the lack of biological indicators able to give information about the extent of radiation-induced damage. Such bio-indicators may help to define a therapeutic strategy adapted to each specific accidental overexposure situation. Recent radiation accidents such as the Tokai Mura accident clearly showed that the therapeutic strategy must be based on the estimate of radiation-induced damage to life threatening physiological systems rather than the dose received by the victim. In fact, these accidents highlighted the heterogeneity of accidental irradiation, even in the most severe cases. Thus, important conceptual changes appeared recently for the treatment of radiation accident victims, such as the questionable role of haematopoietic stem cell transplantation after heterogeneous irradiation. Moreover, growing evidence indicates that ARS should be considered as an interplay of multiple pathologies originating not only from the haematopoietic system, the gastro-intestinal tract and the skin, but also from the neuro-vascular system and the inflammatory reaction rather than the addition of individual syndromes appearing in an ordered fashion according to the radiation dose and the time post-irradiation. Thus, it is important to take into account these new concepts in the medical management of accidentally overexposed victims.
1- The acute radiation syndrome: historical concepts

Classically, the acute radiation syndrome, which is defined as the pathologies developing after an uncontrolled radiation overexposure, is described as appearing in three phases (Figure 1). The first one, the initial syndrome, appears in the first few hours after irradiation. Manifestations are nausea, retching and vomiting, reflex diarrhoea, headache, hypotension, and in the most severe cases, a transient incapacitory syndrome. Additionally, erythema and oedema may transiently appear when local high dose irradiation was received. Importantly, the time of onset, intensity and duration of these symptoms are directly proportional to the global radiation dose received by the victim. Thus, the initial syndrome must be accurately observed, since it constitutes the very first indicator of the severity of radiation-induced damage to the victim (Young, 1987).

Then, after a latency period inversely proportional to the radiation dose received, the manifest phase takes place, with the development of the haematopoietic syndrome, the gastrointestinal syndrome and the neurovascular syndrome. Each of these syndromes was considered as responsible for the death of irradiated victims in a specific dose range (Figure 2), i.e., between 3 and 10 Gy for the haematopoietic syndrome, between 10 and 50 Gy for the gastrointestinal syndrome, and more than 50 Gy for the neurovascular syndrome.

Figure 1: The acute radiation syndrome, with the classically described three phases, the initial syndrome, the latency period and the manifest phase. Each of these three phases are proportional in their severity and duration to the global radiation dose received. The black plan indicates the lethal zone.

Figure 2: Survival time according to the global irradiation dose for several animal species. Note that the irradiation dose is indicated in rads. Adapted from Bond, 1969.
The haematopoietic system is one of the most sensitive systems in the organism, since doses as low as 1 Gy may significantly modify the number of circulating cells (Figure 3). This is mainly due to the radiation induced destruction of bone marrow, which cannot ensure the renewal of blood cells. Thus, the first manifestation of the haematopoietic syndrome is the progressive appearance of a leucopenia which induces risks of opportunistic infections for the patient and a thrombocytopenia which induces risks of bleeding and haemorrhages. In the absence of clinical support, a LD50/30 of 3 to 4 Gy is classically admitted for humans.

For doses higher than 10 to 12 Gy, irradiation induces the killing of intestinal crypt mucosal stem cells which in turn induces a progressive denudation of the intestinal epithelium, resulting in a breakdown of the mucosa and ulceration of the intestine. This results not only in a decreased absorption of nutrients and increased electrolyte and fluid loss, but also in the increased entry of intestinal bacteria, resulting in sepsis that cannot be controlled by the damaged immune system. This results in the death of irradiated victims with a mean survival time of 5 to 10 days. For doses lower than 10 Gy, a regeneration of mucosal cells is possible from surviving stem cells in the crypts. However for doses greater than 10 Gy the electrolyte and fluid loss is so important that the death may arise within few days after irradiation.

The neurovascular syndrome is the least known syndrome. It appears for doses greater than 50 Gy, and induces the death within 48 hours. It is characterized by a permanent incapacitation syndrome with neurological disorders leading to a comatous state. It is though to be mainly due to a general and severe leakage syndrome.

