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EXTRACORPOREAL IRRADIATION OF THE BLOOD AND LYMPH: EXPERIMENTAL STUDIES ON HOMOTRANSPLANTATION AND HUMAN LEUKEMIA

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DISCLAIMER

The studies to be described are truly international in character. The work has been done at the Medical Research Center, Brookhaven National Laboratory, Upton, Long Island, New York, with participants from West Germany, Switzerland, South Africa, India, and Belgium.

Before trying to describe the procedures and objectives it is necessary to review briefly various aspects of lymphocyte behaviour. Lymphocytes are conveniently divided into various sizes and types on the basis of staining characteristics. The larger lymphocytes tend to be quite short-lived, a matter of hours to a few days, and the smaller lymphocytes may have very long life spans, even in excess of a year. It is now well established that there is a fraction of the blood lymphocytes that recycle from the blood to the lymph via the post-capillary venules of the lymph nodes. These cells actually migrate directly through the endothelium of the post-capillary venule rather than between the cells. It has now been conclusively demonstrated that the direction of the migration is from the blood to the lymph and not the reverse direction. When one looks at the size distribution by direct volume measurements of the cells in the cannulated thoracic duct, one sees two clear-cut populations of cells. The larger population measures from roughly 120 cubic microns to about 348 cubic microns. The larger cells constitute about 10 % of the lymph and range from 348 cubic microns to nearly 1600 cubic microns. The smaller class of cells are further sub-divided into those that have a non-basophilic cytoplasm and tend to be longer-lived with a longer generation time, and those with an intensely basophilic cytoplasm that appear to be shorter-lived with a very short generation time. With this general background one is prepared to consider the principles involved in extracorporeal irradiation of the blood or lymph.

Extracorporeal irradiation of the blood is a technique which enables one to divert a fraction of the cardiac output through an irradiation field and thus destroy the radiosensitive lymphocytes. In practice, a cannula is placed in the carotid artery which diverts the flow of blood into the jugular vein. The cannula has a coupling on it that enables one to hook the flowing blood up to the irradiator at will. The operative procedures and handling of the animals for extracorporeal irradiation of the blood will be

shown in a motion picture. Irradiation of the blood in this manner progressively depletes the blood of lymphocytes. Within a few hours of treatment, the blood lymphocytes fall from roughly 6000 per mm^3 to as low as 100 per mm^3.

48 hours of continuous irradiation of the blood results in a marked depletion of lymphocytes in the cuff surrounding the germinal centers of the spleen, and a diminution in the thickness of the cortical densely packed small lymphocytes of lymph nodes. In addition, a striking diminution in the thickness of the cortex of the thymus is observed. One sees considerable nuclear débris in the lungs, lymph nodes and spleen.

Intermittent repetitive irradiation of the blood for a few hours daily will attain equal degrees of depletion and maintain this as long as the irradiation is continued. When the body is depleted of lymphocytes in this manner and the depletion is continued, skin homograft acceptance is prolonged two to three times the normal acceptance.

One can cannulate the thoracic duct and continuously divert the lymph either through a continuous flow centrifuge or an irradiator, and deplete the animal of lymphocytes. When this is done, there is a very rapid fall of the output of the lymphocytes that are smaller than 312 cubic micra. After 5 days this fall continues at a much slower rate for as long as the studies have been carried out. In contrast, the cells larger than 312 cubic micra fall to about half the normal output and then remain relatively constant in their output for the duration of the study. Depletion of the animals in this manner also increases the acceptance time of skin grafts on the anterior part of the body that are not drained by the thoracic duct. Skin grafts on the posterior part of the body are exclusively drained through the afferent lymphatics to the regional lymph nodes, and thence through the thoracic duct. The anatomical interception of the activated lymphocytes from the regional lymph nodes strikingly prolongs the acceptance of the grafts as long as the lymph is irradiated and the activated small lymphocytes are destroyed. Thus it has been demonstrated that the immunologically competent lymphocytes go from the lymphoreticular tissues into the blood to the foreign tissue and there interact with the tissue. Thence there is an obligatory exit from the skin graft via the lymphatics to the afferent entrance to the lymph node. Here the cells undergo transformation and proliferation into immunologically activated small lymphocytes that proceed from the lymph

node only through the afferent lymphatics and into the blood. The interception of these lymphocytes in the thoracic duct and their destruction by irradiation prevents the rejection of the foreign skin for prolonged periods of time.

The procedure of extracorporeal irradiation of the blood has been adapted for use in human beings by utilizing the Teflon-Silastic rubber arterial-venous shunts that have been used so successfully for extracorporeal renal hemodialysis.

To date we have treated acute myelocytic, chronic granulocytic and chronic lymphocytic leukemia. Every case of acute leukemia has shown a drop in the peripheral blood count. Some patients have survived for over a year with treatment by extracorporeal irradiation of the blood only. It appears in some cases that individuals become susceptible once again to chemotherapy after treatment with extracorporeal irradiation of the blood. In addition, one patient who was pregnant at the time of diagnosis, was carried through pregnancy and a few months post-pregnancy by extracorporeal irradiation of the blood before treatment with chemicals.

In chronic granulocytic leukemia, each case has shown a substantial drop in the concentration of cells in the peripheral blood with a diminution in the size of the spleen in some patients. The partial remission has been short-lived.

Chronic lymphocytic leukemia presents an interesting situation. There are some patients who respond dramatically and others in whom there is practically no response. Several patients have had a marked decrease in the size of lymph nodes, lesser decrease in the spleen and marked decreases in the concentration of cells in the peripheral blood, and at times followed by an increase in platelets and a cessation of requirements for blood transfusions.

It appears to be established now that extracorporeal irradiation of the blood has a distinct role in the treatment of selected cases of leukemia, particularly when leukemia occurs during pregnancy, and in certain cases of chronic lymphocytic leukemia.