The Significance of Chromosomal Aberrations in Indium-111-Labeled Lymphocytes

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The technique for labeling isolated blood cells with lipophilic chelates of indium-111 is now widely used experimentally and clinically to follow noninvasively cell kinetics and their localization in the body (*1–10*). Indium-111, a commercially available, cyclotron-produced radionuclide, has a half-life of 67 hours and decays to stable cadmium with emission of two gamma photons: at 173 keV (89%) and 247 keV (94%). The half-life is long enough to permit monitoring of cell migration, but short enough to avoid long-term residual radiation. The two gamma photons are detected efficiently by gamma camera, so that not more than 500 μCi of In-111 need to be injected into a patient. Generally 10 billion platelets or 100 million leukocytes (containing 70–80 million neutrophils and 20–30 million lymphocytes) are used. Within the labeled cells, most of the In-111 binds irreversibly to cytoplasmic or nuclear components (*11,12*).

Indium-111 emits Auger electrons ranging in energy between 0.6 to 25.4 keV and having a short tissue-penetration range between 0.025 to 12.55 μm (*13*). When 100 million lymphocytes are uniformly labeled with 20 μCi of In-111, each lymphocyte receives, on average, ~2600 atoms of radioactive indium. Waters and Silvester have calculated that the radiation dose to a neutrophil, resulting from the decay of a single In-111 atom, is 0.135 rad (*13*). Ignoring the size differences between the neutrophil and lymphocyte, lymphocytes would then receive (2600 × 0.135) or 350 rad for a 20-μCi dose to 100 million cells. At higher radioactive concentrations this dose would increase proportionately. Therefore, when 100 million leukocytes, accompanied by 20–30 million lymphocytes, are labeled with 500 μCi, the In-111 lymphocytes should receive 8750 rad. If the intercellular or intracellular distribution of the radionuclide is not uniform, then the radiation dose per lymphocyte would be even higher.

Lymphocytes are more susceptible to radiation damage than any other circulating blood cells. Unique in morphology, lymphocytes are heterogeneous and have been separated functionally into a spectrum of subpopulations. With a life span of a few days to years, lymphocytes play many critical roles in the immune system. Differentiated lymphocytes carry immunologic memory sometimes for many years. Some lymphocytes have the capacity to circulate and recirculate, reentering the blood many times through the lymphatic system. Upon interaction with specific antigens, they undergo transformation or blastogenesis (*14*), dividing into more cells with the same specific function, including replication of DNA.

Recently much attention has been drawn to the possible consequences of radiation damage to lymphocytes. ten Berg et al. reported increased chromatid and chromosomal aberrations in lymphocytes separated from two human donors and labeled with In-111 oxine (*15*). Without added radioactivity, 3% and 14% of unlabeled cells were abnormal. At a concentration of 30 μCi In-111 per 100 million lymphocytes, 54% of cells were abnormal. At 80–90 μCi per 100 million cells, 90–92% were abnormal, equivalent to the changes produced by 200 rad of x-radiation (*16*). At 300 μCi per 100 million cells, all lymphocytes were abnormal. Since this publication, some investigators have raised ethical questions about the use of In-111-labeled cells beyond animal research (*15*), whereas others are not concerned, and many have continued their clinical studies (*17*). To assess the risks involved, we will attempt to summarize the pertinent facts about the chromosomal aberrations and oncogenic potential of irradiated lymphocytes.

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CHROMOSOME ABERRATIONS AND THEIR ETIOLOGY

Chromosomes are long strands of deoxyribonucleic acid (DNA) in a double-stranded helical configuration (*18*). Each human lymphocyte has 46 chromosomes in 23 pairs. Each chromosome contains about 100,000 genes, and each gene about 1000 nucleotides (*19*). Chromosomes, with their large molecular structure, undergo complex reactions during their duplication, segregation, and differentiation (*19*). Their structure can be altered by many physical and chemical reactions.

Two types of chromosomal abnormalities are described: (a) chromosomal breakage, and (b) changes in chromosome number. Both of these cause genetic disturbances in the cell. Agents that cause chromosomal breaks are "clastogens" and those causing numerical changes are "mitotic poisons" (*20*).

