



## Organs and Tissues

Lymphocytes are found in the lymphatic and blood vessels, the lymphoid tissue, and scattered throughout extravascular tissues of the body. They recycle from the blood into the lymph having a life span of between eight and twenty-four hours.

In some cases, leukemic cells pour from the tissue into the blood as found in exponential leukocytosis of acute leukemia. Leukemic cells can also be found extravascularly in varying numbers while other types of leukemia primarily involve bone marrow. Here there is slower exchange between the bone marrow and the blood. Other abnormal conditions observed are variations in migratory patterns, life span, and their ability to set up sites of proliferation at extravascular sites within the body.

There are two principal methods of deleting the body of normal and/or leukemic leukocytes. They are (1) extracorporeal irradiation of blood, ECIB and (2) extracorporeal irradiation of lymph, ECIL. In ECIL, the thoracic duct lymph is diverted through the irradiator.

To understand the validity of this approach, it is necessary to look at the law of cell radiosensitivity postulated by Bergonie and Tribondeau and to investigate cells relative to their degree of sensitivity.

In 1906, Bergonie and Tribondeau stated that "The radiosensitivity of a tissue is directly proportional to its reproductive capacity and inversely proportional to its degree of differentiation." This means that cells that undergo mitosis very often and have a fairly long mitotic process (prophase to telophase) are very sensitive as are those cells that are functionally primitive.

If we list cells in order of their sensitivity, starting with the most resistant and ending with the most sensitive (least resistant), the following would be apropos.

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|-----------------------------|-------------------------|
| 1. <i>Nerve</i>             | 7. <i>Bile Duct</i>     |
| 2. <i>Bone</i>              | 8. <i>Alveolar</i>      |
| 3. <i>Muscle</i>            | 9. <i>Basal</i>         |
| 4. <i>Connective Tissue</i> | 10. <i>Granulocytes</i> |
| 5. <i>Endothelial</i>       | 11. <i>Lymphocytes</i>  |
| 6. <i>Kidney Tubule</i>     |                         |

Theoretical success of this procedure is evident from the above listing. How do these irradiators work? When using the ECIB, the cells within the blood stream accumulate a radiation dose by making one or more trips through the irradiator. A lethal dose to the cells disintegrates the cell or causes them to be phagocytized or sequestered. The aim is to deliver a lethal dose to the lymphocytes or leukemic cells in a single trip through the irradiator but because of limitations in irradiator design multiple trips are usually necessary.

The objective of the ECIL is to provide a fatal dose to lymphocytes during their irradiator transit time. The ECIL depletes the cells that cycle through the thoracic duct or those newly produced cells from the lymphatic tissue which are drained by the thoracic duct.

If we compare the ECIB and the ECIL, we find in the ECIB that a fraction of all lymphocytes are irradiated and killed. In the ECIL, however, only those cells that enter the thoracic duct are killed. It is not known whether the lymphocytes of the thoracic duct are a random sample of those within the blood.

In the experiments performed by Schiffer and his colleagues, two types of irradiators were used. The animal irradiator (ECIL) contained 1,000 curies of cobalt-60 and had varying lengths of circulating coils which permitted variable irradiation times or transit doses. The human irradiator (ECIB) contained 4,000 curies of cesium-137 and the transit dose was varied by changing the rate of blood flow. The transit dose, as defined by Schiffer, is the radiation dose received by one segment of blood or lymph during one circuit past the irradiation source.

Schiffer, in his experiments, used two types of shunts. Arteriovenous and thoracic duct-venous both made of Teflon and silastic connected to a coil of silastic in the irradiator.

Pumps were not needed for the ECIB nor were anticoagulants used except for those patients having a high platelet count. The ECIL, however, did need a pump and continuous anticoagulation of lymph reservoirs using heparin.

The irradiation time for the ECIB was four (4) hours per day with daily or intermittent irradiation. The transit dose delivered by this irradiator was determined to be approximately 500 rads.

Some complications observed while using the ECIB were minor infections, clotting of shunts, postoperative bleeding in thrombocytopenic patients and mild hemolysis. In leukemic patients, it was found that an increased number of transfusions were required. Patients with renal disease sometimes exhibited a decrease in hemoglobin and an increase in reticulocyte count.

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1. Parts of this presentation were abstracted from Brookhaven National Laboratory Report Number 9726, "Application of Extracorporeal Irradiation of Blood and Lymph in Leukemia and Monotransplantation." Schiffer, L. M. et al.