

Effect of Hypophysectomy on Immunological Recovery after Sublethal Irradiation of Adult Rats* (34064)

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Recent observations (1-6) have focused attention on a relationship of the anterior pituitary, the thymus, and the thymus-dependent lymphoid system. It has been proposed that growth hormone mediates pituitary control of the thymus (2), but the possibility of a more specific thymotropic hormone has not been excluded.

In order to gain more insight into the pituitary control of immunologic function, we have studied immunologic recovery after sublethal irradiation of young adult hypophysectomized rats. The results indicated that hypophysectomy interfered with immunologic recovery after total body irradiation.

Materials and Methods. Male Wistar-Furth rats (A. R. Schmidt Co., Madison, Wisconsin), hypophysectomized at 8 weeks of age, were exposed to 500 R of total body irradiation at 10 weeks of age. Normal, irradiated, and hypophysectomized nonirradiated rats were included as controls. Because hypophysectomized rats do not tolerate low ambient temperatures, all rats were maintained at $84 \pm 2^\circ\text{F}$. They were fed Purina Rat Chow and given tap water *ad libitum*.

Each rat was bled from the tail at 24 hr and again at 7 weeks after irradiation, and the peripheral white blood cell count was determined. Abdominal skin from Sprague-Dawley donors was grafted to the dorsal sur-

face of Wistar-Furth recipients according to procedures previously described (7). The grafts were inspected daily and survival time of the grafts was evaluated from first evidence of sloughing of the graft.

Nine weeks after irradiation each rat was injected intraperitoneally with 0.1 ml/100 g of body weight of 20% sheep erythrocytes. Seven days after immunization rats were bled from the tail and the sera were tested for hemagglutinating antibodies to sheep erythrocytes using the microtiter hemagglutination technique.

Results. One day after total body irradiation with 500 R, both normal and hypophysectomized rats showed a drop in WBC count from greater than 20,000/cu. mm with 70-80% lymphocytes to approximately 3000 per cu. mm with almost no lymphocytes. Seven weeks after irradiation survival for both hypophysectomized and normal rats given this dose of irradiation was 80%. Although the hypophysectomized rats had failed to gain weight after irradiation, they appeared healthy and were free of obvious infection. At the 7 weeks' sampling the peripheral blood leukocyte count was significantly lower ($p < .01$) in the hypophysectomized-irradiated group than in the hypophysectomized control group and the leukocyte count of the normal, irradiated group did not differ from the normal values (Table I).

Hemagglutination titers to sheep erythrocytes were lower in hypophysectomized-irradiated rats than in any of the three control groups (Table II).

Allogeneic skin graft survival was significantly prolonged ($p < .01$) in hypophysecto-

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TABLE I. Peripheral Leukocyte Count of Hypophysectomized and Normal W/FU Rats 7 Weeks after 50 R Total Body Irradiation.

Group	Leukocyte count
Hypophysectomized	23,910 ± 1910 ^a
Hypophysectomized	13,900 ± 2110 ^a
Normal	27,720 ± 2990
Normal irradiated	22,500 ± 2810

^a $p < .01$.

mized-irradiated rats as compared to that observed in hypophysectomized rats (Table III). Skin allografts survived only slightly longer in normal and irradiated rats when they were transplanted 7 weeks after irradiation than in nonirradiated controls.

Discussion. These observations reveal that recovery of total leukocyte count, hemagglutinin formation to sheep erythrocytes, and skin allograft rejection is defective after irradiation in hypophysectomized rats. Thus, the influence of hypophysectomy performed in adult rats of this strain paralleled the effect of adult thymectomy, which is a diminished immunological recovery after irradiation (8, 9).

The relationship between the pituitary and thymus has been proposed for many years (10, 11). Recently, Pierpaoli and Sorokin induced wasting disease, thymus atrophy, and involution of the lymphoid tissue of the spleen with antisera to pituitary extracts (1) or to growth hormone preparations (2). Further, they reported that degranulation of pituitary acidophils regularly occurs after neonatal thymectomy (3). Baroni found that

TABLE II. Hemagglutination Titer to Sheep Erythrocytes Injected 9 Weeks after Irradiation.

Group	Hemagglutination titer ^a
Hypophysectomized	5.90 ± 0.95 ^b
Hypophysectomized and irradiated	2.33 ± 0.27 ^b
Normal	4.83 ± 0.62
Normal irradiated	5.33 ± 0.38

^a Determined 7 days after injection.

^b $p < .05$.

the hereditary recessive pituitary dwarf mouse (Snell-Bagg), which is known to be deficient in pituitary acidophils responsible for growth hormone production, shows lymphoid depletion of thymus and thymus-dependent areas in the spleen and decreased antibody response to sheep erythrocytes (4, 5). We confirm these findings and showed that the immunologic deficiency of Snell-Bagg dwarf mice resembles in several ways an isolated thymic deficiency syndrome such as the III and IV pharyngeal pouch and Nezeloff syndromes of man or neonatal thymectomy of mice. Severe deficiencies of cell-mediated immune responses were characteristic, but plasma cells and immunoglobulins seemed unimpaired (6).

Although the relationship of pituitary and

TABLE III. Allogeneic Skin Graft Survival in Hypophysectomized and Normal W/FU Rats 7 Weeks after Irradiation.

Group	Graft survival time (days)	
	Mean ± SE	Range
Hypophysectomized	13.2 ± 0.91 ^a	11-16
Hypophysectomized and irradiated	24.0 ± 3.20 ^a	18-31
Normal	11.8 ± 1.27	9-18
Normal irradiated	14.2 ± 1.17	10-21

^a $p < .01$.

thymus may, indeed, reflect a function of growth hormone as has been postulated (2), it is also possible that a distinct thymotropic influence exists (10). Hypophysectomy interfering directly with pituitary-thymic influence could compromise the thymic function and lead to faulty recovery of the lymphoid system and its functions after irradiation.

That this relationship has clinical correlates has been revealed by our recent demonstration of abnormal pituitary growth hormone response in some patients with ataxia-telangiectasia. These patients lack normal immunologic development and often have a morphologically underdeveloped thymus which may be due to a defective hypothalamic-pituitary control (Ammann, Duquesnoy, and Good, unpublished observations).

Although it is attractive to postulate from our studies a more specific pituitary-thymus influence, our findings, of course, do not exclude the possibility that lymphoid recovery after irradiation is defective in hypophysectomized rats because of deficiency of other pituitary factors. The endocrinological disturbances after hypophysectomy alter and generally decrease cellular metabolism and could slow down the regeneration of tissues that were damaged by irradiation, particularly the radiosensitive lymphopoietic tissues.

Additional studies of lymphoid recovery after irradiation in which each of the known pituitary hormones and hormones of the gonads and thyroid are individually supplied need to be carried out to evaluate critically the direct or indirect influence of the pituitary on the recovery and function of the lymphoid system.

Summary. Recovery of total leukocyte count, hemagglutinating antibody formation to sheep erythrocytes, and skin allograft rejection was defective after sublethal irradiation in adult hypophysectomized rats. These

findings could possibly be interpreted as interference of thymus function by hypophysectomy in immunologic recovery after irradiation.

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