![Figure 3: Evolution of platelets (upper panel) and Neutrophils (lower panel) after overexposure of different severity. Adapted from Hendry, 1995.](image)

2- Characteristics of accidental irradiation and influence on the medical management of victims

This classical picture of the medical consequences of an accidental overexposure may be complicated by some of the characteristics of accidental irradiation. In fact, when looking at past radiation accidents, it becomes rapidly obvious that each accidental situation is specific and unique. These unique features complicate the estimate of radiation-induced damage and the choice of a therapeutic strategy. However, it is possible to distinguish some common features in these past radiation accidents, that may help in the definition of such a therapeutic strategy (Nenot, 1990).
2.1- Variability in the nature of accidental overexposure

According to the accidental nature of these overexposures, a very large range of radioactive sources might be implicated: gamma or X irradiators, solid sources or powder, or dispersion of radioactive dust consecutive to an intentional or accidental explosion. Thus, each of radiation accident have original characteristics directly linked to the physical nature of the source and its radiological characteristics (Nenot, 1990). Hence, when comparing two similar accidents due to the loss of a radioactive source, it is obvious that the powder form of the source in Goiania (Brazil, 1987) largely contributed to the severity of the accident and the number of victims as compared to the Juarez accident (Mexico, 1983) with a cobalt 60 solid source.

Studies in animal models as well as in in vitro models largely demonstrated the influence of the dose, the dose rate and the nature of ionising radiation on the biological effect (Tubiana, 1990). The consequence is that the medical management of an overexposed victim might take into account the nature of ionizing radiation implicated, but also the dose and the dose rate. However, these parameters are generally not known immediately, even if the radiological nature of the accident is recognized immediately.

2.2- Late recognition of the radiological nature of the accident

The radiological nature of the accident is very often recognized late, and this may contribute to its aggravation. This was noticeably the case in Goiania (Brazil, 1987), where the unknown radioactive nature of the source contributed to its dispersion, but also to the increased number of victims. In fact, sixteen days were necessary to recognize the radiological nature of this accident, resulting in 244 victims (IAEA, 1988). This late recognition of the radiological nature of the accident is a very frequent feature of accidental overexposure, since a mean of 22 days was calculated for 4 recent radiation accidents (Bangkok, Thailand, 2000, Meet Halfa, Egypt, 2 000, Tammiku, Estonia, 1994, and Goiania, Brazil, 1987) (Goans, 2002). The late recognition does not allow a precise reconstitution of the accident, particularly when a reconstitution of dose rate, time of exposure and the spatial configuration of the accident is expected. Moreover, this late recognition does not allow access to the parameters of the initial syndrome, with the occurrence and time of onset of nausea and vomiting, the occurrence and localization of erythema, and the initial decrease of lymphocytes, which constitute the very first signs allowing the diagnosis of the severity of irradiation.

Another factor may contribute to the late recognition of the radiological nature of these accidents. This is the non specificity of the symptoms that can be observed during the initial syndrome. In fact, nausea, vomiting and diarrhoea can be easily confounded with an infectious enterocolitis, and the patient is sent back home with an anti-emetic treatment. In such a case, the non-recognition of the radiological nature of the accident leads to a misdiagnosis and a non adapted charge of the patient that may have lethal consequences.

2.3- Heterogeneity of accidental irradiation

However, the most important common characteristic of almost all radiation overexposure is its heterogeneity, and this is the most sensitive parameter for the medical management of radiation overexposed victims. One of the most demonstrative examples is the accident which occurred in Mol (Belgium, 1965), in which an operator was irradiated from the ground to the head with a mixed field of gamma rays and neutrons. The physical dosimetry reconstruction showed a very high level of heterogeneity, with a gradient from 50 Gy to the left foot down to less than 3 Gy to the back of the head and cervical vertebrae (Figure 4). Fifteen days after irradiation, a small but highly active bone marrow territory was found in the 6th cervical vertebrae. It was estimated that 16% of bone marrow received less than 3 Gy. On this basis, it was chosen not to carry at a bone marrow transplant, and to sustain the patient
with platelet transfusions, antibiotic treatment to prevent opportunistic infections. In fact, the patient showed a complete haematological reconstitution in three months arising from these small bone marrow locations (Jammet, 1966). This is the concept of residual haematopoiesis.

