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STUDY OF SIX CASES OF ACCIDENTAL ACUTE WHOLE-BODY IRRADIATION

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INTRODUCTION

Cases of acute whole-body accidental irradiation are rare. We report here the results from the study of six recent cases. Actually this merits a monograph, and one will be published in the months to come. We have felt, however, that a preliminary article on the dosimetric, clinical and therapeutic aspects would be of interest, inasmuch as bone marrow transfusions were administered. In addition, an article follows this one in which is described the transfusion technique and where are presented the arguments favoring an effective 'take' of the bone marrow graft.

On October 15, 1958 at the Vinca, Yugoslavia, center of nuclear studies, six persons were irradiated by neutrons and gamma rays from a nuclear reaction. Everything indicated that the doses received approached or surpassed those normally regarded as lethal. On the following day the patients were sent to Paris and hospitalized on the radiopathology service of the Curie Foundation. The exact evaluation of the radiation doses received presented difficult problems. It proved necessary to correlate the clinical course with the physical findings in order to determine the course of therapy. This depended on the radiation doses received. Furthermore, the patients appeared to be in different dose ranges, one with a sub-lethal dose, four with doses in the lethal range, and the last with a supra-lethal dose. This

distribution provided an exceptional opportunity for a theoretical study. We were guided solely by the medical requirements which frequently were far removed from the rigid considerations of biologic experimentation. The patient with the lowest dose received nothing but standard treatment, the other five received transfusions of hematopoietic cells. Four of these cases actually survived in satisfactory condition. The most highly irradiated man died of gastro-intestinal complications on the 32nd day after irradiation, although the bone marrow transplant indicated his hematologic recovery. These cases are reported here as studies showing successively the dosimetry, the clinical course and the therapy.

DOSIMETRIC STUDY

Circumstances of the Accident

The accident was caused by an experimental nuclear reactor which must have been operating at practically zero power. It consisted of rods of natural uranium immersed in a moderator of heavy water in a cylindrical metal tank 2 meters in diameter and 2.3 meters high. A reflector was not required, and because of its utilization at a sub-critical level, it did not have a protective shield. Its operation was regulated by changing the level of heavy water. Cadmium safety rods were used to stop the reaction. It is possible to introduce an additional neutron source, (radium-beryllium) (Fig. 1a^{*}).

The reactor rests on a metal support 4 meters high situated in the center of a room of about 100 sq. meters (about 3,000 sq. ft.). Six persons, (V, M, G, D, H, B) were in the room in the positions shown in Fig. 1b. Two of them (G, D) were at the control console situated 4

*Fig. 1a, a photograph of the reactor, is not reproduced in this translation.

meters from the reactor, and the other four (V, M, H, B) were grouped around the electronic equipment located in one corner of the room about a similar distance away. The experiment in progress consisted of carrying out measurements of the neutron flux due to spontaneous fission before and after the addition of the RaBe source.

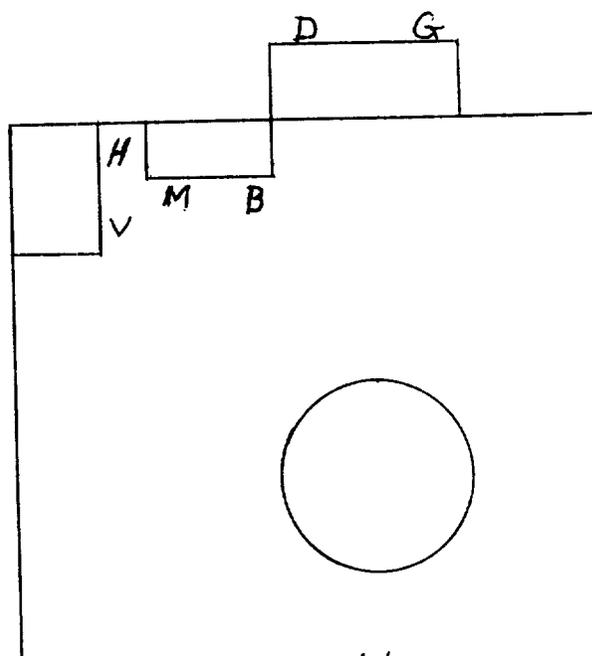


Fig. 1b.

The accident was the result of the combination of several factors including elevation of the level of heavy water, and the introduction of the RaBe source. In this situation the reaction is no longer controlled and there resulted the exposure by neutrons and gamma rays. This radiation originated partly from the nuclear fission, partly from the formation of short-half-life fission products in the interior of the reactor, and partly from the activation of materials located within the room. Dropping the safety rods stopped the reaction after several minutes, 3 to 7, thus stopping the neutron emission, but the gamma ray

irradiation continued with a decay characteristic of the radioelements formed.

Evaluation of Radiation Doses Received (Ref. 4, 6, 11)

The physical measurements made at the scene permitted an estimation of the order of magnitude of the exposure. The total flux of thermal neutrons determined from the induced activity in a number of metallic objects was found to be of the order of 2×10^{11} n/cm². The percentage of fast neutrons with a mean energy of 2.2 MEV in relation to the thermal neutrons is between 6 and 8%. The ratio of gamma rays with a mean energy of 3 to 4 MEV to thermal neutrons lies between 2 and 4 and has been set at 3. Extrapolated back to the time of exposure, the gamma ray dose was estimated to be between 450 and 1,000 r at the position of the six people exposed. The personnel dosimeters, film badges and pocket chambers, being completely saturated, failed to give any information as to the order of magnitude of the exposure.

