Methods for Assessing the Extent of Acute Radiation Injury

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1. INTRODUCTION

Previous radiation accidents have shown that the medical management of exposed persons cannot be performed without the use of "biological indicators" of effect and of repair. For the clinical management of a patient with the acute radiation syndrome, it is essential to obtain information on the subjective symptomatology as well as on laboratory parameters, especially during the first 3 to 6 days after exposure. The medical doctor responsible for the clinical care of patients has to rely on the use of what has been described as "sequential diagnosis" (1). This approach consists essentially of the determination of a limited number of parameters as a function of time. From the analysis of the pattern of the determined and evaluated signs and symptoms in the first hours and days, one is able to characterize patients according to type and severity of symptomatology. This has been clearly demonstrated in the Moscow - Ulm Radiation Accident Database (MURAD) developed in a collaborative project between the Institute of Biophysics in Moscow and the Department of Clinical Physiology and Occupational Medicine of the University of Ulm (2). On the basis of the radiation accident clinical response pattern observed early after irradiation, one is able to develop a first approach for therapeutic strategies.

It is the purpose of this contribution to outline the diagnostic and prognostic significance of blood cell changes and to discuss the following problem areas:

1. Significance and elements of a sequential diagnosis
2. Significance of blood lymphocytes for radiation accident diagnosis
3. Significance of blood granulocyte changes for the prognosis of the acute radiation syndrome

4. Analysis of granulocyte changes by means of feedback regulated system models
5. Utilization of indicators of response and repair for planning therapeutic options

2. SIGNIFICANCE AND ELEMENTS OF THE "SEQUENTIAL DIAGNOSIS"

For the medical doctor, who is called to attend a radiation accident patient, it is important and decisive to come as soon as possible to a clinical evaluation of the situation of the patient on the basis of symptoms and laboratory findings. The following questions require an immediate answer: 1. Has a radiation exposure occurred in a patient or are the symptoms characteristic for alternative causes (for instance skin burns, chemical poisenings, physical injuries)? 2. If there is a high probability for the radiation aetiology of the clinical symptomatology, what is the extent of the radiation injury: Does one have to assume the consequences of an injury to the central nervous system, to the gastrointestinal system or to the hemopoietic system?

The answer to these questions can be derived only to a limited extent through the evaluation of the radiation exposure history. More important are the diagnostically relevant laboratory findings, which show and indicate the extent of strain to the human organism. The reason for this basic consideration is very simple: (table 1) In the case of accidental whole body irradiation exposure it is almost impossible to obtain a sufficiently precise evaluation about a "radiation dose". This is not necessarily due to the missing or insufficient dosimetry. Rather this impossibility to determine quickly the exact dose to the organism is due to the fact that the radiation exposure of the human being is usually not uniform and hence not all parts of the body receive the same radiation dose.

The evaluation of radiation accidents from all over the world (2) indicate that a homogeneous total body exposure usually does not occur in the real world. Rather radiation accidents result as a rule in an inhomogeneous radiation exposure. The pathophysiology of the radiation damage indicates that any inhomogeneity of the exposure of the human being works in favour of the regeneratory potential of the organism. In the clinical setting an estimated radiation dose does not contribute significantly to the consideration of the therapeutic approaches to be taken.

A "sequential diagnosis" supports the attempt to obtain information about the extent of the injury to the critical organ systems within the first hours and days after an acute radiation exposure in order to derive from this assessment conclusions for the therapeutic management. It is not the purpose of a sequential diagnosis to calculate an "exposure dose". The determination of an exposure dose is usually only possible with the help of radiation accident reconstructions. Such dose measurements and estimates may take months or even years or are debatable for many decades as seen in Hiroshima and Nagasaki.

The relationship between the assessment of stress and strain in the case of radiation accident medical management is symbolized in table 1.