There are four types of alterations due to chromosome breaks: fragments, minutes, rings, and dicentrics (*21*). Fragments result from simple breaks across the chromosome, while minutes are usually produced from two breaks close together. Rings are the result of exchange between two breaks on the chromosome. Dicentrics result from an exchange between two broken chromosomes, yielding a chromosome with two centromeres and an acentric fragment. The first three kinds of aberrations involve changes within a single chromosome and result in the loss of a chromosome fragment at mitosis. If the loss is large, it will be lethal. If the loss is small, however, the cell may be viable and transmit the deficiency to the daughter cell. Dicentric aberrations, involving two chromosomes, are usually lethal. Since DNA dominates the growth and differentiation of the cell, alterations in DNA strands may be serious and can lead to mutations or oncogenesis.

"Spontaneous" aberrations have been found in all normal populations, the incidence varying with age, geographic location, and smoking habits (*22*). In general populations, dicentric aberrations increase linearly with age (about 17/100,000 cells per decade) and the incidence at age 50 is about 140/100,000 cells (*23*). In one report, out of 57 "normal" individuals, 33 (57.8%) showed some type of aberration (*24*).

Lubs and Samuelson (*25*) studied 3,720 lymphocyte metaphases from ten normal adults and found 1–20% of cells with one or more breaks. Nichols et al. observed 10% to 20% chromosome breaks in four of 11 control cultures (*26*). Littlefield and Goh (*27*) recently completed a cytogenetic analysis of 11,950 lymphocyte metaphases in 122 cultures from ten control men, and 17,759 lymphocyte metaphases in 183 cultures from 21 women living in New Haven, Conn. They observed in 5.6% metaphases from men and in 6.5% metaphases from women at least one chromosomal aberration.

Many therapeutic agents and diagnostic procedures induce chromosomal aberrations. These include chemotherapeutic drugs, x-rays, and radiation therapy (*28*). The frequency of chromosomal aberrations in peripheral-blood lymphocytes has proven useful in assessing the magnitude of accidental exposure to whole-body radiation (*29*). In patients undergoing angiography, receiving an average absorbed dose of about 50 rad, significant changes in chromosomes and micronuclei have been detected in lymphocytes compared before and after the radiation exposure (*30*). In vitro exposure of lymphocytes to angiographic contrast media for 30 min without any radiation exposure also induced such changes.

Clastogenic effects (chromosomal breaks) are produced by numerous other chemicals. The industrial toxicants have entered into our ecological system through the air, water supply, beverages, and food. They include food additives, pesticides, plastics, suspensions, dusts, and aerosols. Air toxicants have been added by way of fossil fuels for home heating, energy generation, airplanes, and motor vehicles, as well as through pollutants from manufacturing, mining, smelting, and refining. Increasing air concentrations of sulfur oxides, nitrogen oxides, hydrocarbons, and depletion of ozone in minute quantities have induced marked chromosomal aberrations (*31*). In the United States alone, more than 900 different pesticides are used in thousands of mixtures and in ton quantities. They and their degradation products are disseminated from their reservoirs and subsequently into atmosphere. Polycarbonated biphenyls (PCBs), 2,2-bis-(*p*-chlorphenyl)-1,1,1-trichloroethane (DDT), and 2,2-dichlorovinyldimethylphosphate (DDVP), all contaminate our air and cause extensive chromosome aberrations (*31*).

Relatively excessive quantities of certain metal ions such as platnium^{2+}, nickel^{2+}, and recently cadmium^{2+} (>114.2 $\mu g/10^5$ cells/ml) also have been shown to be mutagenic to mammalian cells in culture. These effects have been shown to be associated with single-strand scission of DNA (*32*).

RELATION OF CHROMOSOMAL ABERRATIONS AND ONCOGENESIS

Notwithstanding the existence of chromosomal abnormalities in unirradiated "normal" individuals, radiation increases both the number of these abnormalities in blood cells and other tissues, and the incidence of malignancies. The former may be regarded as a "biological dosimeter" for the latter. Chromosome translocations can be caused by radiation, and similar translocations are found in certain malignancies, particularly in Burkitt's lymphoma. There is no evidence, however, that the increased incidence of chromosomal abnormalities in blood cells is anything more than a "biological dosimeter."