On their arrival in Paris the six irradiated people were counted for the radioactivity induced in their bodies by the neutrons. The instrument used was a 25-channel gamma ray spectrometer, permitting in particular the measurement of Na²⁴ formed in the body. The individual values obtained by comparison with a tissue-equivalent phantom are given in μ C in the first column of Table I. From these results one may calculate the doses received, taking into consideration the weight of each person. The neutron doses expressed in rem are given in the second column of Table I. By adopting a factor of 3 for the gamma-thermal neutron ratio, the doses received from the gamma exposure are given in column 3 of Table I. The next column gives for each person exposed the total dose in rem, the sum of the preceding doses from both neutrons and gamma rays.

This method of evaluating the dose received is too uncertain and does not take everything into account: the gamma exposure lasted

longer than the neutron exposure, the neutron radiation was relatively homogeneous while, because of the multiplicity of sources of emission, the gamma exposure was heterogeneous throughout the room.

TABLE I

	1	2	3	4	5	6
	Na ²⁴ (μ C)	Dose n (rem)	Estimated gamma Dose (rem)	Total Dose calcu- lated from (2)&(3) (rem)	Extreme limits of gamma exposure (rem)	Total Dose (rem)
V	82	210	630	840	450-1000	1000-1200
M	75	214	642	856	450-1000	700-1000
G	76	230	690	920	450-1000	700-1000
D	63	256	768	1024	450-1000	700-1000
H	53	174	522	696	450-1000	600- 800
B	45	102	306	408	250- 500	300- 500

In addition, certain of the persons moved around during the course of the exposure: M, G, D and H stayed more or less in one place, while V approached close to the reactor after the shut-down, receiving additional exposure; B left the room for three minutes during the accident, during which time his rate of exposure was reduced by about a half. Column 5 of Table I gives the extreme limits of the

gamma exposure. The last column, 6, indicates the most probable range of the total dose in rem.

It turns out that the six persons can be placed in three groups. The first of these, V, received a very high dose of the order of 1,000 rem. Four others (M, G, D, H) received between 600 and 1,000 rem. The last, B, did not receive more than about 400 rem.

The lack of precision in the dosimetry made therapeutic decisions difficult and delicate. On the other hand, the clinical changes fully confirmed the classification of the six patients in order of decreasing exposure. Lastly, the conclusions reached as a result of study of the autopsy specimens were fully compatible with an exposure of between 700 and 1200 rem.

CLINICAL STUDY

General Symptomatology

The general symptomatology of the six persons receiving the whole-body irradiation developed along the lines of what is known of the acute radiation syndrome (1, 3, 4, 12). After an initial phase of radiologic shock, a latent period lasting two to three weeks developed. This was followed by a prolonged critical phase during the fourth, fifth and sixth weeks. Improvement was then noticed, although it was interrupted constantly with disturbing complications.

After the first hour following the accident and during the course of the first day, the exposed persons showed the alarming signs of the acute radiation syndrome: asthenia, weakness, psychic depression, anorexia, nausea, vomiting, paresthesias of the upper extremities, sweating. B, the man with the lowest exposure, did not vomit, while the most heavily exposed, V, was afflicted in addition with diarrhoea (Table II).

In the course of the three-week latent period the patients' relatively good general conditions contrasted with the development of the hematologic changes and those related to the skin and viscera. The most heavily exposed, V, always showed a profound disturbance in

TABLE II

	Fatigue	Nausea	Vomiting	Diarrhoea	Perspiration	Confusion
V	+++ 1st da	+++ 1st da	+++ 1st da	+ 4 da	+++	+++ 24-32 da
M	+++ 1st da	+++ 1st da	+++ 1st da	0	++	++ 24-30 da
G	+++ 1st da	++ 1st da	++ 1st da	0	+++	± 30-35 da
D	++ 1st da	++ 1st da	++ 1st da	0	++	± 30-35 da
H	++ 1st da	++ 1st da	++ 1st da	0	+++	+ 32-38 da
B	+ 1st da	+ 1st da	0	0	++	0

his general condition as shown by febrile episodes from the fourth through the fifteenth days. The principal changes noted during the latent period were: loss of weight of from 0.3 to 2.3 kg, with the low point reached at the end of the first week, persistent fatigue, profuse sweating, insomnia, and intractable headache (Tables II & III).

During the critical period, from the fourth to the seventh week, there was noted a collapse of the general condition. Significant febrile episodes occurred during the fourth and fifth weeks, with the exception of the least exposed, B. The patients became confused, while anorexia and nausea reappeared; the sweats became profuse, together with a diminution of the diuresis. Only the least exposed, B, failed to show this alarming picture.

After treatment and after the bone marrow grafts in particular, four of the patients (M, G, D, H) showed at the end of the seventh week a progressive improvement in their general condition, although this was hampered by gastro-intestinal disturbances. Convalescence did not actually begin until the end of the third month. The most seriously exposed patient, V, succumbed during the critical period on the 32nd day. B, although the least affected, made the slowest recovery.