The organ system that is most important for executing a meaningful sequential diagnosis in the case of an acute radiation exposure, is the blood cell formation. A second organ system that is of great importance for assessing the consequences of radiation exposure is the skin. In case of skin injury (for instance thermal or radioactive exposure of Chernobyl patients) it is essential to not only assess the effects on the blood cell forming tissue, but also the extent of damage to the skin. In these cases the diagnosis and treatment of skin injuries must take preference and requires classical approaches in order to assure the immediate survival of the patient.

As far as the assessment of injury to the blood cell forming tissues is concerned, one has to find as soon as possible an answer to the following question: Has the stem cell pool of blood cell formation been injured "irreversibly" or "reversibly"? If the damage to the stem cell pool would be diagnosed as being "irreversible", then in principle a stem cell transplantation, be it autologous or allogeneic, needs to be considered. If the damage is most likely "reversible", then one would have to answer the question in what way therapeutic measures are capable to bridge the expected transitory hemopoietic failure and/or to use possibilities to shorten such a period of hemopoietic failure. In parallel to the evaluation of the blood cell forming tissues, one would naturally have to consider other important organ systems, such as the gastrointestinal system, the metabolic organs, but also the lung, the cardiovascular system and the central nervous system. Based on the results of the hematological "pacemaker"-evaluation, it is quite possible and the rule that other special diagnostic and therapeutic measures are indicated.

3. THE SIGNIFICANCE OF BLOOD LYMPHOCYTES IN A "SEQUENTIAL DIAGNOSIS"

If one is analyzing blood lymphocytes as a function of time after an acute radiation exposure, one can after exposure give an answer to the question "Has a radiation exposure occurred and what clinical symptomatology might be expected?" within a few hours. In figure 1 a-d the lymphocyte curves of 52 persons that were exposed in radiation accidents can be seen. One fact is common to all curves: Within less than 10 days a new level of lymphocyte concentration is reached that does not change drastically in the next days or weeks. In other words, the regeneration is slow. If one correlates the lymphocyte patterns with the severity of the clinical courses observed, one can show that the clinical courses of the patients can be correlated with a particular lymphocyte pattern.

In the case of a "very severe" clinical course one can show that there is a decrease of blood lymphocytes within 2 to 4 days to concentrations of less than 200/mm^3 blood (group d). In the case of "severe" forms of the acute radiation syndrome, the lymphocytes fall within 4 days to values between 200 and 800/mm^3 blood (group c). In the case of "moderate" effects (group b) the lymphocytes decrease to concentrations between 800 and 1.100/mm^3 blood. If there is a minimal injury, then the lymphocyte changes are very unspecific, but as a rule do not decrease below 1000/mm^3 blood (group a). Therefore, it is possible to derive from this assessment that lymphocyte changes in the blood beyond 10 days after the radiation accident are of low diagnostic value and cannot necessarily predict whether a spontaneous recovery can be expected or not. The regeneration of the lymphocyte system can be shown in all radiation accident cases to take many weeks or even months.

However, a primary diagnostic answer is possible within hours after accidental radiation exposure. One can say with high probability whether a clinically significant radiation exposure has occurred or whether one is dealing most likely with a moderately severe course of the acute radiation syndrome. In figure 2 one can see the lymphocyte course in patients that were exposed in major radiation accidents. In the case of the radiation exposure of Marshall Island victims (1954) the slow lymphocyte decrease in the first 3 days indicates a light or moderate degree of radiation effects on the victims. In case of the accident in Los Alamos (1946) one can see that the lymphocyte concentration

decreases within 1 day to less than 10 % of normal. In this case, the patient died within a few days from severe hemopoietic failure. The Oak Ridge patients and the Chernobyl patients shown in the graph had a moderate decrease within the first 3 days to about 30 % of normal. In these cases a spontaneous hemopoietic recovery occurred.

In conclusion it is suggested that the lymphocyte changes in the blood as a function of time after accidental whole body radiation exposure allow one to predict with high probability whether there is a causal relationship between the clinical symptomatology and the radiation exposure and whether a very severe or a more moderate course of the radiation syndrome can be expected.

