

Re: Labeling with Indium-111 Has Detrimental Effects on Human Lymphocytes

I have read with great concern the recent article by ten Berge et al. (1) about their hypothesis in the last paragraph: "Thus, one could envisage a possibility that, by infusing In-111-labeled lymphocytes, a transformed cell is introduced that, after proliferation, may cause a malignant process. Moreover, similar hazards may occur when, for the detection of abscesses in patients, In-111-labeled granulocyte suspensions are infused, because such suspensions may still contain up to 20% of lymphocytes. Further studies are required to establish the viability and oncogenic potential of the lymphocytes contaminating such cell suspensions."

The Editor has apparently appreciated the significance of these statements by having Dr. Watson prepare a teaching editorial on the subject in the same volume (2), but Watson's article merely summarizes the history of the issue without really coming to grips with the issue itself. The ramifications of such statements, if true, are of serious concern to the nuclear medicine community because of uncertainty among the physicians concerned and because of potential sensationalism by the press. None of us would like to read "Your Doctor is Giving You Cancer" in the morning paper. There should have been a stronger effort on the part of the *Journal* to investigate further the statements of ten Berge et al. For these reasons I think it essential to consider this hypothesis in greater detail, especially since I believe that there is existing evidence to support the conclusion that this alarming possibility is, in fact, quite unlikely.

First, let us consider whether a human population exists in which a small percentage of mature lymphocytes received a large radiation exposure whereas the bone marrow (stem cells) received very little (as in our In-111 WBC patients), and for whom leukemia statistics are available. We are in luck. Consider the population of over 36,000 hyperthyroid patients included in the Cooperative Thyrotoxicosis Follow-Up Study (3). This study was designed to detect increased incidence of leukemia in patients treated with I-131 for their hyperthyroidism; the controls were hyperthyroid patients treated with surgery. The findings included "an age-adjusted leukemia incidence rate per 100,000 patient-years of 11 in the I-131-treated patients and 14 in patients treated by thyroidectomy. There is no evidence of an increased risk of leukemia in this population after total-body doses of 13 to 14 rads." But what about the lymphocytes in the thyroid gland? They must have received thousands of rads, as they were close to the thyroid cells. In Graves' disease, according to Robbins (4), "The interacinic stroma demonstrates a striking increase in the amount of lymphoid tissue and, in some areas, large lymphoid follicles are produced." Surely there must have been many complex cytogenetic abnormalities induced in these lymphocytes, yet we do not see an increased leukemia rate.

Second, let us consider the question of whether complex cytogenetic abnormalities in mature, circulating lymphocytes per se are indicators of increased risk of leukemogenesis and lymphomagenesis. After all, there is abundant evidence that human malignancy has a chromosomal basis (5), so this is a reasonable question. Data obtained by the Atomic Bomb Casualty Commission (6) (now R.E.R.F.) showed that among persons 30 yr old or younger at the time of the blast who received a dose of at least 200 rad, 34% had complex cytogenetic abnormalities in cultured lymphocytes 20 yr later (compared with 1% for controls). Among those over 30 yr old at the time of the blast who received at least 200 rad, 61% had abnormalities (compared with 16% for controls). Atomic-bomb survivors of all ages from both cities with T65 doses below 10 rads died of leukemia at a rate of 4.4 per 100,000 per year during 1950-1972, whereas for those exposed to 100 rad or more the rate was 51.2 (7). It is tempting to assume that the cytogenetic

abnormalities observed may be responsible for the leukemias noted. However, this is not necessarily so. The atomic-bomb survivors suffered *total-body irradiation, which included hemopoietic stem cells in the bone marrow*. In light of present knowledge, it is almost certain that the leukemias arose from radiation damage to stem cells (5), and that abnormalities seen in circulating lymphocytes are simply "flags" to alert one to the fact that stem cells were damaged as well. Mature lymphocytes may circulate without dividing for a decade or more (8); it is probable that most of the abnormal cells had been circulating without division since the bomb, as many that are forced to divide (e.g., with phytohemagglutinin) die due to severe chromosomal imbalances after mitosis. To quote Yunis (5), "The general finding of shared chromosomal defects among certain leukemias and lymphomas implies that primary chromosomal defects in neoplasias affect stem cells and that the number of sequences initiating the common human neoplasias may be small." When we label mature, circulating lymphocytes with In-111 oxine, we may well expect to find significant cytogenetic abnormalities in these cells when we force them to divide, *but we are not labeling the stem cells*, which receive only low-dose irradiation. This is probably why we do not see increased leukemogenesis in the I-131 thyroid patients; the hemopoietic stem cells receive relatively low levels of radiation.

In conclusion, I think it safe to assume that if there is any increased risk of leukemia or lymphoma from administration of lymphocytes tagged with In-111, this risk is exceedingly small and therefore not important. I will not suggest a "megaperson-megabuck research project" to measure it, since it would probably be of questionable value (9). However, if one wishes to settle the issue firmly, a relatively practical experiment is possible. Cytogenetic abnormalities in cultured lymphocytes may be scored in patients with Graves' disease before (let's not forget toxicity from PTU and tapazole), shortly after, and several years after receiving I-131 therapy. Since we know they have no significant leukemia risk, we will be able to assess the significance of any cytogenetic abnormalities with reasonable confidence.

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