A large proportion of the radiation damage to chromosomes is repaired spontaneously within 30 to 90 min

(*33*). Nevertheless, some chromosomal aberrations may persist for many years. For example, one group of spondylitic patients who had received 1500 rad of partial-body irradiation (whole spine and sacroiliac joints) was followed for 20 yr by Buckton et al. (*34*). The cytogenetic changes in blood lymphocytes persisted during the entire period, but with progressively decreasing frequency. The cytogenetic damage was probably induced in the stem cells of the irradiated marrow. These authors considered the relation between the cell damage and increased frequency of malignancies an enigma (*34*).

Early investigators of human chromosomes thought that aberrations were initiating events of the neoplastic process (*35*). Recently, however, Levan concluded that most chromosomal disturbances do not lead to cancer (*35–36*). Nowell believed that it was impossible to identify which individuals will eventually develop leukemia on the basis of chromosomal abnormalities (*37*). Furthermore, he regarded aberrations in a single analysis as insufficient evidence that an individual is at risk. Finally he considered chromosomal aberrations produced by radiation, viruses, or chemicals as relatively crude indicators of genetic and carcinogenic consequences. Of course, no aberrant chromosomes are desirable, but their incidence is ubiquitous.

In-111 LYMPHOCYTES AND ONCOGENESIS

In clinical studies with In-111 mixed-leukocyte suspensions, generally a maximum of about 30 million lymphocytes are labeled. When isolated lymphocytes are used, a maximum of 1 billion cells are labeled (*38*). Upon reinjection, the labeled cells are dispersed in an estimated total lymphocyte pool of 1 trillion in an adult human (*39*). Hence the percentages of cells exposed to internal radiation are approximately 0.003% and 0.1%, respectively. Even if all these lymphocytes had abberant chromosomes, these numbers add little to the percentage of abnormal lymphocytes already existing in the body. Nonetheless, some workers believe malignancies may represent the progeny of a single abnormal cell (*40*).

In subjects given In-111-labeled mixed leukocytes for abscess localization, the average cell receives more than 8000 rad, an excessive dose for lymphocyte killing (*41*). From the experiments of Vos, lymph-node cells receiving approximately 6000 rad die immediately (*42*). A review of animal data suggests that blood lymphocytes are somewhat more radioresistant than those of other tissues, and transformed metabolically active cells are more resistant than resting ones (*43*). Some authors have found a "resistant" subpopulation of T lymphocytes, whereas others have not (*44*). Less than 1% of T cells can proliferate in response to alloantigens after 370 rad (*44*). The single-dose D_0 for human blood lymphocytes in different in vitro studies in the literature varies from 50 to 550 rad (*45*). The corresponding D_0 for lymphocytes exposed in vivo from radiation accidents is about 210 rads. In patients undergoing extracorporeal irradiation, the estimated D_0 for blood lymphocytes is 300–380 rad (*43*).

Rannie et al. have pointed out already that the risk of oncogenesis is small even for lymphocytes labeled with In-111 (*5*). Is it possible to give even a crude estimate of this risk? The age-standardized rate of deaths from cancer is about 1665/yr per million of population (*46*). Based on the linear-nonthreshold hypothesis, the excess fatal cancers from low-LET radiation averaged over a period of 28 yr is about 5.8 per million of population per rad/yr, as derived from follow-up studies of Japanese A-bomb survivors (*47*). The absolute risk of fatal leukemia in the population is averaged at 1.72 per million/yr/rad kerma (*48*). The incidence of excess lymphoma is about 47%, and excess multiple myeloma is about 11% of the excess leukemia incidence. The latent interval before radiogenic lymphoma and multiple myeloma become apparent is 20 yr or more (*49*). Assuming that the risk of radiogenic leukemia is about 1.0 per million population/yr/rad (absorbed dose), the excess risk of all hematological malignancies should be about 1.6. Over a remaining lifetime period of 30 yr, the risk becomes 48 per million population/rad.

If oncogenesis is directly related to the incidence of chromosomal abnormalities in lymphocytes, the excess risk of lymphoid malignancy from In-111 should be similar to that of the x-ray dose producing equivalent chromosomal abnormalities. From the data of ten Berge (*15*), 90 μCi In-111 per 100 million lymphocytes produce chromosomal damage with the same frequency as 200 rad of x-radiation—i.e., about 90% abnormal cells (*16*). For this dose of x-radiation to total body, the excess risk of hematological malignancy during a 30-yr lifetime should be 9600/million population. In keeping with the hypothesis that somatic mutation is the initial step in radiation-induced malignant transformation, the number of cells irradiated is as important as the radiation dose (*50*). When only 100 million cells (=0.01% of the total body lymphocytes) are labeled with 100 μCi of In-111, the equivalent excess risk of fatal hematological malignancy over 30 yr should be 0.01% of 9600/million, or about one per million population.