Cutaneous manifestations

The cutaneous manifestations were of interest during the course of the disease. From the first day all of those exposed with the exception of B showed a definite erythema accompanied by conjunctivitis. Some pigmentation could be made out at the end of the second week, but in all cases there developed a dryness of the skin, which was accompanied by desquamation in the case of V, the most heavily exposed. All the patients developed epilation, the onset appearing on the 14th day in the case of V, on the 20th day for B with the lowest exposure (Table III). Although the whole body was involved, the epilation was most pronounced over the scalp, especially the frontal and occipital surfaces (Fig. 2).* The male patients with the exception of B showed

*Fig. 2 contains 4 photographs showing the extensive epilation. It is omitted from this translation because of difficulties in reproduction.

epilation of the beard. It should be noted that with several of them the craniofacial epilation was asymmetrical in character (Fig. 2)*,

TABLE III

	Erythema	Conjunctivitis	Epilation	Weight	Changes in Sperm	Complications & Other Signs
V	++ 1st da	++ 1st da	Hair-14da Beard-14da	-2.3kg- 8da -1.0kg- 28da	+++	Abdominal pain ⁺ Intest. Perforation, Obstruction, Anuria, Terminal Icterus
M	++ 1st da	+ 1st da	Hair-16da Beard-16da	-1.6kg- 6da -3.0kg-118da	+++	Abdominal pain ⁺
G	+ 1st da	+ 1st da	Hair-18da Beard-18da	-0.5kg- 6da -6.2kg-118da	++	Abdominal Pain ⁺ Herpes
D	+ 1st da	+ 1st da	Hair-14da	-1.3kg- 6da +9.0kg-120da		Abdominal pain ⁺ Menstrual Irreg. Herpes
H	+ 1st da	+ 1st da	Hair-17da Beard-17da	-0.3kg- 6da +5.6kg-106da	+++	Abdominal pain Sub-icterus Partial obstruction
B	0	+ 1st da	Hair-20da	+0.6kg- 10da -3.3kg- 82da -2.6kg-120da	+	Abdominal pain

*Fig. 2 contains 4 photographs showing the extensive epilation. It is omitted from this translation because of difficulties in reproduction.

resulting presumably from the heterogeneous distribution of the secondary gamma radiation. The epilation of the scalp was virtually total in the cases of V, M, D and H. The regrowth of hair became evident at the end of three months. It is perhaps useful to point out that the regular ophthalmologic examinations failed to reveal a single lenticular anomaly, and only in the case of H was there a retinal edema coincident with his purpura.

The Hematologic Syndrome

The hematologic changes were followed principally by observation of the peripheral blood with routine studies every two or three days. The tests were carried out in duplicate by two different laboratories. It should be mentioned here that the results reflected the effect of the treatment on the hematologic course.

The examinations carried out prior to the accident showed a normal hematologic state for all of the exposed persons except D who showed a moderate decrease in the number of red and white blood cells.

The counts made the first day served as a new baseline for the subsequent findings. It should be noted, however, that there was an immediate reaction in the form of a leucocytosis ranging from 9,000 to 11,000 cells per mm³, with an incipient lymphopenia.

During the latent period there was a progressive decrease in the number of blood cells. The slope of this decrease, different for different types of cells, was steepest for lymphocytes, most gradual for red cells, with the granulocytes and platelets in-between. The lymphocytes virtually disappeared in the first five days with a fluctuating level thereafter. The granulocytes decreased more gradually although there were sharp increases at the end of the first and the second weeks. The drop in platelets followed a course much the same as that of the granulocytes. The reticulocytes had practically disappeared after the first few days although there was one

reticulocyte 'spike' at the end of the second week. The number of red cells remained essentially unchanged during the latent period of the first three weeks.

The critical period is characterized by an exacerbation of the earlier findings, indicating an almost-complete bone marrow aplasia. Only the lymphocytes remained at the low level reached during the first week. The granulocytes passed through a minimum towards the end of the fourth week, falling below 50 per mm^3 except in the case of B, the least exposed, where they reached 900 per mm^3 . The minimum for the platelets was reached a little earlier in the fourth week, the level dropping below 30,000 per mm^3 for all save B.

After their brief outpouring the reticulocytes again practically disappeared towards the end of the fourth week. The number of red cells, stable up to that time, began to decrease towards the end of the fourth week reaching values in the vicinity of 3,000,000 per mm^3 , save for B who always had more than 4,000,000 and for H and D who showed definite anemias of 2,200,000 and 1,400,000 respectively.

The bone marrow transfusions were given during the fifth week. In the eight days following this therapeutic measure the blood picture changed radically. There was an immediate three-fold increase in the thrombocytes, the granulocytes, and the reticulocytes. The red cell increase followed the reticulocyte rise. The lymphocytes were not affected and continued their former fluctuations. The details concerning the influence of the bone marrow transplant on the hematologic course are given in the accompanying paper (9).

After the second month, the blood levels except for the lymphocytes, returned essentially to normal, although with considerable fluctuations. This hematologic improvement was the result of the effect of the marrow transplant and the medullary recovery itself. It is impossible to specify exactly the part played by each of these two factors, except for the erythrocytes, which can be identified by

