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Fetal Liver: A Source of Immunoglobulin Producing Cells in the Mouse.* (31951)

M. L. TYAN, L. J. COLE, AND L. A. HERZENBERG
U. S. Naval Radiological Defense Laboratory, San Franciso and Department of Genetics, Stanford Medical School, Palo Alto, Calif.

It has been shown in studies of the ontogeny of the mouse immune system that the cells which participate in "delayed hypersensitivity" and homograft reactions are derived from fetal liver(1-3), and that these cells are dependent upon the thymus for their functional maturation(4). The ontogenesis of the cells responsible for antibody production in the mammal is not known, although it has been suggested that the appendix or Peyer's patch-type structures may serve as the source of these cells(5). This idea finds support in work with the chick which shows that the bursa of Fabricius, a gut associated lymphoepithelioid structure, is critically involved in the development and regulation of antibody forming cells(6-8). On the other hand, studies in the mouse suggest that antibody forming cells, regardless of their site of origin, are dependent upon intact thymic function for their functional maturation or proliferation or both(9-12). It was felt, therefore, that further work was needed before definite conclusions could be drawn with regard to the origin and regulation of mammalian antibody forming cells. In this report, data are presented which demonstrate that cells from fetal liver are capable of producing immunoglobulins in thymectomized as well as in intact hosts.

Materials and methods. Twelve-week-old thymectomized and nonoperated (C57L $\times$ A)F_1 mice received 870 rad whole body X radiation, and immediately thereafter they were given an intraperitoneal injection of 33 $\times$ 10^6 nucleated cells derived from the livers of 17 day C57Bl/6 $\times$ C57Bl/6 embryos (care was taken to exclude gut or gut associated structures from the sample). These strains were chosen because of their independently determined gamma-globulin allo-

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TABLE I. Production of Gamma-2a Globulins by C57Bl/6 Fetal Liver Cells in Lethally Irradiated Thymectomized and Nonoperated (C57L × A)F_1 Mice.

		Gamma-globulin allotype levels in host sera* (Days after radiation)			
		30	45	58	
Thymectomy	Mouse No.	Donor	Donor	Donor	Host
No	1	1+	2+	3+ (20)	4+ (21)
	2	—	1+	1+ (8)	4+ (30)
	3	1+	2+	2+ (10)	4+ (20)
	4	2+	3+	4+ (20)	3+ (30)
	5	1+	2+	3+ (12)	4+ (20)
Yes	1	±	1+	1+ (8)	3+ (8)
	2	1+	3+	3+ (23)	4+ (9)
	3	1+	3+	4+ (30)	4+ (8)
	4	±	2+	2+ (10)	4+ (18)
	5	—	—	1+ (4)	4+ (18)

* The results are expressed as semi-quantitative estimates (*i.e.*, 0 to 4+). Figures in parentheses represent percentage of specific gamma-globulin allotype present in the serum as compared to that present in the standard reference sera.

types(13). The mice were bled from the retro-orbital plexus 30, 45 and 58 days after irradiation. The sera were assayed for donor type gamma-globulins by a semiquantitative double-diffusion-in-gel method. In addition, the sera obtained 58 days after irradiation were quantitatively tested for both donor and host type gamma-globulins by an inhibition of precipitation assay with I^{125} labelled antigen as described previously(14). Standard serum pools of donor or host allotype were used as reference sera.

Results and discussion. As can be seen in Table I, donor type gamma-globulin was first detected in small quantities 30 days after injection of the donor cells; by 45 days after irradiation both the nonoperated and the *thymectomized* mice had appreciable quantities of donor type gamma-globulin in their sera. At 58 days all the mice had roughly the same levels of donor and host type gamma-globulins. These results demonstrate that cells derived from fetal liver are capable of producing gamma-globulins whether placed in thymectomized or in intact irradiated hosts. As it is known that under these experimental conditions, thymectomized mice produce little or no antibody in response to specific antigenic challenge(9,10), the nature of the donor "immunoglobulins" found in these thymectomized hosts is of great interest. A knowledge of the molecular structure of these globulins and of whether they represent specific antibody or immunologically inert proteins might add greatly to our understanding of the mechanism of specific immunoglobulin synthesis and the role played by the thymus in this process. Studies are being conducted in an effort to answer some of these questions.

Summary. Thymectomized and nonoperated adult mice were give a potentially lethal dose of X radiation and protected with allogeneic fetal liver cells. Immunoglobulins of donor as well as host type were found in the sera of the *thymectomized* and intact hosts as early as 30 days after irradiation.

NOTE ADDED IN PROOF:

Additional chimeras have been produced using fetal liver cells from 14-21 day C57Bl/6 × C57Bl/6 embryos. All of these mice, thymectomized (21) as well as intact (10) had significant quantities of donor-type γ-globulins in their sera. These mice were sensitized to a synthetic polypeptide (TGAL) and their sera were tested for total and in three instances for donor-type anti-TGAL antibody. All of the fetal liver cell chimeras (intact thymus) produced specific antibody (10/10), while none of the thymectomized chimeras (0/21) had detectable antibody. Of the three mice tested in the intact-thymus group, from 10% to 75% of the specific antibody was of donor origin.

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