
By Georges Mathé

THE GRAFTING of isologous, homologous or heterologous hematopoietic cells, from myeloid, splenic or lymph node tissues is now possible. It is tempting to apply this finding to the treatment of leukemia: (a) either to restore blood and hematopoietic cells which have been destroyed by irradiation or chemotherapy (when given at high doses in order to destroy leukemic cells completely); (b) or to obtain from the cells so grafted immune reactions against leukemic cells (or against eventual leukemic antigens).

It is our purpose in this paper: (a) to sum up the actual status of our knowledge concerning the grafting of myeloid, splenic and lymph node cells in nonleukemic subjects; (b) to describe the application of this method in the "prophylactic" treatment of some leukemias; (c) to compile the results thus far obtained in laboratory animals and man in the treatment of leukemia.

HEMATOPOIETIC CELL GRAFTS. A BRIEF SUMMARY

Animal Experiments

Infusion of autologous or isologous hematopoietic cells.—It is generally accepted that neither an autologous nor an isologous graft brings about any particular immunologic response in the host. However these kinds of grafts may give rise to technical problems. One of the interesting aspects of these types of grafts is the finding that the venous route of administration is superior to other routes for giving a good functional graft.

Such autologous or isologous grafts have been performed in animals whose marrow and other hematopoietic tissues had been rendered aplastic or hypoplastic by irradiation,1,11,25,26,49,53 or by antimitotic agents.78,84 The intravenous infusion in these animals of their own bone marrow (obtained before...
the aplasia-inducing treatment), or of bone marrow from animals of the same strain, can considerably diminish their death rate. Marrow repopulation and consequent correction of blood cytopenia rapidly follows such treatment.

**Infusion of homologous or heterologous hematopoietic cells.**—Animals submitted to an LD100 dose of total-body irradiation can survive if treated by an infusion of homologous marrow cells. Animals irradiated with a sublethal dose are generally not protected by this procedure. It is widely recognized that the LD100 dose allows survival of the homograft by inhibiting the recipient’s immunologic defense mechanisms. The homograft is not effective in protecting against a sublethal dose since the immune responses of the recipient are not sufficiently suppressed. Evidence that the hematopoietic (myeloid and lymphoid) tissues of the host are repopulated by the transplanted cells has been obtained by different chemical, cytologic and serologic methods. The graft can be permanent or transitory: in the latter case, the donor bone marrow cells are replaced sooner or later by the host-type cells. Attempts at preparing adult animals for marrow homografts by chemical substances, such as alkylating agents (TEM, nitrogen mustard and derivatives of myleran) have failed. However, survival of marrow homografts may be obtained without any attempt at previous conditioning by injecting the cells into newborn animals (acquired immunologic tolerance).

Many experiments have also demonstrated the possibility of marrow heterografts under certain circumstances. Thus, rat marrow has been grafted in lethally irradiated mice. Animals which have been irradiated and subsequently restored by an isologous marrow graft have a nearly normal survival; however, most of the animals protected by an homologous or heterologous graft develop a secondary syndrome (“homologous” or “heterologous” disease) which begins between the twentieth and the one hundredth day after the injection of the donor cells. The period of incubation of this disease may be considerably shortened if lymphoid cells are administered simultaneously with marrow cells. The manifestations of the “secondary syndrome” include: (a) clinical phenomena: loss of appetite, diarrhea, loss of weight, dermatoses, decreased resistance to infections; (b) hematologic symptoms: lymphopenia, anemia; (c) histologic lesions: lymphoid aplasia, reticuloendothelial and plasma cell hyperplasia, tendency to necrosis of tissues (especially fibrinoid necrosis). Expression of this syndrome varies from species to species and depends, in large measure, on the strains of donor and recipient animals. If the graft of marrow cells or lymphoid cells is performed at birth, the disorder is called “runt disease.”