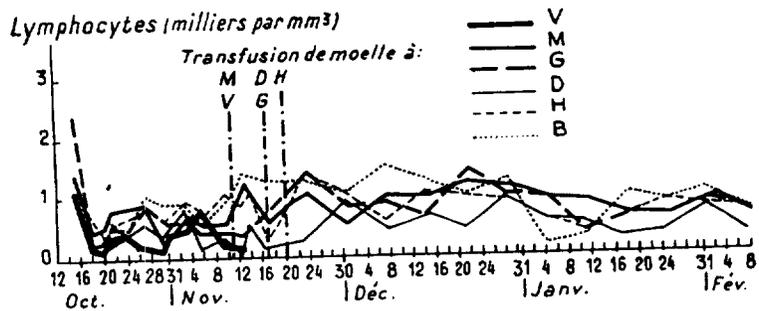


Fig. 3

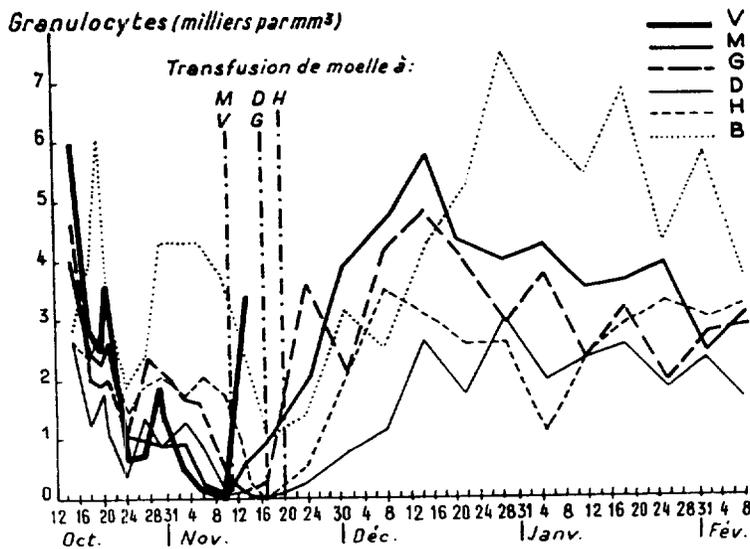


Fig. 4

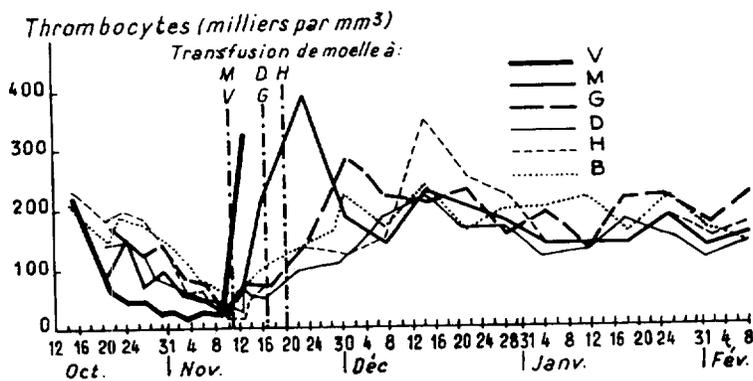


Fig. 5

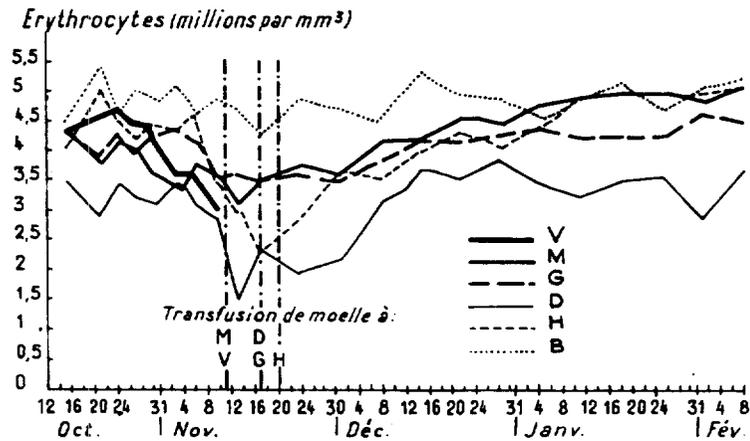


Fig. 6

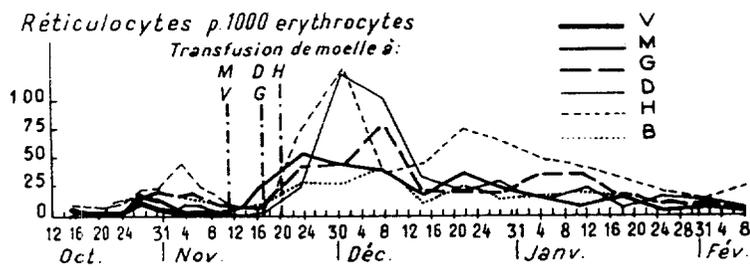


Fig. 7

agglutination methods. The details of this subject will be found in the following article (9). These findings refer to patients, M, G, D and H; for the most heavily exposed, V, death came on the 32nd day, but his blood picture followed an identical course after the bone marrow transplant. On the other hand, the least irradiated, B, showed a slower spontaneous recovery than that of the treated cases.

The details of the hematology are given in Table IV and the curves in Figs. 3 to 7.

It is worth noting that there was an elevation of the monocyte level after the marrow transplant. In addition, in the case of one of the patients, M, a strong eosinophilic reaction was observed.

The examinations of the peripheral blood were supported by bone marrow biopsies taken each ten days. One could observe after the first week a severe medullary aplasia and, by the end of the latent period, a total aplasia. In the two weeks following the transplant there was a repopulation of the bone marrow which resulted in a nearly normal appearance.