The reason for the fact that one cannot draw clinically significant prognostic conclusions from the initial lymphocyte decline, is seen in the fact that an initial decrease of the lymphocyte count may also be observed after an inhomogeneous or large volume partial body irradiation. Under these circumstance a spontaneous recovery of the hemopoietic system is quite possible, regardless of the fact that a severe damage of several organ systems has to be assumed. From the viewpoint of pathophysiology the lymphocyte pattern is not only determined by the radiation sensitivity of these cells, but also by the sensitivity of the lymphocyte recirculation from blood via the lymph to the lymph nodes and back to the blood.

4. THE SIGFICANCE OF BLOOD GRANULOCYTES IN THE "SEQUENTIAL DIAGNOSIS"

The changes of granulocyte concentration in the peripheral blood as a function of time after a single acute radiation exposure have found to be an important, if not decisive indicator for the performance of a sequential diagnosis. The granulocyte changes can be considered as the key indicator for determining the prognosis of a patient and for the therapeutic planning. It should be mentioned at this point that the assessment of changes of platelets, of erythrocytes or reticulocytes result in a very similar evaluation in comparision to granulocyte changes. However, granulocyte changes can be determined more quickly and precisely even with automated equipment and are therefore the preferred indicators.

For the sequential diagnosis the granulocyte concentrations in the first 6 days after radiation exposure are of particular importance. If one finds an initial granulocytosis with values well above 10.000 mm^3 in the first 2 days and especially, if one finds beween the 4th and the 6th day after exposure, a progressive decrease of cell numbers to values below 200 mm^3 blood one can take this pattern as an indicator for the most severe form of the acute radiation syndrome resulting in an essentially "irreversible damage" to the stem cell system of hemopoiesis, which is distributed in the skeletal system of the organsim (see fig. 3).

If, however, one finds in the first 6 days after radiation exposure an initial moderate granulocytosis (values most likely between 5.000 and 15.000 mm^3 blood) and if one finds beyond the 4th day a moderate decrease of granulocytes to values between 200 and 1.000/mm^3 blood (which can be clearly depicted, if one is performing a graphic demonstration of granulocyte values), one can predict significant damage to the hemopoietic system. However, such a pattern is compatible with a reversible damage to the hemopoietic stem cell system. In this case, one would aim for a therapy of "bridging the hemopoietic failure" or "stimulating" hemopoiesis for a more enhanced regeneration. The analysis of radiation accident case reports, which are collected in the Moscow - Ulm Radiation Accident Database (MURAD), indicates that there are very clearcut granulocyte patterns to be associated with the notion of a "reversible damage" of the stem cell pool (2) (see fig. 4).

In these cases of a severe form of the acute radiation syndrome with however reversible blood formation damage (fig. 4) one can recognize a granulocyte pattern which is characterized by an initial granulocytosis, a moderate, but not critical granulocyte decrease towards the 10th day, a transitory increase or a "inbetween plateau" until the 20th to the 25th day and by a final regeneration beyond the 30th day after exposure. In the patients with an even lighter form of the acute radiation syndrome the pattern of decrease, the abortive regeneration, the inbetween plateau and the regeneration beyond the 30th day is very characteristic. This course is compatible with a significant, but nevertheless benign course of the acute radiation syndrome. The patients with a light form of the acute radiation syndrome show such a pattern only in a mild form. A statistically significant difference between the groups can most likely be obtained, if one evaluates the blood counts about 30 days after exposure.

A chromosomal analysis in such patients is of importance not necessarily to calculate a "dose", but to document conclusively that irradiation exposure has occurred and not alternative causes of injury. Therefore, under any circumstances, a chromosomal analysis should be attempted even for forensic reasons.

In conclusion one can state that lymphocyte changes after total body radiation exposure can be considered as an important "retrospective indicator" (Does one have to assume a significant radiation exposure or not?"), but that granulocyte changes (and in parallel the changes of platelets and reticulocytes) need to be considered as a "prospective indicator" of effect and repair. This is most important for the planning execution and continuous evaluation of the therapy. The pathophysiological justification for this conclusion is given in other publications.