This accident, but also numerous others, highlight the heterogeneity of accidental overexposure, even in high dose irradiated victims. Hence, in the recent accident of Tokai Mura, three victims were irradiated in a mixed field of gamma rays and neutrons, with a dose estimate of 7.4 GyEq in one of them. This patient received a stem cell transplantation on day 9 after irradiation. Despite a prophylactic treatment for GVHD and graft rejection, a transient engraftment was observed, followed by a progressive graft rejection and a full autologous recovery on day 51 after transplantation (60 days after irradiation)(Nagayama, 2002). Such a graft rejection may arise only if there is an active residual haematopoiesis, able to generate sufficient number of functional immune cells. In this specific case, the heterogeneity was due to the pattern of energy deposition by neutron in living tissues. However, such heterogeneity can also be observed with pure gamma rays. This was the case in the Algerian accident, in which an Iridium source was found and stored in a house. Dosimetric reconstruction showed a high degree of heterogeneity for people living in this house during the 38 day exposure (Mettler, 2001). These examples clearly show that even in the case of a high global irradiation dose, there is somewhat heterogeneity in the exposure, whatever the origin of this, implicating the existence of a residual haematopoiesis. This characteristic of almost all radiation overexposures is a crucial parameter that must be taken into account for the medical management of irradiated persons.

3- The radiation-induced multiple organ dysfunction syndrome (RiMODS)

Such heterogeneous irradiation induces a modification in the rather simple picture of pathophysiological consequences of accidental overexposure classically depicted. Moreover, in the past 15 years, numerous experimental evidence showed that modifications in physiological regulations and in intercellular communications appeared for doses lower than the dose range for which morphological modifications are observed. For instance, it was shown that the release of neurotensin, a neuropeptide implicated in the regulation of intestine is modified for irradiation doses as low as 2 Gy in animal models (Linard, 1997). As well, irradiation doses as low as 2 Gy modify the expression of adhesion molecules and cytokine production by endothelial cells (Gaugler, 1997, 1998), and in the central nervous system,
brain electrical activity disturbances were observed at doses of few Gy such as paroxystic discharges of spike and waves, burst of slow waves and slowing. Thus, the acute radiation syndrome appears as a mixed pathology, involving complex modifications of several physiological functions and for radiation doses lower than previously admitted, rather than the sum of individual syndromes that appear with morphological manifestations in an ordered fashion according to the radiation dose and the time after irradiation (Figure 5).

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Figure 5: Morphological and functional modifications after irradiation overexposure. The acute radiation syndrome appears as a mixed pathology, involving numerous functional modifications for doses as low as 1 Gy.

Thus, the overall picture of the acute radiation syndrome is rather a multiple organ disease involving simultaneously or successively disturbances of the haematopoietic system, the gastrointestinal system and the neurovascular system and complicated by the influence of other elements such as the inflammatory response of the organism to irradiation. Such a radiation-induced multiple organ disease (RiIMODS) was observed in two recent radiation accidents, the Nesvizh accident (Belarus, 1991) (AIEA, 1996, Baranov, 1994), and the Tokai Mura accident (Japan, 1999) (Nagayama, 2002, Hirama, 2003).

It is not appropriate to describe these two accidents in detail, that has been the subject of several publications (Baranov, 1994, AIEA, 1996, Hirama, 2002, Nagayama, 2003). A summary of the clinical course for the Tokai Mura victim that received the highest dose (i.e. 15 GyEq) is presented in figure 6. A common picture can be drawn from the clinical course of these accidents. According to the time after irradiation, two phases of the RiMODS can be distinguished. The first phase with a duration of few to several weeks (depending on the radiation dose and heterogeneity) correspond to the progressive development of the haematopoietic syndrome and the gastrointestinal disease. During this phase, severe clinical manifestations of all injured systems is observed, and ask for intensive care. This is the critical period for both the haematopoietic syndrome with a profound leucopenia and thrombocytopenia and the gastrointestinal disease with haemorrhagic diarrhoea and water stools. Thereafter, a second phase takes place, during which the initial treatment give evident results. Hence, the patient at that time generally survive to the haematopoietic syndrome and to the gastrointestinal disease. However, during this period, new complications developed, with the possible implication of lungs, kidney and skin, as well as the appearance of metabolic changes. According to the global irradiation dose, these metabolic and functional changes may lead to the death of the patient. Of course, this is a general picture which is strongly dependent on the global dose received, the level of heterogeneity, and other parameters specific for each accident. Nevertheless, a important feature that was particularly highlighted in the medical management of victims from Tokai
Mura is the possible role inter-organ communications in the development of RiMOD, especially during the late phase. Hence, radiation burns with associated rhabdomyolysis that were observed in the two highest irradiated victims were thought to play a role in the late kidney dysfunction. Furthermore, the radiation burns in several high dose irradiated patients after the Chernobyl accident were thought to have complicated the treatment of haematopoietic and gastrointestinal syndromes. Thus the treatment of high dose irradiated victims is clearly complicated by the interplay of the radiation damage to different organs.