The secondary syndrome, which does not complicate autologous or isologous grafts, may be produced in nonirradiated or lightly irradiated animals (infusion of homologous marrow or lymphoid cells at birth or infusion of lymphoid cells from a parental strain into F1 hybrids). This disorder seems to be due, at least in greatest part, to an immune reaction of the grafted cells or of certain of them against the host. This has been shown by many experiments, especially those involving the
administration of parental cells to F₁ hybrids. From a physiopathologic point of view, the chief mechanism of the secondary syndrome could be the lymphoid aplasia (or, more particularly, after irradiation, a delay in recovery of the lymphoid tissue).

In order to obviate the undesirable consequences of the immunization of grafted cells against the host, it has been proposed to protect irradiated animals with embryonic hematopoietic cells rather than adult marrow cells. With certain strain combinations, the disease can be avoided, but with certain other combinations it occurs nevertheless.

It should be noted that certain therapeutic agents including cortisone and folic acid antagonists have apparently given encouraging results in ameliorating the graft's host reaction.

Human Experiments

Infusion of autologous or isologous hematopoietic cells.—Several authors have published reports of cases of malignant disease treated with various doses of radiation and later injected with autologous bone marrow, which had been obtained before irradiation and kept frozen at very low temperatures. Such injections have apparently facilitated repopulation of hematopoietic organs.

A few cases of infusion of isologous marrow cells in man have been reported. In some of them, the leukemic twin was heavily irradiated and then given marrow cells from the healthy twin. Marrow recovery was quite rapid.

Infusion of homologous hematopoietic cells.—Attempts at infusion of homologous marrow cells in patients with leukemia previously treated with high doses of corticoids or with sublethal doses of radiation have failed, except in one patient, who, conditioned by an irradiation of 450 r, produced during 20 days red cells containing an antigen of the bone marrow donor.

The infusion of homologous bone marrow in five subjects accidentally submitted to high doses of radiation (between 650 and 1000 rem) has been successful. Survival of the graft could be demonstrated by indirect as well as direct proofs and especially by the fact that a population of erythrocytes produced by the grafted cells of the donor could be shown to be present in the patient's blood. The graft was only transitory, and none of the patients displayed the manifestations of the "secondary syndrome."

Six patients with acute leukemia were submitted, during a phase of complete remission, to irradiation with a dose of 830 to 900 rad (given by a cobalt bomb), followed by infusion of homologous bone marrow. Two subjects did not show any bone marrow recovery and died in aplasia. In the four other patients, myeloid restoration occurred. Functional transplantation of the bone marrow was indicated by erythrocytic antigens in three and by

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*The rad is the unit of absorbed dose and is 100 ergs per gram. The rem (roentgen-equivalent man) is a relative measure of biological efficacy, for the use of mixed radiations such as fast and slow neutrons and gamma rays. One rem is the estimated amount of energy absorbed in tissue which is biologically equivalent in man to 1 r of gamma or x-rays.
the granulocytic sex-linked appendixes in a boy who received bone marrow from a female donor.

Two of these patients received bone marrow from unrelated donors. Their clinical status was satisfactory until the forty-fifth day. At that time, a "secondary syndrome" appeared, characterized by moderate fever, skin infections, cough and digestive symptoms (anorexia, nausea, vomiting, diarrhea). One of the two patients (who received bone marrow from two different donors) developed an elevated level of cold agglutinins and a hypergammaglobulinemia; the other one (who received bone marrow from only one donor) developed a marked hypogammaglobulinemia. This secondary syndrome was improved by symptomatic measures and disappeared after a month and a half. At that point the population of donor erythrocytes had diminished and the blood lymphocytes had increased. Lymph nodes were taken from one patient 90 days after irradiation, when donor red blood cells were still present. The findings in these lymph nodes were those usually seen in the lymph nodes of mice or dogs8 treated by a homologous bone marrow graft: aplasia of lymphoid nodules and reticular hyperplasia. A lymph node was taken from the other patient on the one hundred and twenty-fifth day (when practically no more red cells of the transfused marrow phenotype were found); it was characterized by marked sclerosis but, at the periphery, there were a few lymphoid nodules, and beginning regeneration could be found. After the disappearance of the secondary syndrome, the two patients were in excellent health until the sixth month after irradiation for one, and the fifth month for the other, when the leukemic process recurred.