The available data on oncogenetic effects of ionizing radiation in man were obtained from irradiation of the total body, or relatively large areas of the body. It is generally assumed that leukemogenesis originates from the stem cells of the marrow rather than from peripheral leukocytes (*50*). The induced leukemia may be acute or chronic myelogenous or monocytic; on the other hand, no increase in chronic lymphocytic leukemia has been demonstrated in any irradiated human population (*50*).

One report indicates that the liver and spleen both receive about 20% of the In-111 at 24 hr after the ad-

ministration of labeled leukocytes (*51*). In addition, some In-111 radioactivity from labeled leukocytes localizes in the erythropoietic marrow. From quantitative whole-body scans at 3 and 24 hr, about 20% of the administered activity is located in the spleen, 20% in the liver, and 20% in the marrow (unpublished data, Fueger GF and Nicoletti R). This estimate of marrow concentration is higher than in previous reports (*52*), and would result in a diffuse marrow radiation dose of 0.95 rad/500 μCi (calculated from MIRD "S" factors). Using the same distribution data, lymphocytes with a long residence time in the spleen would receive 9.0 rad/500 μCi, and those in the liver 1.5 rads/500 μCi. To assess the possible consequences of this diffuse radiation dose to marrow and blood organs, one should recall the results of long-term follow-up studies of radioiodine therapy in hyperthyroid patients. The marrow dose from I-131 in 802 patients treated to achieve euthyroidism averaged 13 rad, and the blood dose, 16.6 rad (*53*). Several follow-up studies of such patients have not detected an increased incidence of leukemia. For example, Pochin found 18 cases of leukemia compared with an expected incidence of 12 to 28 in 59,200 patients (*54*).

ten Berge et al. showed that some labeled lymphocytes with damaged chromosomes were capable of proliferating after stimulation in vitro (*15*). After a labeling dose of 150 μCi In-111 per 100 million lymphocytes, 93% of cells had chromosomal aberrations, but their proliferative capacity in cultures was reduced only 50%. Obviously, proliferation of lymphocytes in vitro could not be equated to malignant transformation in vivo. What would be the fate of such irradiated cells in vivo? From extracorporeal shunt irradiation of blood before renal transplantation, a high incidence of chromosomal aberrations was demonstrated in PHA-stimulated cultures with doses of 300–380 rad (*43*). In this situation, most of the radiation dose to the cells was delivered instantaneously during their initial transit through the shunt. Some cells were immediately killed in interphase and about half failed to undergo mitosis. Kinetics of the irradiated circulating cells, based on the chromosomal aberrations as marker, showed a mean residence time in the blood of only 2 min. Because of this rapid removal, the aberration yield per lymphocyte was unchanged compared with the yield before irradiation. No lymphopenia was induced, so that the damaged cells must have been replaced rapidly by normal lymphocyte turnover. These findings were confirmed in a subsequent study of irradiated human lymphocytes obtained by thoracic-duct cannulation (*55*). Chromium-51-irradiated cells localized rapidly in the reticuloendothelial organs.

CONCLUSIONS

One alternative for the future is the development of new agents that label only the cell membrane or cytoplasm of the lymphocyte, thereby reducing the particulate radiation to the cell nucleus.

In the meantime, we agree with ten Berge et al. that more studies are needed on the fate of irradiated peripheral-blood lymphocytes. However, the data now available indicate that:

1. Chromosome damage does result from the labeling of lymphocytes with radionuclides.
2. Although a fraction of irradiated peripheral-blood lymphocytes are capable of proliferating in vitro, their mean survival time in circulation is extremely short.
3. With the administration of labeled lymphocytes, the increased burden of chromosomal aberration is relatively small compared with that induced by other environmental causes.
4. The risk of lymphoid malignancy due to different types of chromosome damage appears to be small, and is acceptable.
5. For short-term migration studies, pure lymphocytes should be labeled with no more than 100 μCi of In-111 per 100 million cells.
6. Lymphocytes incidentally labeled with In-111 in mixed leukocyte preparations for abscess localization are killed by the radiation and pose no long-term risk.
7. The information to date indicates that studies with In-111-labeled blood cells need not be suspended.

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