4- Bio-indicators and evaluation of the radiation induced damage

As can be seen from the description of RiMOD, the initial evaluation of radiation damage appears as a key element for the choice of a therapeutic strategy. In fact, the knowledge of the global irradiation dose is important but not sufficient by itself. The main reason for that is the heterogeneity of accidental overexposure, but also the variability in the individual response to ionising radiation. Thus, there is a crucial need for biological indicators that are able to give information on the extent of damage and on the prognosis.

![Diagram of clinical course and biological indicators](image)

**Figure 6:** Summary of the clinical course of the Tokai Mura patient who received 15GyEq. Adapted from Futami, 2000.

**Figure 7:** The decrease of lymphocyte number during the first 48 hours after irradiation as a biological indicator of the severity of irradiation (adapted from Andrews, 1980).
The first useful biological indicator of radiation damage is the time of onset and severity of the initial syndrome, and particularly retching and vomiting. In fact, an emergency triage can be made on the basis of onset of these symptoms, especially in the case of a large number of victims (Young, 1987). Thereafter, the use of the slope of the decrease in circulating lymphocyte numbers during the first 48 hours after irradiation may help to refine the initial triage (Andrews, 1980). In fact, the rate of decrease in lymphocyte number was used after the Chernobyl accident (Silini 1991) and allowed the triage of a large number of victims in four categories of injury (Figure 7).

However, both of these two biological indicators are able to give information about the dose range received by the victim, but they are neither specific of a physiological function nor predictive of radiation induced damage. Thus a more general approach was developed (Fliedner, 2001), by using clinical signs of the initial syndrome in association with numerous biochemical parameters such as serum amylase, ASAT, ALAT, γGT, urea, creatinine, but also blood cell count and formula and numerous other parameters. None of these parameters of blood biochemistry is specific to radiation-induced damage (Donadieu-Claraz, 1999), with the noticeable exception of the increase of serum amylase, which is specific of a radiation damage to the parotid glands (Barrett, 1982, Junglee, 1986). Thus, serum amylase increase can be considered as a specific biological indicator of heterogeneity of irradiation. Nevertheless, this global approach of multiparametric analysis of biological indicators leads to a system in which each overexposed patient can be categorized according to four physiological functions, namely the haematopoietic system, the gastrointestinal system, the neurovascular system and the skin, with four levels of severity for each system (Fliedner, 2001). Of course, such multiparametric analysis must include information obtained from physical and biological dosimetry and accidental reconstitution.

More recently, two biological indicators specific for a physiological function have been evidenced, that may provide useful help in the estimation of radiation induced damage. These are the follow up of Flt3 ligand concentration in the blood for radiation-induced damage to the bone marrow (Bertho, 2001, Huchet, 2003) and the follow up of citrulline concentration in the blood as biological indicator of damage to the intestinal epithelium (Lutgens, 2003). Interestingly, it was shown that variations of Flt3 ligand in the blood of irradiated patients was proportional to both the radiation dose received and the percent of irradiated bone marrow (Huchet, 2003). Thus, such a biological indicator may be useful in order to define the extent of heterogeneity of radiation-induced damage to the bone marrow. With the exception of serum amylase, these two biological indicators are the first described that are specific for a physiological system of vital importance in the management of radiation induced victims. However, a multiparametric approach seems to be of fundamental importance in order to define as precisely as possible the extent of damage, in order to help to define a therapeutic strategy.