In the two other patients who received bone marrow from their mothers, the clinical status was not ameliorated by the myeloid restoration as with the former patients. Rather, their condition worsened. An erythematous desquamating dermatosis appeared, and high fever, with marked oscillations, continued. A marked lymphopenia contrasted with normal or high figures for neutrophils.

One of these patients developed severe digestive symptoms, Cheyne-Stokes respiration, and convulsions; death occurred after a period of coma. At postmortem, several cerebral necrotic areas were found, containing numerous fungic filaments. The histologic examination showed total lymphoid aplasia, intestinal crypt loss, hepatic necrosis, and the same cutaneous lesions (acanthosis, hyperkeratosis and parakeratosis) observed by De Vries and co-workers86 in mice and monkeys with dermatosis accompanying homologous disease.

The other patient developed icterus, asphyxial syndrome and died. The most important postmortem findings were: intestinal and cutaneous lesions and lymphoid aplasia as in the former patient; necrosis and dissociation of hepatic parenchyma; fibrinous interstitial pneumonitis; and several areas of focal necrosis in the spleen.

The following features of the secondary syndrome occurring in experimental animals have thus been encountered in these two patients: (a) restoration of myelopoiesis (in the last one, there was significant extramedullary myelopoiesis in the spleen); (b) lymphopenia and lymphoid aplasia; (c) intestinal crypt loss; (d) hepatic necrosis; (e) dermatosis; (f) death by infectious disease.
HEMATOPOIETIC CELL GRAFTS IN LEUKEMIA TREATMENT

APPLICATION TO THE "PROPHYLACTIC" TREATMENT OF LEUKEMIA AND ALLIED DISEASES

The literature provides numerous experiments which underline the interest of this method as a possible "prophylactic" treatment.

Grafted Leukemias

It is known that total roentgen irradiation can condition an animal of one strain to leukemic grafts of another strain. The shielding of the spleen or of a given section of the bone marrow during irradiation (which is equivalent to an autograft of spleen or bone marrow cells) prevents the homograft of leukemia. The shielding of bone marrow is, in this regard, more efficient than that of the spleen.

Induced Leukemias

Total body x-irradiation can induce a high percentage of leukemia in certain strains of mice. Lead shielding of the spleen or of certain areas of bone marrow during irradiation or infusion of isologous bone marrow or spleen after irradiation reduces the incidence of x-ray-induced lymphomas in these animals. The actual mechanisms by which such protection is afforded is not yet elucidated.

Spontaneous Leukemias

The intravenous injection of bone marrow cells from C3H mice (a low leukemic strain) to (C3H x Akr) F1 hybrids at an early age decreases the incidence of spontaneous leukemias from 32 to 13 per cent. Recently, Duplan compared the effects of sublethal (460 r) or lethal (600 r) irradiation followed by restoration with isologous or homologous embryonic myeloid cells on the incidence of the spontaneous Ak leukemia in mice. He found that: (a) irradiation followed by isologous restoration is not efficacious at a sublethal dose; (b) at lethal doses, this maneuver delays the appearance of leukemia but does not reduce its frequency; (c) irradiation followed by homologous bone marrow is not efficacious at a sublethal dose; (d) at a lethal dose, it delays the appearance of leukemia and significantly decreases the incidence of leukemia (40 instead of 75 per cent).

This result, together with those previously described, underlines the ne-

*It should be noted that Lorenz, Law and Congdon did not diminish the rate of leukemia in (C3H x Akr) F1 by irradiation (4 divided exposures of 225 r each) followed by intraperitoneal injection of C3H bone marrow. The discrepancy between their results and those of Duplan may perhaps be accounted for the difference in the sites of injection or the divided exposures.
cessity of a successful graft of myeloid cells as a condition of their efficacy in the preventive treatment of leukemia. The difference in the effect of isologous cells as compared with homologous suggests the intervention of some immune process.

