• Development of Blood Irradiators

Extracorporeal irradiation of blood, using repeated brief exposures, has been shown to suppress rejection of tissue transplants and to inhibit progression of chronic lymphocytic leukemia. This project is designed to study the basic processes by which blood irradiation produces such effects, to establish the conditions of dose administration which optimize therapeutic effect, to improve the techniques of blood irradiation through the development of improved and portable blood irradiators, and to move this technique toward clinical applications.

BLOOD IRRADIATOR MEDICAL APPLICATIONS

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A portable blood irradiator, consisting of a vitreous carbon body and thulium-170 radiation source, was attached to dogs via a carotid-jugular shunt, and its effects on the immune system measured. The device has demonstrated both significant suppression of circulating lymphocytes and prolonged retention of skin allografts. The units used on dogs have had limited success because of difficulties in protecting the shunt tubing from the animal's natural efforts to scratch and bite the device. This year's effort was devoted largely to improving the supportive hardware.

Previously, we produced a portable blood irradiator for potential clinical use in treating leukemia and in controlling immune reactions during organ or tissue transplantation. It consists of nonthrombogenic vitreous carbon containing stable thulium, which becomes the beta radiation source, thulium-170, after neutron activation.

In the present phase of the work we have established methods for maintaining long-term function and assessing the effects of the device in beagle dogs. The carotid artery and jugular vein are the most accessible and useful vessels for establishing a long-term shunt in animals. To minimize the length of tubing, we have placed the irradiator and supportive hardware either under the animal's head or on its back at the level of the shoulder. The shoulder position has the potential advantage of easier access for the investigator and reduced accessibility to the dog. To support the units securely atop the shoulder we used a nylon mesh jacket, designed for dog research by A. Chatham, 5043 Oaknoll Avenue, Los Angeles, CA. The jackets are sized for beagle dogs and can accommodate individual animals by adjusting the lacings.

To limit sideways shifting of the unit, the irradiator was attached to the mesh of the jacket by a series of linen or nylon ties through a thermoplastic strip in the shape of an inverted U. A protective cover of thermoplastic was also attached to the mesh of the jacket in such a way that it could be readily opened for access to the irradiator. The shunt tubing was tunneled beneath the skin on each side to the midlateral portion of the neck, and was protected from that point by the thermoplastic cover over the irradiator.

Despite our attempts to adjust the lacings for a snug fit on the animal, the weight of the shielded irradiator unit (approximately 500 g) gradually shifted it so that, on one side or the other, the shunt became stressed. This produced severe irritation by the Teflon vessel tips on the artery and vein, with consequent loss of shunt flow. None of our attempts to limit this lateral movement were successful. The shoulder position was therefore abandoned in favor of attempts to develop a way of mounting the irradiators under the animal's neck.

Earlier chest-mounted holders had failed to fully protect the shunt tubing

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from damage by the dog, and had offered only limited access for shunt maintenance, i.e., restoration of blood flow and replacement of irradiator units when flow stopped. A new holder was therefore developed using thin-walled aluminum tubing, 5 cm in diameter, to hold the irradiator and protect the shunt in the area where it connects with the irradiator. This tubing was mounted to a semi-rigid unit which wraps around the thoracic cage with holes for the forelimbs. This unit is thermoplastic, and padded around the leg holes with lamb's wool to minimize chafing. We have two of these padded "vests," so that they can be exchanged, washed and dried each week, and ready for use by the following week.

This unit was tested on dog 1305, using an irradiator giving a 27-rad transient dose (assuming a flow of 100 ml/min). The irradiator remained functional throughout the test (30 days), but was periodically removed when flow stopped. At such times, the obstructing thrombi in the vessel tip region were removed by aspiration, the irradiator was cleaned and resterilized with a solution of benzalkonium chloride, followed with a sterile saline rinse, and reinstalled. At no time was there evidence of primary obstruction occurring in the irradiator. The test was terminated at 30 days when skin grafts failed and there was no apparent benefit from further treatment. The shunt was still operational and, after removal, examination of the artery and vein connection to the vessel tips indicated that flow could have been maintained for a substantially longer time.

Results of the test on dog 1305 showed strong suppression of circulating lymphocyte levels, as in previous tests. Allograft rejection could not be evaluated because of early subgraft bleeding, so that little (if any) vascularity was attained in the graft. The same problem prevented autograft adhesion; all skin patches came off at approximately the same time.

The new hardware provided encouragement that further testing with dogs is feasible, with the expectation that shunt patency can be maintained throughout the test period.