5- The treatment of radiation-induced multiple organ disease

It is out of the scope of this revue to give an overview of what is applicable for the treatment of radiation accident victims, mainly for two reasons. The first reason is the unique clinical course of each overexposed patient, due to the disparity in accident scenarios, and the second reason is the multiple ways that can be used to treat an overexposed victim. Thus, this revue will focus on few specific points.

5.1- The treatment of radiation-induced damage to the bone marrow.

Since the haematopoietic syndrome is the first life threatening syndrome to appear, a lot of attention has been directed towards it. When looking at past radiation accidents, essentially two kinds of therapeutic strategies was applied. The first one is the “wait and see” one, i.e. waiting for the autologous recovery from the residual haematopoiesis. This strategy was
successfully applied after the Mol accident (Parmentier 1966, Jammet, 1966). Such a strategy may be efficient in each situation where the overexposure is obviously heterogeneous. An evolution of this “wait and see” strategy is the use of cytokine treatment such as GM-CSF and G-CSF. GM-CSF was the first cytokine to be used in the treatment of radiation accident victims in 1987 after the Goiania accident. Thereafter, GM-CSF was used in several accidents, either alone or in combination with IL-3, as it was the case in the treatment of the Soreq victim (Israel, 1990)(IAEA, 1993). However, the use of these cytokines is limited for several reasons, including deleterious secondary effects. In fact, at the present time, most of cytokines are not available for use in humans, with some exceptions such as EPO and G-CSF. Moreover, several studies in animal models pointed out that the efficiency of cytokine treatment was greatly improved when cytokines are administered as soon as possible after irradiation (Mouthon, 1999, Herodin, 2003). Thus, the late recognition of the radiation nature of an accident may reduce the efficiency of cytokine therapy. Lastly, cytokine therapy might be efficient only in the case of an heterogeneous irradiation overexposure. Despite these limitations in the use of cytokine therapy, it is probably the safest therapy for the patient, especially when based upon the use of G-CSF.

The second strategy to be applied is the use of stem cell transplantation. It is interesting to note that the first bone marrow transplantation made in humans was done for the treatment of victims of the Vinca accident (Yugoslavia, 1958)(Mathé, 1964). Since that time, more than 30 stem cell transplantations have been carried out for radiation accident victims. However, the results suggest that stem cell transplantation might be used very carefully. Hence, in a retrospective study of transplanted patients, Densow and colleagues indicated that the overall survival of grafted victims was no better as compared to non grafted victims (Densow, 1997). This is due to several reasons. The first one is the difficulty to find a compatible donor in an emergency situation. Thus it become necessary to use immunosuppressive drugs which may favour the development of opportunistic infections despite prophylactic treatments with antibiotics. A second reason is the heterogeneity of accidental irradiation and the associated residual haematopoiesis, which might be sufficient to reject the graft. This was in fact the case in the Tokai Mura accident in which one of the engrafted patient finally rejected this and fully reconstituted in an autologous way (Nagayama, 2003). Moreover, the presence of damage to other organs and especially to the gastrointestinal tract and to the skin may limit the stem cell engraftment. Thus stem cell transplantation might be selected only for a limited number of patients for which a high irradiation dose with no or very low heterogeneity is suspected.

According to these remarks, two opposite strategies can be used. The first strategy was applied in the Tokai Mura accident, for the victim irradiated at a 7.4 GyEq dose. The idea is to make a transient stem cell transplantation, by the use of a “soft” conditioning regime (i.e. anti-lymphocyte serum) before the transplantation of cord blood cells, and a prophylactic treatment of graft rejection (i.e. cyclosporine A). The patient showed an engraftment of donor cells with 50% of circulating cells 9 days after transplantation, a neutrophil recovery on day 15 post transplantation, and a transfusion independency on day 27 after transplantation. However, the chimerism analysis showed a progressive reappearance of host cells in the blood, and a complete graft rejection on day 51 after transplantation. In this case, the stem cell transplantation was used as a mean to provide circulating cells to the patient, a kind of cellular therapy that reduces risks of haemorrhages and opportunistic infections.