5. QUANTIFICATION OF GRANULOCYTE COURSES WITH THE HELP OF FEEDBACK REGULATED SYSTEM MODELS

The question was whether it is possible to simulate the granulocyte changes after total body exposure with the help of a biomathematical systems model. Such a quantification and characterization was considered to be decisive in order to determine the number of "virtual" stem cells in the bone marrow necessary to produce a sufficient number of granulocytes to keep their level in the blood constant. Such a quantification of the stem cell number would be essential to predict whether a autochthonous regeneration of the stem cell pool and thus, of the entire hemopoietic system can be expected or not. In other words, if it is possible to assess the damage to the hemopoietic system is reversible or irreversible.

The basic model of granulocytopoiesis was developed in several steps due to an intensive collaboration between the Department of Clinical Physiology and the Department of Measurement Regulation and Microtechniques of the University of Ulm (3). The model (fig. 5) that is presently used consists of 7 cell and 2 regulatory compartments and is based on the assumption, supported by experimental evidence, that in a homeostatic equilibrium between cell production and cell removal, which exist in hemopoiesis, each granulocyte that is moving out of the blood by ageing or immigration is replaced by a granulocyte from the bone marrow (compartment F). For each granulocyte

delivered to the blood stream one has to assume a netto increase of one cell by cell division (compartments S, CBM, P). One knows the life span of the granulocytic precursor cells and the frequency of cell division and one has evidence for a humoral regulation of the entire system. The present system considers 2 regulatory compartments REG I und REG II. All in all it is the question whether the stem cell compartment is capable to replace the cell loss in the blood by cell production in the proliferative compartments. In order to model such a system, 37 differential equations were necessary. The details of this biomathematical compartment model were published elsewhere (3). The pattern of granulocyte changes in the different categories of the course of the acute radiation syndrome can be simulated, if one assumes that there is not only a destruction of stem cells in the system by radiation exposure, but that some of the stem cells are injured, but apparently capable of repair. It has been shown previously that radiation response data of the hemopoietic system can only be explained, if one assumes that the radiation exposure results in stem cells that are completely repaired and hence are able of an unlimited replication and differentiation and other stem cells in which the replicative capability is limited and hence the clon may die out. These assumptions were published and discussed elsewhere (4). With the help of such a biomathematical simulation model it is now possible to assess the damage of radiation to the stem cell pool on the basis of granulocyte changes. Each granulocyte pattern can be correlated to a virtual stem cell number. Important is the number of uncommitted virtual stem cells (S) that are capable to initiate a final granulocyte recovery beyond 25 to 30 days.

In fig. 3 the radiation accident granulocyte response patterns are simulated in which the granulocyte values decrease within 5 to 6 days to minimal values (below 300 per mm^3 blood). This pattern, as indicated before, is correlated with an irreversibility of the damage to the stem cell pool.

If one takes a look at the course of the Sor-Van accident and finds that the granulocyte regeneration was found beyond the 14th day, one can underline the thesis: in this particular case there was a bone marrow cell transfusion on day 5, which led within 10 days to the signs of a "take". In the accident case Moscow 1991 one did not want to use a bone marrow transplantation. This patient died 3 months after the accidental exposure inspite of intensive cytokine therapy and without a sign of a permanent regeneration.

In fig. 4 four curves are demonstrated which are typical for severe, but nevertheless reversible courses of the radiation accident syndrome.

In table 2 the numbers of virtual stem cells that were calculated on the basis of the model are demonstrated. One can see that the values for intact stem cells should be above 6/10.000, in order to be able to predict a reversible course of the acute radiation syndrome. Values below 6/10.000 are compatible with an irreversible damage of the stem cell system. This evaluation can be made within a very few days (maximally 5 to 6 days after radiation exposure) and forms a rational basis for further diagnostic and therapeutic measures. It goes without saying that, in addition, one has to consider the status of other organ systems, such as CNS, heart, circulation, renal system, skin and so on. It is of course necessary to perform more research in order to develop this model and models for other cell systems even further in order to be able to improve clinical decision making in radiation accidents.