**ATTEMPTS AT "CURATIVE" TREATMENT**

Here again, we shall consider successively grafted, spontaneous and induced leukemias.*

**Grafted Leukemias**

Several works have investigated the effects of lethal or supralethal doses of radiation followed by a graft of isologous or homologous hematopoietic cells. In order to investigate the respective effects of radiation and graft of hematopoietic cells on the leukemia on one hand, and on the host on the other, we have used the following system: (a) grafted leukemia L. 1210 from the strain DBA<sub>2</sub> (either 10,000 or one million cells); (b) host (C57Bl<sub>6</sub> x DBA<sub>2</sub>) F<sub>1</sub>; (c) irradiation at the LD<sub>100/30</sub> in certain groups; (d) grafted hematopoietic cells variable from one group to the other but in such a way that the graft should be possible without irradiation (so that some groups should not be irradiated): bone marrow cells from adult (C57Bl<sub>6</sub> x DBA<sub>2</sub>) F<sub>1</sub> or C57Bl<sub>6</sub>; splenic cells from these adult F<sub>1</sub> or C57Bl<sub>6</sub>; bone marrow and splenic cells from these adult F<sub>1</sub> or C57Bl<sub>6</sub>; embryonic myeloid cells from C57Bl<sub>6</sub>. From these various studies, the following can be concluded: (a) irradiation at the LD<sub>100/30</sub> level followed by a graft of bone marrow cells incapable of immune reaction against leukemia (isologous) practically never cures the animals of leukemia and the most that can be expected is retardation of death.† (b) The treatment is more efficient when the animals are treated soon after the graft of the leukemia or are grafted with a smaller number of leukemic cells. Moreover, when such a treatment is applied to animals with advanced leukemias, it can accelerate their death; the destruction of leukemic cells appears to be of importance in this phenomenon.† (c) Supralethal irradiation followed by a graft of isologous bone marrow cells can give only retardation of death or cure some animals. The dose should be divided or delivered at a slow rate. (d) Simultaneous administration of adult isologous bone marrow and lymph node cells after irradiation at the LD<sub>100/30</sub> level is significantly more effective in delaying the death of animals than bone marrow cells alone. The mechanism of this phenomenon is not known. (e) Irradiation at the LD<sub>100/30</sub> level or at a supralethal dose followed by the graft of homologous bone marrow cells allows better survival times than those obtained with the graft of isologous bone marrow cells after similar irradiation. Even eradication of some leukemias can be obtained in this way. This

*Results being variable from one form of leukemia to the other and according to various factors, the survey of the data available will be purposely schematic.
†The dose expected to sterilize a population of leukemic cells by irradiation alone is about 4000 r.
result seems to be due to the immunization against leukemia of the (or some) hematopoietic cells. Most unfortunately, in most of the mice that are irradiated and then restored by homologous adult bone marrow cells, secondary homologous syndrome is to be expected. This will kill them starting about the 20th day following restoration. (f) As has been stated above, it seems that restoration (after irradiation) by myeloid homologous embryonic cells is less often followed by this homologous disease. It was therefore tempting to test this treatment in leukemic animals. The results have been disappointing, the survival being inferior to that of irradiated animals treated by homologous adult bone marrow cells. (f) In view of these results, it is plausible to believe that embryonic cells, which are immunologically immature, do not develop an immune reaction against the leukemia. (g) In other experiments, attempts have been made to increase the immune effect against leukemia by substituting homologous spleen cells for adult bone marrow cells or else by giving bone marrow and spleen cells or bone marrow and lymph node cells simultaneously. In these experiments, death occurred very rapidly within seven or ten days due to acute homologous syndrome, but without any macroscopic or microscopic symptoms of leukemia. Therefore, this method cannot be used as a treatment of leukemia. (h) It should be pointed out that this immune antileukemic effect of homologous bone marrow or spleen cells from an adult (when given intravenously and if the graft is successful) can be detected only after irradiation and, in our hands, only when the number of leukemic cells in the recipient is small.