The second strategy was highlighted recently in a French workshop (Jouet, 2003), and is an new evolution of the “wait an see” strategy. The main underlying concept is the existence of a residual haematopoiesis in virtually all radiation accidents, that might be responsible for autologous recovery. In order to favour such autologous recovery, the patient is placed in a protected environment, is provided with prophylactic treatment for opportunistic infections and haemorrhages, and is treated with cytokines, mainly G-CSF, as soon as possible, and for a 3 week period at least. Such a period may allow an endogeneous recovery, and if it is not the case, this 3 week delay might be sufficient to find a compatible donor for a stem cell
transplantation (Jouet, 2003). However, all these strategies must be adapted to each specific case, and may evolve with new therapeutic opportunities.

5.2- The treatment of radiation-induced damage to the gastrointestinal tract.

In the case of gastrointestinal injury in the accident situation several priorities exist and for which success to date is limited. The therapeutic strategies available for GI damage involve several approaches: [i] limitation of prodromal effects such as vomiting and reflex diarrhoea and involve the use of anti-emetics (5-HT3 receptor antagonists granisetron) and anti-diarrhoeal agents (spasmolytics, anti-cholinergics); [ii] stimulation of mucosal growth with enteral nutrition [glutamine] or growth factors (under investigation) and [iii] protection of the GI mucosa using anti-inflammatory agents [corticosteroids] to reduce intestinal inflammatory responses and ensuing lesions or reduction of acid secretion using H2 receptor antagonists. Indeed a review of treatments used at Chernobyl, Nesvizh and Tokai Mura indicates that for severe GI damage with substantial mucosal loss in addition to haemorrhaging treatment remains symptomatic with much the same pharmacopoeia (Moscow-Ulm Radiation Accident Clinical Data Base, Hirama, 2003).

The search for useful protective treatment in the domain of oncology and in the treatment of inflammatory bowel diseases however seems to be providing at least some promising approaches (Sandborn, 2002, Hauer-Jensen, 2003). The growth factor/cytokine approach involves several aspects (a) increase radiation resistance by using a cell cycle inhibitory factor, (b) stimulation of stem cell numbers to increase probability of stem cell survival, (c) treatment after exposure with a stimulatory factor to increase regeneration and (d) a combination of prophylactic inhibitory factor and therapeutic stimulatory factor. These approaches with regard to the GI system (contrary to the haematopoietic system are considered to be in "their infancy" particularly in the radiation accident situation. It should also be appreciated that some haematopoietic growth factors may have beneficial (G-CSF) or harmful (GM-CSF) effects on the GI tract.

With the loss of mucosal epithelial cells the intestine loses the capacity to synthesise and secrete naturally-occurring mitogenic and/or motogenic factors which would help to restore mucosal homeostasis. A number of growth factors have been shown to be effective in either protecting the GI tract against radiotherapy or in experimental situations where treatments are applied after exposure; these include growth hormone (GH), basic Fibroblast Growth Factor (bFGF), Keratinocyte Growth Factor (KGF), Epidermal Growth Factor (EGF) and Transforming Growth Factor-β (TGF-β). Interestingly the enteroendocrine and goblet cells of the GI tract also secrete mediators which are trophic for the intestinal mucosa such as gastrin, and glucagon like peptide-2 (GLP-2) and trefoil peptides respectively. However to date these have been little explored in relation to use after radiation exposure. Similarly molecules which are under investigation for the treatment of inflammatory bowel disease such as agents with anti-TNFα or NF-κB activity or cytokines with anti-inflammatory properties such as IL-10 and IL-11 may also be of use.

Treatment of GI damage consists not only of restoring the epithelium but also on the surrounding environment. Endothelial cells, given the intimate connections between tissue and blood, have a primordial role in tissue homeostasis, repair and damage. It has recently been shown that treatment with bFGF increases vascular integrity and so promoting intestinal recovery following high dose exposure (Paris, 2001).

Thus for successful treatment of GI injury a combination of protective and restorative are necessary. Several modalities appear promising in terms of growth factors and protective agents but in the case of accidental exposure use is limited to after the event. A major goal, similar to the use of blood transfusions, should be to gain time with the use of protective agents either anti-inflammatory molecules or reinforce the mediators produced normally by
this organ. This would allow stem cells that remain to multiply and so restore the epithelium. This has been shown for the haematopoietic system where viable territories are capable of restoring blood cells particularly in the case of the Tokai Mura accident as well as in Mol. It could be for the GI tract that the time required is too great. Intestinal transplantation for which there appears to be an increased amount of data could be a possibility but much would depend on the general health status of the patient.