The study of the hemorrhagic tendencies was carried out with conventional methods for measuring the bleeding and clotting times, by the tourniquet test, and also by analysis of the prothrombin complex and tests for tolerance to heparin. In general ways the results furnished by these tests have not been significant. One could always demonstrate a positive tourniquet test after several repetitions, especially in the cases of patients H, G and B. The prothrombin complex was normal for all of the patients except D, a female, and in her case the accelerin and the proconvertin levels were lowered. On several repeats with different patients the prothrombin time was found to be increased.

Tests also were made by the thrombo-elastographic method carried out each week. The results showed significant perturbations indicating a functional thrombocytic abnormality. After the end of the latent phase and during the critical period the clotting time was clearly increased and the size of clot decreased. In the case of patient H there were skin manifestations coincident with the appearance of purpura, but these decreased noticeably following platelet transfusions. (The thrombo-elastographic tracings in Fig. 8 well illustrate

these facts)*

The hemorrhagic syndrome was manifest only to a moderate degree for most of the patients; it consisted essentially of bleeding from the gums during the critical period. D and V had epistaxis, H showed

TABLE IV

	Red Cells	Retics.	Plate.	PMN	Lymphs	Hemorrhagic Signs
V	3,100,000 25th da	0.4/1000 25th da	19,000 18th da	15 25th da	132 5th da	Epistaxis-14th da Bleeding gums-30th da Hematemesis-27-32 da Hemoptysis, 30-32 da
M	3,100,000 28th da	0.4/1000 25th da	28,000 25th da	48 25th da	230 15th da	Bleeding gums while brushing teeth
G	3,500,000 45th da	2/1000 5th da	14,000 25th da	42 28th da	240 3rd da	Bleeding gums while brushing teeth
D	1,430,000 28th da	0.03/1000 32nd da	25,000 28th da	6 29th da	80 28th da	Epistaxis-12th da Menorrhagia ⁺⁺ 26-43da Bleeding gums while brushing teeth
H	2,240,000 32nd da	4.3/1000 32nd da	14,000 25th da	18 32nd da	276 32nd da	Purpura 26th da Bleeding gums while brushing teeth
B	4,260,000	7.6/1000	53,400	916	390	Bleeding gums while brushing teeth

*This technique is not in common use in America and the illustration in Fig. 8 is not reproduced in this translation.

purpura of the lower extremities for two weeks after the 26th day. D developed menorrhagia of sufficient severity to produce an anemia of less than 2,000,000 red cells per mm³. But the individual most heavily exposed, V, developed very serious hemorrhages, gastro-intestinal and pulmonary, during the fifth week. Melena, hematemesis and hemoptysis became of increasing severity; these hemorrhages were massive in nature and ended finally in death. The autopsy showed a generalized purpuric state of the G.I. tract, pulmonary infarctions, and renal and vesical petechiae.

Visceral and Genito-urinary Problems

The gastro-intestinal symptoms, while only moderate in the case of B with the lowest exposure, were disturbing with some of the others and were dramatic in the case of V. With the four patients, M, G, D and H, there were observed no pulmonary or cardiac signs except for some fluctuations of the blood pressure. The hepato-renal symptoms were negligible except in the case of H who showed a low-grade icterus at the end of the critical period. All showed at this same time digestive tract symptoms characterized by superficial gingivostomatitis, diffuse and persistent abdominal pain with occasional colicky cramps and disturbances in intestinal peristalsis. One patient, H, even showed an episode of partial intestinal obstruction towards the end of the critical period. It is to be noted that the mental confusion during this critical period masked the digestive symptoms and rendered evaluation difficult.

In the case of the most heavily exposed, V, the extremely grave G.I. complications appeared in the course of the fourth week, culminating finally in death. The first of these consisted of a generalized peritoneal reaction extending progressively through the abdominal cavity, then regressing under the effect of antibiotics. Three days later signs of intestinal obstruction appeared; the autopsy was to

show that he developed double ileocecal and cecocolic intussusceptions. A secondary anuria and icterus developed to complicate an already dramatic situation. There developed at the same time a generalized denudation of the digestive and pulmonary mucosae accompanied by massive hemorrhages. The autopsy allowed a careful study of the injury to the different viscera, primarily the lungs, stomach, intestines, colon, adrenals and kidneys.

Of the five male patients, sperm counts after the second week showed a marked decrease and definite morphologic and functional changes. The later examinations showed a complete disappearance of sperm in two cases, M and H, and nearly complete disappearance in the two others, G and B. The autopsy on V showed a total depopulation of the seminiferous tubules.

Case D demonstrated interference with the menstrual cycle: irregularity and shortening of flow. The most severe bleeding occurred when her normal menstrual period occurred during the critical period.

Biochemical Studies

Many routine biochemical tests were carried out to follow the metabolic course and to provide the data needed for therapy. They did not represent the total of what might have provided interesting data, but a complete study would have necessitated too many withdrawals of blood.

In a general way blood chemistry studies did not indicate definitively any important changes (Fig. 9). The physical constants did not vary and the electrolyte balance showed no appreciable deviation except during the first week and during the critical period: hypochloremia, hyponatremia, hyperkalemia. The total proteins were somewhat lowered as was the serum albumin during this same period. Electrophoretic examination during the first week showed only a diminution of the gamma globulin (it should be noted that injections

of gamma globulin were given later) and occasionally an increase in the alpha and beta globulins. In the course of the first week a mild hyperazotemia was observed.