It should be mentioned that an examination of the bone marrow by particle smears and by histological section can greatly assist in the evaluation of the radiation exposed patient. The bone marrow smear will show within 12 to 24 hours the effects of the radiation exposure on marrow cells. This requires, however, bone marrow particle smears and this should be done by an experienced hematologist. He would distinguish between cell pyknosis and cell edema from cells with mitotically connected abnomalities (.....). One would also expect that within this time one would find an excessive increase of apoptotic cells.

Most recently, further studies in our group have shown that the granulocyte regeneration simulation can also be used in stem cell transplanted patients. Under these circumstances one can find that granulocyte regeneration patterns are directly proportional to the number of $CD34^+$ cells transfused. Thus, one has now a way to correlate the biomathematically calculated "virtual stem cells" with the number of remaining intact stem cells as determined by biological means ($CD34^+$ cells essential to be in a transfusate to induce hemopoietic regeneration).

6. CONSEQUENCES FOR THE PLANNING OF THERAPY

It is not the purpose of this presentation to discuss extensively the present therapeutic concepts for the treatment of the acute radiation syndrome. However, it is important to point out the following facts: If the diagnosis is that of an "irreversible damage" to the stem cell system based on the analysis and the calculation of the granulocyte course, it is highly recommended to treat such patients with stem cell transplantation. This should be done as soon as possible. Of large significance would be an autologous stem cell transplantation. However, this is of course only possible, if one would take blood stem cells by means of continuous cell centrifugation before radiation exposure. This leads to the question whether it might be advisable to convince "persons at particular risk" to set up a "stem cell bank" of their own stem cells. Such a approach might be used in persons who may have an increased risk of accidental exposure due to clean-up or rescue operations.

However, as a rule, one has to find appropriate stem cell donors essentially similar to the approach that is being used in the oncological services for the therapy of leukaemic patients or of patients with other systemic neoplasias. Related donors are preferred to non-related donors. In general, the treatment of such an "irreversible damage" to hemopoiesis is identical to the treatment used in cases of severe aplastic anemia.

If the initial diagnosis with the help of the analysis of the granulocyte pattern as an indicator shows that hemopoiesis was damaged, but that a spontaneous regeneration might occur ("reversible damage"), one has to discuss in what way one can bridge the transitory pancytopenia and shorten it.

Such a bridging therapy aims at the prophylaxis and therapy of granulocytopenia as a course of infection. This results in the recommendation of the treatment of such a person in the isolationbed-system under germfree conditions (gnotobiotic therapy) and to the treatment of these patients after careful evaluation of the sensitivity of the microorganisms to the therapy with antibiotics, antimycotics and virostatic substances. Most recently one is trying to shorten the phase of transitory pancytopenia. This can be done by the application of hemopoietic stimulation factors, for instance IL-3. It can be shown that these factors are capable of shortening the duration of pancytopenia in cases of pancytopenic conditions. This therapeutic form is only

effective, if the stem cell pool contains a sufficient number of intact hemopoietic stem cells that have survived the radiation exposure. Only, if there is such a sufficient number, then this pool can react to such recombinant factors. One has, however, also to consider the problem of stem cell competition.

If one considers the platelet course, then the therapeutic approaches have to result in a platelet concentration above 15.000 - 20.000/mm^3 blood. This can be achieved by platelet transfusion, with histocompatible platelets. Such a thrombocyte transfusion therapy has to be continued until the spontaneous regeneration of hemopoiesis has occurred. At the present time many studies are on their way to try to shorten the period of thrombocytopenia by the application of recombinant stimulatory factors. One can show that the factor IL-3 alone or in combination with IL-6 may play a very good role.