6- The cutaneous syndrome

According to the characteristics of accidental overexposure, the cutaneous radiation syndrome is either a component of the mixed pathology of the RIMODS (as it was the case after the Tokai Mura accident) or is the unique manifestation of the localized radiation induced damage with a radiological source. The cutaneous syndrome is a dose-dependent, complex syndrome characterized by a succession of clinical signs such as erythema, swelling, dry desquamation, moist desquamation ulceration and in the most severe cases necrosis. The cutaneous syndrome has a major impact on morbidity/mortality if the radiation-induced damage extend to 40% or more of the body surface, or if deep structures (muscles, blood vessels, nerves and bones) are reached by highly penetrating ionizing radiation.

The main feature of the cutaneous radiation syndrome is a dynamic lesion which develops with time in an unpredictable way. The evolution of the lesion is a succession of inflammatory waves leading to the progressive extension of the lesion in three dimensions. After a prodromal phase of transient oedema and erythema and a latent period, the manifest phase develops with dry desquamation, blistering, bullae, ulcers and deep necrosis for radiation doses greater than 25 Gy. Pain is a major symptom of the cutaneous radiation syndrome, and is resistant to opiates. Pain occurrence is a sign of forthcoming inflammatory wave and extension of the lesions. If these acute and sub-acute phases of radiation syndromes are overcome with the treatment, a late phase can take place during several months or years, with fibrosis, atrophy, telangestasia and keratinosis, together with high risks of ulceration and necrosis.

The classical treatment of the cutaneous radiation syndrome includes the removing of devitalized tissues, the use of bacteriostatic agents coated onto non-adherent dressings, opiate-based drugs and non steroidal anti-inflammatory drugs. When ulceration and necrosis appear, the classical treatment is the conservative surgery for superficial lesions of extremities, with ulcerectomy or necrectomy and a wound closure by rotation flap. In the case of a large and deep necrosis, the therapeutic strategy is the same as compared to thermal burn treatment. Any radiological lesion of epidermis lasting for more than one month has to be engrafted in order to avoid secondary infection and to allow wound healing. Temporary xenografts or artificial skin can be used in order to check for the stability of the necrotic process. Final covering of the lesions with autologous skin graft obtained in a non- or less-irradiated area can be planed when the lack of evolution of the wound bed is obvious. However, unlike thermal burns, the outcome of the treatment in unpredictable, due to the possible outgrowth of necrosis after each exeresis and skin graft. In the most severe cases with a skin graft failure, an omentum flap covered by an epidermal autograft might be a solution for the control of evolution. These lesions can occur on the long term after irradiation, and the cicatrisation process is very long, fragile, and unpredictable. Moreover, the interplay of radiological burns with other radiation-induced syndromes may worsen the situation.

7- Conclusions

From an historical point of view, the accidental radiation-induced pathologies were considered as the addition of individual syndromes, i.e. the haematopoietic syndrome, the gastrointestinal disease and the neurovascular disease. Thus, the therapeutic action was focused on the haematopoietic syndrome, with antibiotic treatments and transfusions, since
the gastrointestinal syndrome and the neurovascular syndrome were considered as impossible to treat. Recent radiation accidents showed that today there are different ways to treat efficiently the haematopoietic syndrome. Moreover, progress in intensive care as well as in the evaluation of heterogeneity of irradiation allowed a increase in the survival of radiation overexposed people. Thus, the understanding of radiation induced physiopathology changed from the classical Acute Radiation Syndrome to the radiation induced multiple organ dysfunction syndrome. This RiMODS shows a mixed pathology of the haematopoietic, gastrointestinal, neurovascular and cutaneous systems, but also with the influence of damage to late responding organs such as the kidney, the lungs and the liver, and with the interplay of these pathologies. Overall, it is possible to make a victim of high dose radiation overexposure to survive several months. Nevertheless, in order to progress in the treatment of those victims, research efforts are needed, especially for the development of new models of radiation induced multiple organ dysfunction syndrome. Such models will help not only to better understand this complex pathology, but also to develop new therapeutic strategies.

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