The administration of chemotherapeutic agents such as thioguanine followed by the graft of isologous bone marrow cells in animals bearing tumors can also give appreciable survivals. The graft is then correcting the bone marrow aplasia which results from the high dose of the compound which is possible with replacement therapy. Unfortunately, as stated above, chemotherapeutic agents do not seem to be capable of conditioning the host to accept a graft of homologous hematopoietic cells. Nevertheless, some workers have obtained interesting results in tumor-bearing mice by treating them with thioguanine followed by injection of homologous bone marrow cells.

Spontaneous or Induced Leukemias and Allied Diseases

Since in the human, leukemias are either induced or spontaneous, the closest experimental situation is found in the treatment of induced or spontaneous leukemia in mice.

Animal leukemias.—We first investigated mice bearing spontaneous leukemias at a comparatively late stage. Once the diagnosis of leukemia was firmly established, the animals were submitted to various doses of x-irradiation, ranging from 600 to 1100 r, and injected within 24 hours with 10⁷ myeloid cells from: (a) either adult C57 or C3BBl bone marrow (normal or

*If the adult myeloid homologous cells are taken from animals immunized against leukemia, both antileukemic effect and toxic effect against the host increase in parallel.*
immunized against Ak leukemic cells), (b) or embryonic liver from these strains.

Many animals died within 10 days following the treatment, and the early mortality (which did not occur in nonleukemic Ak mice submitted to an identical treatment) was apparently due to a necrotizing process found in various organs. It appeared in those organs which were apparently not or only slightly infiltrated by leukemic cells such as the liver, but in most cases, it appeared in areas which were heavily infiltrated and, in these places, the necrosis was either very extensive. In the most favorable cases, in which the survival was more than 30 days (20 per cent of animals restored by C3H cells), death occurred between the thirtieth and the one hundredth day (with the exception of two animals which survived 125 and 269 days, respectively). In most instances, death was due to leukemia, and sometimes to the secondary syndrome. A very high dose of irradiation was more favorable when divided into stages than when given in one; i.e., when the radiation energy was lowered. The results were better when the donor myeloid cells came from C3H mice (same alleles in H2 locus*) rather than from C57Bl6 mice (different alleles in this locus). The results were not improved when we tried to restore leukemic mice: either by bone marrow from mice previously immunized against leukemic cells, or by embryonic myeloid cells.

Two main conclusions can be drawn from this work: (a) the irradiation at the LD100/30 of animals with extensive leukemic disease is very often complicated by a widespread and lethal necrotizing process; (b) the maximal dose of radiation that we have been using (1100 r) is not sufficient to destroy all leukemic cells, the sensitivity of which is very variable from one animal to the other and is probably variable from one type of leukemia to the other.

Others3 have treated Ak and C3H mice which had spontaneous leukemias by roentgen irradiation followed by the infusion of isologous bone marrow cells. Their results also are rather disappointing, since no survival exceeding three months has been recorded.

These poor results and the frequency of necrosis involving organs infiltrated by leukemia have let us to explore treatment in the early stage of leukemia instead of in its late phase. In a series of experiments, we have been treating 6 month old Ak mice without any macroscopic sign of leukemia by irradiation of 750 r, followed by the injection of myeloid cells from C3H or C57Bl6 adult mice or from embryonic livers of the same strains. This experiment is still in progress, but it can already be stated that many animals so treated die from the secondary syndrome before the date they would have died from leukemia (unpublished data).