7. CONCLUSIONS AND SUMMARY

The questions posed at the beginning of this contribution can be answered - in summary - as follows:

1. Using the approach of "sequential diagnosis", it is feasible to assess the damage to the organism, its organs and functional systems after accidental whole body radiation exposure within a very few days (4-6 days at the most) to such an extent that a prognosis is possible as a basis of planning the therapeutic options. A "sequential diagnosis" is based on the determination of a few biological indicators of effect and repair as a function of time (for instance every 6 hours for 6 days) and their evaluation on the basis of the pathophysiology of the acute radiation syndrome.

2. The canges observed in the concentration of lymphocytes in the peripheral blood can be used only as a "retrospective" indicator of effect: If there is a decrease of lymphocytes below 50 % of normal within 24 hours after exposure, one has to assume the development of a severe course of the acute radiation syndrome. However, one cannot predict whether a spontaneous hemopoietic recovery can be expected or not.

3. In contrast, the pattern of granulocyte concentration changes in the blood stream can be considered to be the most important "prospective" indicator of effect and repair. Within 4 - 6 days after an exposure, the pattern of

granulocyte changes and the extent of decrease between days 4 and 6 allows one to predict whether the blood cell forming bone marrow has been damaged to an essentially "irreversible" extent or whether the clinical course is most likely a "reversible" one. The therapeutic measures to be taken are quite different based on such an assessment.

4. Using a biomathematical simulation model of granulocytopoiesis it has been possible to determine the number of "virtual" stem cells that have remained after radiation exposure in the hematopoietic tissue and that can be associated with a particular granulocyte response pattern. Due to the collection of clinical case histories of radiation accident patients in the Moscow-Ulm Radiation Accident Database (MURAD) it was possible to determine the number of "virtual" stem cells that are essential to allow an autochthonous hemopoietic recovery. This number can be used as an important prognostic indicator.

5. If the number of remaining intact "virtual" stem cells is below ... % of normal, the hematopoietic damage is essentially irreversible. Under these circumstances a stem cell transplantation has to be performed using the same approach as in the treatment of severe aplastic anemia. If the number of remaining intact "virtual" stem cells is well above 95 % of normal, one can assure that appropriate cytokines can act and shorten significantly the autochthonous hemopoietic recovery. Even under these circumstances, a gnotobiotic therapy in a germfree setting and systemic antibiotics and platelet transfusions may be essential.

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Table 1

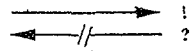
Stress	Strain
(as a consequence of ionizing radiation)	
Exposure	Biological consequences (CNS, organ systems)
(external, internal)	influencing variables
Type	Genetic factors
Quality	Age
Duration	Previous health impairments
Rate	Sex (?)
Etc. (to be determined by physical and chemical indicators)	Etc. (to be determined by physical examination and tests to evaluate extent of reparable and irreparable damage)
	!
	?

Table 2

	Remaining Intact Stem Cells % (Cell Number)	Remaining Injured Stem Cells % (Cell Number)	Destroyed Stem Cells % (Cell Number)
Patient ID: 4	0,06 ($7,5 \cdot 10^5$)	5,6 ($7,0 \cdot 10^{10}$)	94,34
Patient ID: 5	0,26 ($3,25 \cdot 10^6$)	8,0 ($1,0 \cdot 10^8$)	91,74
Patient ID: 1	0,0004 ($5,0 \cdot 10^3$)	5,28 ($6,6 \cdot 10^7$)	94,72
Patient ID: 3	0,0006 ($7,5 \cdot 10^3$)	9,12 ($1,14 \cdot 10^8$)	90,88
Brescia Case	0,0 (0)	0,0 (0)	100,0
Norway Case	0,0 (0)	0,0 (0)	100,0
Sor-Van Case	0,0 (0)	0,0 (0)	100,0
Moscow Case	0,0 (0)	0,001 ($1,25 \cdot 10^4$)	99,999

