diet was accentuated by gonadectomy, attesting to residual testis function in intact protein-depleted rats. Sex accessories of gonadectomized protein-deficient rats responded to the same low levels of estradiol benzoate or testosterone propionate effective in gonadectomized control animals, indicating that sensitivity of these organs to exogenous hormone was unaffected by the diet. A subnormal response of accessory organs to high doses of testosterone was noted, however, in male protein-deficient rats.

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Effect of Allogeneic Bone Marrow on Lethally Irradiated Thymectomized Mice.* (30449)

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Allogeneic adult bone marrow has long been shown capable of inducing graft-*versus*-host reactions in irradiated mice(1,2). Recently, Miller and others(3,4,5,6) have shown that the complete recovery of immunologic competence by lethally irradiated mice seeded with syngeneic marrow depends on the presence of the adult thymus. This implies that the action of the host thymus is necessary for development of immunologic competence in the donor marrow. The absence of the thymus might then be expected to preclude development of a graft-*versus*-host reaction in allogeneic radiation chimeras. The present studies were designed to test this hypothesis.

Materials and methods. The experimental design is outlined in Fig. 1. CBA/JAX‡ male mice, 7-8 weeks old, were divided into 5 groups of 18-22 animals each. The animals of 2 of the groups were thymectomized and of 2 others, sham-thymectomized. The fifth group served as an unoperated control. One week after operation, all the animals were lethally irradiated with a dose of 850 R at 50 R/min. The X-ray facilities consisted of a cross-fire arrangement of 2 tubes run at 184 kvp, 30 ma; filtration 0.28 mm Cu and 0.50 mm Al; target distance 72 cm from each tube. The animals were irradiated in

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‡ All mice were obtained from Jackson Memorial Laboratories, Bar Harbor, Maine.

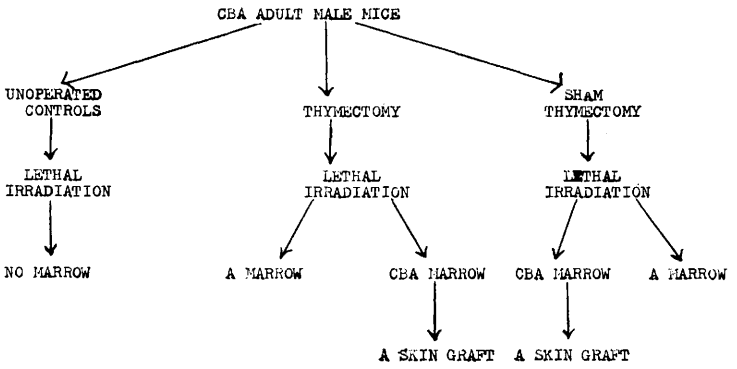

FIG. 1. Experimental design.

groups of 6 in lucite cages. Immediately following irradiation, the animals of the 4 operated groups were injected intravenously with five million bone marrow cells freshly removed from the femurs of either CBA/JAX or A/JAX mice of the same age. Animals in the unoperated group received no marrow injection. Animals were individually marked for identification, kept in colony cages of 7-10 animals each, and fed on an *ad lib* diet of standard laboratory chow and water. Each animal was weighed twice weekly. All dead were autopsied and the liver, spleen and nodes taken for histologic study. Tissue specimens were fixed in formalin, sectioned at 7 μ and stained with hematoxylin and eosin. The complete absence of the thymus was histologically confirmed in thymectomized animals at time of death.

Surviving recipients of syngeneic bone marrow were grafted with A skin one month following irradiation by the method of Billingham and Medawar(7). These grafts were inspected 6 days following grafting and the tempo of rejection assessed by gross inspection thereafter.

Results. The results are summarized in Fig. 2 and Table I. In the first 5 days following irradiation and bone marrow infusion, all the animals lost approximately 20% of their initial weight. All animals which did not receive bone marrow died within the first week following irradiation.

The recipients of A marrow began to regain their pre-irradiation weight but seldom reached that level before a secondary weight loss began, terminating in death. There was no difference in the weight curves or mortality of sham-thymectomized or thymectomized recipients of A marrow. All had died 50 days following irradiation. At autopsy, there was generalized hypoplasia of spleen and lymph

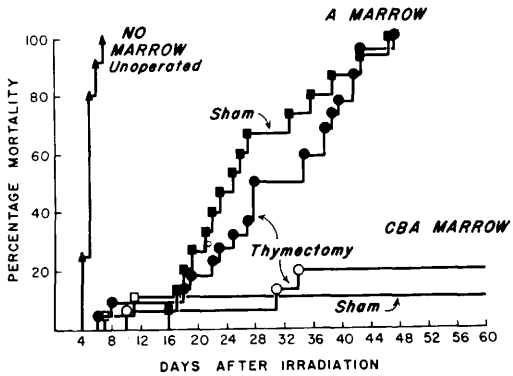

FIG. 2. Cumulative mortality of male CBA mice lethally X-irradiated (850 R) and treated with CBA or A marrow one week following either thymectomy or sham thymectomy. Each curve represents 18-22 animals.

TABLE I. Survival Time of A/JAX Skin Grafts on CBA/JAX Mice One Month Following Lethal Irradiation and Infusion of CBA Bone Marrow.