In experiments dealing with leukemias induced by dimethylbenzanthracene or filtrates of leukemic tissues, the survivals after irradiation and restoration with isologous spleen cells are longer when the animals are treated at an earlier stage. Survival is shorter when homologous spleen cells are used.78

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*The strongest histocompatibility locus, which governs susceptibility and resistance to homografts, and has at least 10 known alleles.
HEMATOPOIETIC CELL GRAFTS IN LEUKEMIA TREATMENT

Human leukemia.—Different attempts at treatment of human leukemia or similar diseases have recently been made.

Total body irradiation followed by infusion of autologous bone marrow has been utilized by McGovern, Russel, Atkins and Webster in three cases of acute leukemia. The marrow was obtained during an apparently complete remission, stored at -70 C. and reinjected after irradiation of 600 r at the time of relapse. Marrow restoration was achieved in only one of the three patients. The rapidity of its appearance was considered by the authors as a point in favor of a successful autograft. However, the remission obtained was soon followed by a relapse and eventually death due to leukemia (personal communication). This suggests that the dose of radiation used was not sufficient by itself to “eradicate” an acute leukemia.

Recently, McFarland, Granville and Dameshek have published five cases of lymphoma; the subjects were treated with high doses of nitrogen mustard followed by infusion of their own marrow. Two of the patients died from infection, but the remaining three had a transitory remission after the usual phase of marrow aplasia.

The use of the marrow autograft has the advantage of causing no immunologic reaction, and, because of this, it becomes unnecessary that irradiation attain lethal doses or that the number of injected cells be very large. These is also no possibility that a secondary syndrome will develop. However, the autograft has two disadvantages: (a) it has no antileukemic effect, and it is known that, in animals, irradiation at lethal doses is not generally sufficient to “cure” a leukemic subject; (b) it seems reasonable to believe that the marrow of a case of acute leukemia in remission, even if it looks entirely normal, still contains leukemic cells (or “factors”) which are then reinjected after the irradiation.

Total-body irradiation followed by the infusion of isologous bone marrow has been utilized in identical twins, one of which was afflicted with leukemia. Atkinson et al. have obtained complete disappearance of leukemic cells with subsequent repopulation of the hematopoietic tissues by normal cells in a twin with leukemia in relapse, following irradiation at 225 r followed by the intravenous administration of his brother's marrow. However, the remission lasted only seven weeks. Thomas, Lochte, Cannon, Sahler and Ferrebee have treated in the same way two patients. Both had a rapid restoration to normal of their marrow and peripheral blood, but the remission lasted only 60 days in the patient who had received 1150 r, and 42 days in the one who had been irradiated with 850 r (midplane air dose).

This method has the great advantage of not causing any immunologic reaction, but its practical value is small because identical twins are found only rarely among humans. The patients of Thomas et al. demonstrate that irradiation only, even at a lethal dose, cannot “eradicate” human acute leukemia.

*These two patients were treated at a time when their disease was quite active. The results might have been different had the treatment taken place during a remission, at which time the number of abnormal cells is very small.
It thus seems reasonable to think that irradiation followed by infusion of homologous hematopoietic cells deserves at the present time more attention than some other methods for the treatment of leukemia: (a) because it is the only transplantation procedure that usually can be done; (b) because the animal experiments suggest that this kind of graft adds to the effect of radiation an immunologic action. Since, in certain mouse leukemias, this immunologic effect seems to take place only when the number of leukemic cells is small, we believe that the patients should be treated during a phase of remission.

The two patients previously referred to and who had been treated according to these principles had a complete remission for six and five months, respectively. But only repeated attempts will enable one to assess the value of homograft therapy.

Many experiments will be necessary to solve the numerous problems that still remain: (a) as far as radiation is concerned, the sensitivity of the different human leukemias and related diseases, according to the kind of cell involved, to the degree of hyperplasia, to the moment at which the patient is seen, to the modalities of irradiation utilized, etc.; (b) as far as immunology is concerned, the relationships between the antileukemic effect of the graft, the type of cells involved, the relationships between donors and patients, the secondary syndrome, its influence on the pre-existing disease, its pathologic physiology, the ways that should be taken to master its manifestations therapeutically, etc.