Figure 1

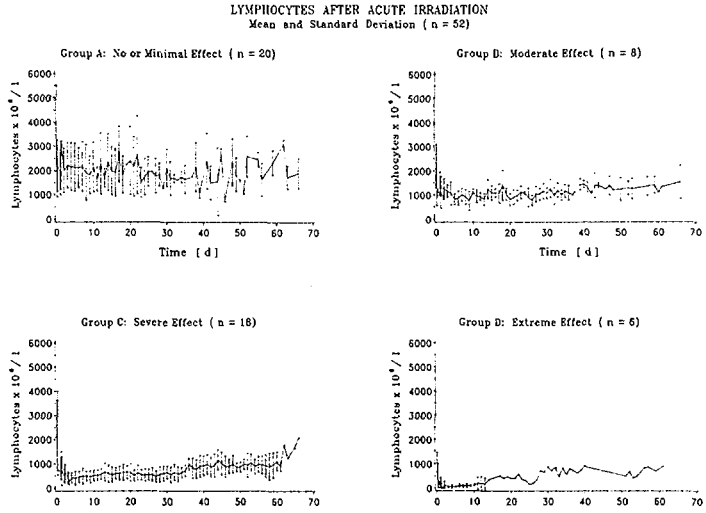

LYMPHOCYTES AFTER ACUTE IRRADIATION
Mean and Standard Deviation (n = 52)
Group A: No or Minimal Effect (n = 20)
Group B: Moderate Effect (n = 8)
Group C: Severe Effect (n = 18)
Group D: Extreme Effect (n = 6)
Lymphocytes x 10⁶ / l
Time [d]
0
1000
2000
3000
4000
5000
6000
0
10
20
30
40
50
60
70

Figure 2

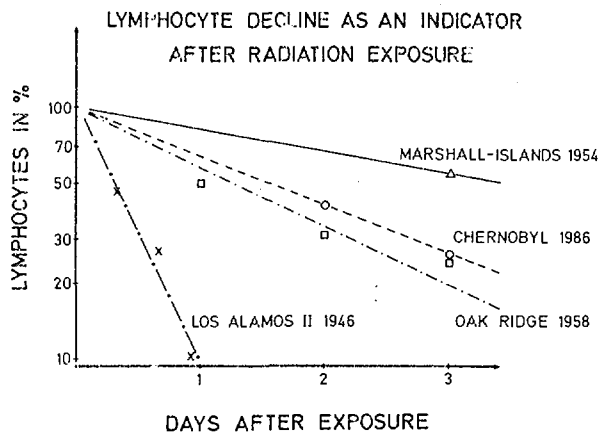

LYMPHOCYTE DECLINE AS AN INDICATOR
AFTER RADIATION EXPOSURE
LYMPHOCYTES IN %
100
70
50
30
20
10
MARSHALL-ISLANDS 1954
CHERNOBYL 1986
LOS ALAMOS II 1946
OAK RIDGE 1958
1
2
3
DAYS AFTER EXPOSURE