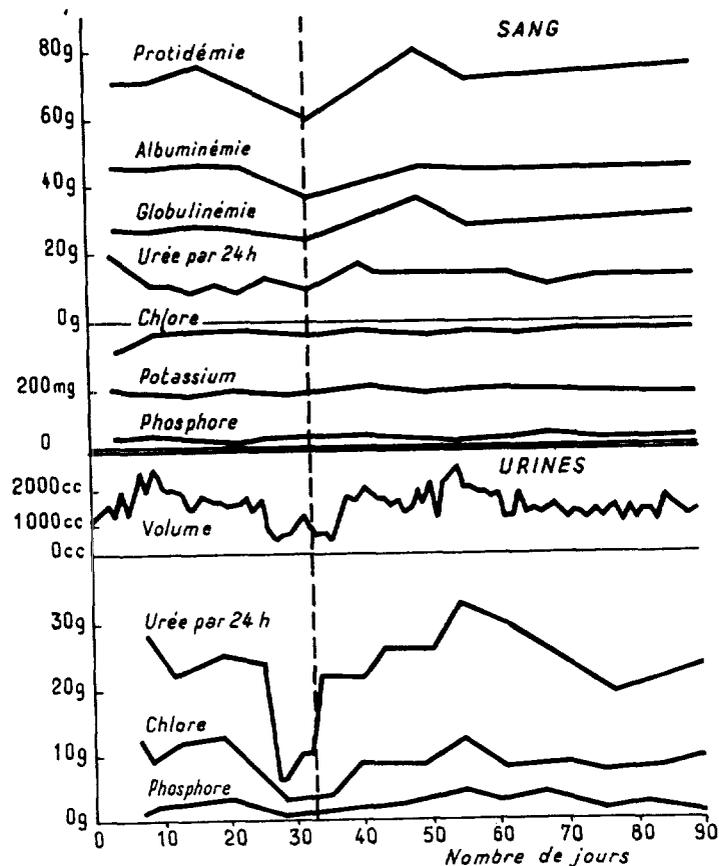


Fig. 9

Diuresis was abundant (two to three liters a day) during the course of the illness except at the peak of the critical period when there was a definite oliguria. The excretion of urea and minerals underwent comparable fluctuations. Glycosuria was not observed although there was an albuminuria during the early weeks. One could demonstrate in an irregular fashion the presence of pigment, urobilinogen, etc. Chromatographic examination demonstrated an increase in the

excretion of the normal amino acids, which, especially after the first week, remained high until the period of convalescence. At the beginning some abnormal amino acids were seen such as proline, phenylalanine, tryptophane, threonine, aspartic acid (Fig. 10)*. In the case of the most heavily exposed man, urinary casts were observed in the terminal phase.

THERAPEUTIC STUDY

The therapeutic regime depended on a few simple guiding principles: get the patients in the best possible condition by bedside care and an appropriate diet, protecting them particularly from all risk of exogenous infection. In view of the vagueness of the data concerning the dosimetry, it was the clinical course which directed a classic, symptomatic course of therapy, avoiding as much as possible any act which might be incompatible with subsequent treatment. Faced with a desperate situation threatening a fatal outcome, modern therapy based on the most recent experimental evidence was attempted.

General Therapy

The first day, before the departure for Paris, the patients received various anti-shock medications and antibiotics. On their arrival at the Curie Foundation they were isolated under conditions of rigid asepsis and antisepsis with visits limited to medical and hospital personnel, spraying of antiseptics with particular care for the natural orifices, etc. The course of treatment consisted of strict rest, but confinement to bed was not total until the period from the third to the

*Fig. 10 consists of reproductions of chromatographs. They are of poor quality in the original reprint and could not be copied.

seventh weeks. House diet was permitted during the latent period. A "hypotoxic" regime was prescribed during the first part of the critical

TABLE V

	Penicillin	Streptomycin	Terramycin	Chloramphenicol	Vitamin Therapy	Hormone Therapy
V	2,000,000 u 4-15 da	1 g 4-15 da	600-800 mg I.M. 22-32 da	3 g 29-32 da	B Complex C,D,K,PP Cortine ⁺	Liver extract
M	2,000,000 u 22-25 da	1 g 22-25 da	600 mg 26-37 da	3 g 29-32 da	B Complex C,D,K,PP	Lobamine Cysteine
G	0	1 g 35-38 da	400 mg I.M. 29-40 da 2 g p.d. 84-88 da	3 g 24-33 da	B Complex C,D,K,PP	
D	2,000,000 u 4-13 da 4,000,000 u 27-37 da	1 g 4-13 da 1 g 27-37 da	0	3 g 31 da	B Complex C,D,K,PP	Testosterone Progesterone
H	4,000,000 u 51-54 da	1 g 51-54 da	600 mg 34-41 da 49-58 da	3 g 29-32 da	B Complex C,D,K,PP	
B	2,000,000 u 12-19 da	1 g 12-19 da	0	0	B Complex C,D,K,PP	

period, and this was followed by a special diet entirely liquid until the seventh week. This dietary regime contained a very considerable quantity of water (about 3 l), was balanced in proteins (110 g), fats (50 g), carbohydrates (340 g), mineral salts (12 g), and provided 2,400

calories a day. After the critical period had passed, there was a gradual return to the hypotoxic regime, then to the normal hospital diet, with supplementary soft solids permitting an intake superior to the preceding one. There was no need for parenteral feeding, except in the case of V during the terminal phase of his gastro-intestinal complications.

This dietary regime was rounded out with intensive vitamin therapy, B Complex, C, D, K and PP. Adreno-cortical and hepatic extracts were administered regularly. A therapeutic complement of particular amino acids such as lobamine and cysteine was brought into play.