SUMMARY

A brief summary has been given of the present knowledge concerning transfusion of hematopoietic cells in laboratory animals and also in man.

A survey has been made of the possible application of grafts of hematopoietic cells in the "preventive" treatment of experimental leukemia with emphasis on irradiation-induced and spontaneous leukemias.

Numerous articles have been devoted to describing attempts at curing experimental leukemias, especially the transplantable varieties, by irradiation followed by transfusion of hematopoietic cells. The results vary from one leukemia to the other. Most authors admit the rarity of eradicating leukemia by irradiation with lethal or supralethal doses followed by transfusion of isologous hematopoietic cells. It has been shown that eradication can eventually be obtained when irradiation is followed by transfusion of homologous hematopoietic cells. This, most probably, is due to an immune reaction of those cells against the leukemic cells. Furthermore, even when the leukemia can be eradicated, the animals usually die from the secondary syndrome.

A detailed analysis is given of the reported literature dealing with attempts at treating human leukemia by irradiation followed by transfusion of autologous, isologous or homologous bone marrow.

*This is a fourth remission; the previous one has lasted only 26 days.
†This is a second remission which, before this therapeutic essay, was incomplete (with 20 p. 100 of lymphoblasts in bone marrow).
SUMMARIO IN INTERLINGUA

Es presentate un breve summario del presente cognoscentias in re le transfusion de cellulas hematopoietic in animales laboratorial e etiam in humanos.

Esseva examinate le possibile application de graffage de cellulas hematopoietic al tractamento “preventive” de leucemia experimental con emphase super le leucemias spontanee e illos inducite per irradiation.

Numerose articulos ha essite dedicate al description de tentativas de curar leucemias experimental—specialmente leucemias del varietates transplantabile—per medio de irradiation sequite per transfusion de cellulas hematopoietic. Le resultatos es variabile secundo le typo de leucemia tractate. Le majoritate del autores admitte le raritate del eradication de leucemia per medio de irradiation con dosages letal o supraletal sequite per transfusion de isologe cellulas hematopoietic. Isto es le plus probablemente debite a un reaction immun de iste cellulas contra le cellulas leucemic. In plus, mesmo quando le leucemia pote esser eradicate, le animales generalmente mon plus tarde ab le syndrome secundari.

Es presentate un analyse detaliate del litteratura concernente tentativas de tractar leucemia human per medio de irradiation sequite per transfusion de autologe, isologe, o homologe medulla ossee.

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In the years 1951-1957 86 cases of Hodgkin's disease were studied, including 34 women and 52 men. The average age was 35 years. In 52 patients the diagnosis was established by lymph node biopsy. Osseous lesions may arise by: (1) simultaneous infiltration in the reticular system of the marrow; (2) direct invasion from diseased lymph nodes to the periosteum and bone; (3) Lymphatic and blood-borne metastases. The lesions were most commonly by direct invasion. Of 86 patients, osseous lesions were found in 22. The radiologic picture is not pathognomonic: it may appear in the form of osteoporosis, osteolysis, osteosclerosis, and sometimes in the form of subperiosteal infiltrations. Usually the picture was mixed. The most frequent localization of lesions in the skeleton was as follows: spine, pelvis, sternum, long bones, ribs.—E. K.


On the basis of a 3 to 5 year observation of 4 patients with myelosclerosis, the following conclusions are drawn. (1) In the course of myelosclerosis symptoms of thrombocytopenic purpura and those associated with granulocytopenia may develop. (2) The deepening of bi- or trisystem cytopenia runs parallel with a growing splenomegaly and with the progress of radiologic lesions in the bones. (3) Myeloid metaplasia in the spleen and myelosclerosis may precede by 3 to 4 years radiologic evidence of osteosclerotic lesions. (4) A course of over 20 years' duration in 1 case indicates a prognosis different from that of leukemia.—E. K.

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