Figure 3

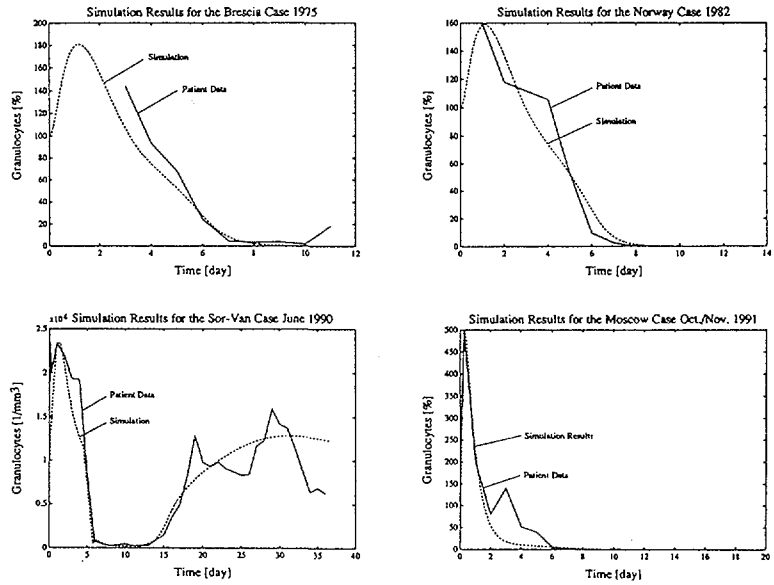

Simulation Results for the Brescia Case 1975
Granulocytes [%]
Time [day]
Simulation
Patient Data
Simulation Results for the Norway Case 1982
Granulocytes [%]
Time [day]
Patient Data
Simulation
x10^4 Simulation Results for the Sor-Van Case June 1990
Granulocytes [1/mm3]
Time [day]
Patient Data
Simulation
Simulation Results for the Moscow Case Oct./Nov. 1991
Granulocytes [%]
Time [day]
Simulation Results
Patient Data

Figure 4

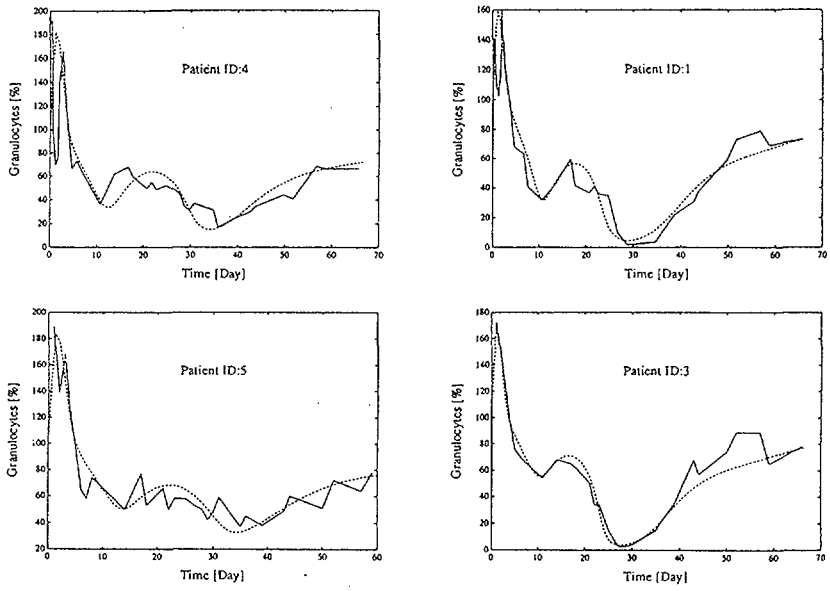
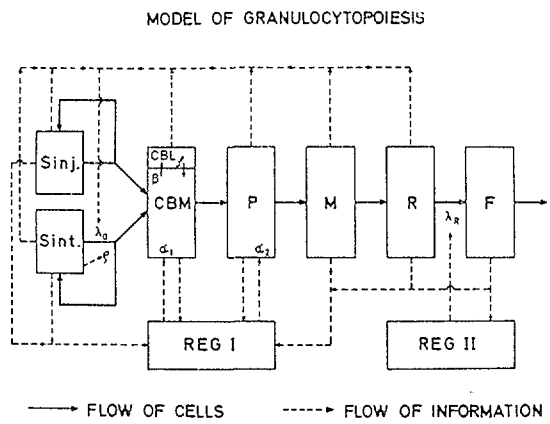

Patient ID:4
Granulocytes [%]
Time [Day]
Patient ID:1
Granulocytes [%]
Time [Day]
Patient ID:5
Granulocytes [%]
Time [Day]
Patient ID:3
Granulocytes [%]
Time [Day]

Figure 5


MODEL OF GRANULOCYTOPOIESIS
Sinj.
Sint.
CBL
CBM
P
M
R
F
REG I
REG II
FLOW OF CELLS
FLOW OF INFORMATION