The antibiotics were prescribed only when indicated in order not to confuse the blood picture, and they were chosen according to the indications. Those most used were penicillin, streptomycin and terramycin. Chloramphenicol was used only to combat G.I. complications (Table V).

Hematologic Treatment

In treating the hematopoietic system, the customary procedures were used with discretion. One small transfusion of 150 ml of whole blood, of debatable usefulness, was given on the third day to compensate for the repeated withdrawals of blood required by the initial examinations. For the two patients D and H who presented an anemia in the course of the critical period, packed red cells were injected. Because of the hemorrhagic tendency in the cases of V, D (menorrhagia) and H (purpura), transfusions of platelets were administered in massive doses. Injections of gamma globulin were administered in the latent and critical periods to four of the patients (Table VI).

When the near-certainty of a fatal outcome, first for V and then successively for M, G, D and H, became apparent, the decision was reached to attempt a transfusion of hematopoietic tissue. The

information relative to V's exposure and the alarming initial signs indicated the need for fast action. In the face of the possible risks

TABLE VI

	Whole Blood	Red Cells	Platelets	Globulin	Exchange Transfusion	Bone Marrow Transplant
V	150 cc	0	500×10^9 9da 16 da	20cc 9da	5.5 l 28 da	Embryonal 4.2×10^9 -14 da Medullary 8.5×10^9 -27 da 211 cc
M	150 cc 3 da 500 cc 23 da	0	0	20cc 9da	0	Medullary 11×10^9 cell-27 da 183 cc
G	150 cc 3 da	0	0	20cc 9da 20cc 34da	0	Medullary 12×10^9 cell-33 da 270 cc
D	150 cc 3 da	0.5 l 29da 1 l 30da	750×10^9 29 da	20cc 9da 20cc 34da	0	Medullary 8.5×10^9 cell-33 da 300 cc
H	150 cc 3 da	1 l 34da	750×10^9 29 da	0	0	Medullary 14×10^9 cell-36 da 300 cc
B	150 cc 3 da	0	0	0	0	0

of a secondary anaphylactic reaction following a transfusion of adult tissue, it was decided to give preference to embryonic hematopoietic tissue. This was attempted on the fourteenth day with an injection of 4.2 billion cells of fetal liver.

Failure to respond to treatment and the fact that the patients were getting worse prompted us to attempt venous transfusions of adult bone marrow from a single donor of blood type as similar as possible to the patient. These transfusions were given to V and M on the 27th day, to G and D the 33rd day, and to H the 36th day, the volumes injected ranging from 180 cc to 300 cc and the number of cells from 8.5 to 14 billion. One will find in the following article (9) all the details of the techniques utilized and the arguments in favor of attempting the transplant. The marrow transplant was followed by a spectacular increase in the cells of the myeloid series in the circulating blood, as shown in the curves (Figs. 3 to 7), a phenomenon not shown by B, the least exposed patient, who was not grafted. Also, after a post-transfusion reaction of 48 hours the general condition showed a profound change for the better. The disappearance of mental confusion was accompanied by increased energy and euphoria. The return of appetite was followed by an increase in weight going beyond the starting point contrasting with the stubborn weight loss of the untransfused patient, B.

Special Treatment

The above discussion applies only to patients M, G, D and H. Patient B with the smallest exposure got the same basic treatment, had the same diet, received the same vitamins and hormones, but he received no specific therapy for his blood changes. V, with the largest exposure and because of infections and visceral complications, got in addition: an exchange transfusion of 5.5 l on the 28th day, continuous aspiration for his intestinal obstruction, extra-renal filtration by

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artificial kidney (on the service of J. Hamburger) to combat the anuria, and artificial respiration in the terminal phase.

CONCLUSIONS

The preceding observations are of interest because of the rarity of cases of accidental whole-body irradiation. But it is possible in addition to derive from the dosimetric, clinical and therapeutic studies lessons for the future.

Dosimetry

Concerning the dosimetry, it cannot be denied that the uncertainty of the data on the radiation doses increases the difficulties of therapy. Exposure to neutrons alone can be evaluated a posteriori by measurement of the radiation induced in the human body. There is a need for gamma ray detectors, fixed or portable, capable of registering doses ranging from 50 to 1,000 roentgens. In particular the wearing by people with a potential exposure of individual detectors such as pocket chambers, chemical dosimeters, gold foils, etc., is of definite interest.

Clinical

The clinical study has confirmed the validity of the early signs such as nausea, vomiting and diarrhoea. The cutaneous signs are also of significant interest, especially the erythema and the conjunctivitis at the onset, and also the epilation following the third week, just before the critical period. Among the blood studies, it seems that the alterations in the various cell levels as a function of dose received are more marked and more easily interpreted for the granulocytes than for the lymphocytes or the platelets. Thus the minimum level of

neutrophilic granulocytes was 916 for the man with the lowest exposure, ranging down to 48 for the others. The spreads between the levels of the lymphocytes and platelets were not as great, being 390 to 276 and 53,000 to 20,000 respectively. It appears that the customary biochemical tests do not reflect the severity of the exposure, except in the case of the urinary excretion of amino acids. Finally the difficulties caused by the mental confusion in treating the gastrointestinal complications during the critical period should be pointed out.

Therapeutic

As a basis for the therapeutic indications, the six patients illustrate in a remarkable manner all aspects of the range of the radiation doses received.