Group	No. of CBA mice	No. showing skin graft survival for: <17 days	20-60 days	>60 days
Sham thymectomy	20	17	3	0
Thymectomy	19	1	3	15

nodes. The liver of both the sham-thymectomized and thymectomized recipients of A marrow showed the highly specific perivenular lymphocytic infiltration characteristic of graft-*versus*-host reactions in mice(8). Animals dying in the first ten days following irradiation did not show these hepatic changes although generalized lymphoid atrophy was present.

The recipients of CBA marrow regained their pre-irradiation weight approximately 20 days following irradiation and thereafter continued to gain. Sixty days following irradiation, their mean weight was 15% greater than the pre-irradiation weights. Only 2 animals died after the initial 10-day post-irradiation period and these died at the time of skin grafting.

The survival of A skin grafts on the recipients of CBA marrow are shown in Table I. Thymectomized animals showed marked prolongation of graft survival compared to sham-thymectomized mice.

Discussion. It has been shown that injection of syngeneic or allogeneic bone marrow suspensions into lethally irradiated animals results in total replacement of host lymphocytic tissue by donor cells(9,10). The immunological competence of such animals is thus dependent on the activity of donor bone marrow precursors which have differentiated into immunologically competent lymphoid cells. Miller and others have demonstrated that the ablation of the adult mouse thymus prevents the restoration of immunological competence in synegeneic radiation chimeras (3,4,5,6). In our presently reported experiments, we have confirmed these observations, since graft rejection is markedly prolonged in thymectomized irradiated recipients of syngeneic bone marrow. From these results, it has been inferred that bone marrow is not intrinsically immunologically competent and that it develops competence only in the presence of the adult thymus(3). Support for this argument has also been provided by Van Putten, who has shown that the death of xenogeneic radiation chimeras was delayed if prior thymectomy had been performed(11).

In contrast, our study shows that allogeneic bone marrow, in the strain combination used, is capable of mounting a prompt and vigorous graft-*versus*-host reaction resulting in the death of the host even in the absence of the host thymus. From this, one could infer either that the bone marrow of the A strain is immunologically competent at time of injection or that the development of immunologic competence by allogeneic bone marrow precursors does not involve any thymic mechanism.

In support of the latter alternative hypothesis, Hirsch *et al*(12) have shown that syngeneic bone marrow injection was necessary for regeneration of thymic tissue in irradiated mice. In their experiments thymic regeneration did not take place in irradiated animals infused with allogeneic marrow even when secondary disease was precluded by the appropriate choice of strain combinations. Ford and Micklem(13) have shown that the reformation of lymphoid tissue following irradiation and syngeneic marrow injection occurs first in the thymus. It is therefore possible that syngeneic and allogeneic marrow precursors recolonize irradiated host lymphoid tissue and attain immunologic competence *via* different pathways. The syngeneic marrow may repopulate the thymus initially and thereafter seed other lymphoid tissue. The allogeneic marrow may bypass the thymus and preferentially repopulate peripheral lymphoid tissue.

Summary. Thymectomized and sham-thymectomized mice were lethally X-irradiated and given syngeneic and allogeneic bone marrow. Whereas the irradiated syngeneic chimeras failed to reject allogeneic skin grafts in the absence of the thymus, a secondary graft-*versus*-host disease developed with equal rapidity in both thymectomized and sham-thymectomized allogeneic chimeras. The possibility that bone marrow precursors of lymphoid tissue differentiate *via* different routes in irradiated syngeneic and allogeneic chimeras is suggested.

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Elevation of Peripheral Vascular Resistance in Renoprival Hypertension.* (30450)

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Bilateral nephrectomy of the dog followed by dietary protein and parenteral sodium is associated with acute hypertensive cardiovascular disease (renoprival hypertension)(1,2). In mongrel dogs so treated, the renoprival hypertension is significant for 8 of 10 animals within 4 days, provided there is no major weight loss through vomiting and/or diarrhea. This communication records a concomitant significant elevation of the total peripheral vascular resistance (TPR) in this form of renoprival hypertension.

Material and methods. Mongrel dogs of either sex, weighing between 7 and 10.6 kg, were used. The arterial pressure was obtained by direct femoral artery puncture after the animal became accustomed to the procedure. It was recorded by means of a transducer and Sanborn Twin-Viso recorder. The control pressure was determined by averaging the readings for 4 to 7 days before the nephrectomies. After the nephrectomies, the pressure was taken daily for 4 days when the experiment was terminated. Bilateral nephrectomy was performed at one sitting under ether anesthesia, as previously described(1). Each day thereafter, the animal was fed a diet containing about 3 g of casein per kg and infused with 16 ml per kg of physiologic saline as previously described(1). Total water intake by mouth amounted to 4.5 ml per kg. Under these conditions and without dialysis, nephrectomized dogs maintain a satisfactory clinical state for the 4 days of study.

Cardiac output was measured by the dye-dilution technic using cardio-green according to the procedure of Gilford(3). A Gilford cuvette-densitometer and attached Texas Instruments recorder with second timer were used. A polyethylene tube was threaded through the femoral artery to the lower abdominal aorta and a similar tube was threaded through a brachial vein to the superior vena cava to establish the circuit through the cuvette. The dye curve was analyzed according to Lilienfeld and Kovach(4).

The TPR was derived according to Bohr's recommendations(5) in which TPR = MAP $\div$ CO/kg, when TPR = total peripheral resistance in peripheral resistance units per kg, MAP is mean arterial pressure in mmHg and CO/kg is cardiac output in ml per kg body weight. In determining TPR, the pressure and cardiac output were determined at the same sitting.

In 6 experiments, TPR was determined before the nephrectomies and on the fourth day

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