The least exposed, B, demonstrates sublethal irradiation, below 500 rem. Isolation, bed rest, and an appropriate diet, with a few adjuvant medications seems to suffice. It should always be remembered that the restoration of the general condition and the hematologic recovery is a slow process. This drawback does not in our eyes justify an attempt at bone marrow transplant, an uncertain and possibly dangerous procedure.

It is quite different if the dose is lethal, falling between 500 and 1,000 rems, a situation exemplified by the four patients, M, G, D and H. In their cases isolation, bed rest and suitable diet, even when helped by symptomatic treatment did not seem adequate. The indication for bone marrow transplant seemed reasonable, and this seemed to be the only thing which would permit the body to wait for the spontaneous recovery of its own myeloid tissue with some hope of survival. As to the selection of the time for this intervention, it seems that one may temporize up to the beginning of the critical

period in order to verify the fact that the clinical course fully confirms the dosimetric data.

But in the case of a supralethal exposure at or above 1,000 rem, of which V can be taken as an example, it appears essential to attempt the bone marrow transplant as early as possible. This will permit the patient to be in the best possible hematologic and general condition to face the visceral complications of the critical period and to permit subsequent necessary treatment (even surgical).

Prognosis

At the present time it is difficult to venture a prognosis on the five survivors.

In the immediate future, for the four who were given the hematopoietic transfusion with bone marrow transplant, the possibility of a secondary immunologic reaction cannot be excluded. It is difficult to extrapolate from animal experimentation to man, knowing the differences existing between the medullary tissues.

For the five patients it seems that one must wait a short time, several months at least, on the fluctuations in the blood picture and the spermatogenic anomalies, as well as the persistence of weakness, forbidding any premature return to work.

As for the distant future, the probability of inducing leukemia or certain cancers is presumably increased. It is difficult to predict anything as to the eventual shortening of the life span.

This story has been a sad one, especially as one of the victims died. Nevertheless, because of the range of the doses received, this radiation accident has presented an exceptional opportunity and, so to

speaking, demanded that one show in man the efficacy of treatment which had been successfully tried in animals for several years. These findings postulate the specific indications for the treatment which has already been tried on leukemics in the form of bone marrow transplant following whole body irradiation.

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SUMMARY

Six persons were accidentally exposed while working near an atomic reactor to sublethal, lethal and supralethal doses of radiation. The clinical course confirmed the physical findings just as the magnitude of the dose paralleled the severity of the signs and symptoms. After a phase of initial shock and a latent period of about three weeks, an extremely serious hematologic crisis occurred and that brought the authors to attempt homologous grafts of bone marrow cells in five of the cases. In four cases, a rapid improvement followed. However the patient who had received supralethal doses of radiation died from visceral complications. The sixth patient, who had been the less irradiated and in whom the graft had not been attempted, recovered spontaneously but slowly.

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BIBLIOGRAPHIE

1. ANDREWS (G. A.). Communication personnelle.
2. CASTER (W. O.) et ARMSTRONG (W. D.). Electrolyte balances following total body X-irradiation (Proc. Soc. Exper. Biol. Med., 1955, 90, 56).
3. GOUSKOVA (A. K.) et BAISSOGOLOV (G. D.). Deux cas aigus de mal des rayons chez l'homme (traduction française) (Conf. Int. Genève, 1955, 11, 39).
4. HASTERLIK (R. J.) et MARINELLI (L. D.). Dosimétrie physique et observations cliniques sur quatre humains atteints par les rayonnements à la suite d'une fuite accidentelle dans un ensemble critique (Conf. Int. Genève, 1955, 11, 27).
5. HEMPELMANN (L. H.), LISCO (H.) et HOFFMAN (J. G.). The acute radiation syndrome: A Study of nine cases and a review of the problem. (Ann. Int. Rad., 1952, 36, 279).
6. HOFFMAN (J. G.) et HEMPELMANN (L. H.). Estimation of whole-body radiation doses in accidental fission bursts (Am. J. Roentgen., 1957, 77, 144).
7. JACKSON (D. P.), CRONKITE (E. P.), LEROY (G. V.) et HALPERN (B.). Further studies on the nature of the hemorrhagic state in radiation injury (J. Lab. Clin. Med., 1952, 39, 449).
8. KATZ (E. J.) et HASTERLIK (R.). Aminoacidemia following total body irradiation in the human (J. Nat. Cancer Inst., 1955, 15, 1085).
9. MATHÉ (G.), JAMMET (H.), PENDIC (B.), SCHWARZENBERG (L.), DUPLAN (J.-F.), MAUPIN (B.), LATARJET (R.), LARRIEU (M. -J.), KALIC (D.) et DJUKIC (Z.). Transfusions et greffes de moelle osseuse homologue chez des humains irradiés à haute dose accidentellement (Rev. Franc. Études clin. biol., 1959, 4, 226).
10. POPOVIC (D.). The bare critical assembly of natural uranium and heavy water (Conf. Int. Genève 1958, n° 491).

11. UNION CARBIDE NUCLEAR CO. Accidental radiation excursion at the Y 12 plant. Final Report (Report n° Y 1234, 1958).
12. WARREN (S.) et BOWERS (J. Z.). The acute radiation syndrome in man (Ann. Int. Med., 1950, 32, 207).
13. WOODS (M. C.), GAMBLE (F. N.), FURTH (J.) et BIGELOW (R. R.). Control of the post-irradiation hemorrhagic state by platelet transfusion (Blood, 1953, 8, 545).