Proc. Natl. Acad. Sci. USA
Vol. 81, pp. 4945–4949, August 1984
Medical Sciences

Immunodeficiency with defective T-cell response to interleukin 1

(T-cell deficiency/interleukin 1 receptor/interleukin 2 deficiency)

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Communicated by Baruj Benacerraf, April 16, 1984

ABSTRACT **Normal proliferation of T cells *in vitro* requires production of and response to the lymphokine interleukin 2 (IL-2). Optimal IL-2 production by T cells is dependent on the monokine interleukin 1 (IL-1). A 10-year-old male with recurrent infections and failure to thrive was evaluated for possible defects in the production and response to IL-1 and IL-2. The patient had normal levels of serum immunoglobulins and a normal distribution of circulating T-cell subsets. However, the *in vitro* proliferative response of his peripheral blood mononuclear cells (PBMC) to phytohemagglutinin was depressed (40% of normal) and the response of his PBMC to antigens was absent. Delayed hypersensitivity skin tests and *in vitro* response to tetanus toxoid remained absent despite repeated immunizations. Monocyte function in this patient was normal as judged by the following criteria: normal expression of Ia antigens (77% +), normal IL-1 production, and normal capacity to present tetanus toxoid to a maternal T-cell line specific for tetanus toxoid antigen. The abnormal phytohemagglutinin response of the patient's PBMC was corrected by the addition of exogenous IL-2. IL-2 production by the patient's phytohemagglutin-stimulated PBMC was severely deficient but was corrected by the addition of phorbol 12-myristate 13-acetate, suggesting a defective response to IL-1. T-cell blasts derived from a normal subject but not T-cell blasts derived from the patient absorbed out IL-1 activity from a preparation of purified human IL-1. These results indicate that the patient's T-cell deficiency was due to a defective T-cell response to IL-1 and suggest that IL-1 plays an important role in the *in vivo* immune response.**

The proliferative response of human T cells to antigen requires the recognition of antigen processed by Ia^+ accessory cells and the monokine interleukin 1 (IL-1). These two requirements can be separated by irradiation of the antigen-pulsed accessory cells with UV light, which inhibits the production of IL-1 (1–4). The failure of T cells to proliferate to UV-treated antigen-pulsed monocytes (Mo) is reversed by the addition of purified IL-1 (3). The requirement for IL-1 for T-cell proliferation to mitogens such as phytohemagglutinin (PHA) and Con A is less clear. Rabbit antibody to human IL-1 does not inhibit the proliferation of peripheral blood mononuclear cells (PBMC) to mitogens cells but readily inhibits the proliferation of PBMC to antigen such as tetanus toxoid (TT) (3, 5). IL-1 induces T cells that have interacted with lectins to secrete interleukin 2 (IL-1) (6, 7). In turn, IL-2 causes the proliferation of activated T cells, which express IL-2 receptors. We now describe a patient with an inability to generate IL-2 due to a defect in his T-cell response to IL-1.

CASE REPORT

A 10-year-old Lebanese male had a history of recurrent pneumonias and otitis media beginning at the age of 2 months. At age 3 years, he had an episode of severe herpes zoster. He has failed to grow in height and weight for several years. Family history revealed that three male siblings died in infancy because of recurrent infections, whereas five other siblings remain healthy. Total leukocyte count was 15,400 cells per mm^3 with 55% lymphocytes. Seventy-three percent of his PBMC formed rosettes with sheep erythrocytes, 67% reacted with T3, 41% with T4, 30% with T8, and 0% with T6. Serum immunoglobulin levels were IgG, 700 mg/dl; IgM, 184 mg/dl; IgA, 260 mg/dl; and IgE, 8 international units/ml. Delayed hypersensitivity skin tests to tuberculin, monilia, and TT antigens were negative.

MATERIALS AND METHODS

Cells and Cell Cultures. The isolations of PBMC and of highly enriched populations of Mo and of T cells were done as described (8). Proliferation of PBMC to antigens and mitogens was performed as described in ref. 9.

Production and Assay of IL-2. IL-2 was generated by culturing nonadherent irradiated (1000 rads; 1 rad = 0.01 gray) PBMC (10^6 cells per ml) with PHA for 48 hr as described (10). IL-2 activity in the supernatants was assayed on Con A-induced IL-2-dependent T-cell lines as described in ref. 10. PHA-free IL-2 was a gift of A. Krensky (Dana–Farber Cancer Institute, Boston) and was added at 2 units/ml.

TT-Specific T-Cell Lines. TT-specific T-cell lines were generated as described by Kurnick *et al.* (11). The cell lines were resuspended every 3–4 days in fresh medium containing 25% IL-2-containing supernatants and were stimulated every 7–10 days with autologous irradiated (5000 rads) PBMC and TT.

Generation and Testing of IL-1-Containing Supernatants. IL-1-containing supernatants were generated by incubating adherent PBMC ($2–5 \times 10^6$ per ml) with Con A (20 μg/ml) for 18 hr, collecting the supernatants, and adding α-methyl-D-mannoside (25 mg/ml) as described in ref. 10. Such supernatants contain IL-1 activity, as assessed by a thymocyte costimulator assay (3), and can substitute for IL-1 in reconstituting the human T-cell proliferative response to TT-pulsed UV-irradiated Mo (3). IL-1 activity in the supernatants was assayed as in ref. 3. Briefly, Mo in Petri dishes were incubated with TT (50 μg/ml) for 18 hr, washed, irradiated with UV light (1.2 joules/m^2 per sec, 230–350 nm) for 60 sec, and then added at a ratio of 1:10 to nylon wool-purified autologous T cells in the presence or absence of supernatants to be tested for IL-1 activity.

Partially Purified Human IL-1/Leukocytic Pyrogen (LP). IL-1 was partially purified as described in ref. 12. This human IL-1 copurifies with human LP down to a single band of M_r of ≈15,000 on 7.5% $NaDodSO_4$/polyacrylamide gel electrophoresis. This material is highly active in the rabbit pyro-

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Abbreviations: IL-1 and -2, interleukins 1 and 2; Mo, monocyte(s); PBMC, peripheral blood mononuclear cell(s); PHA, phytohemagglutinin; PMA, phorbol 12-myristate 13-acetate; TT, tetanus toxoid; PWM, pokeweed mitogen; LP, leukocytic pyrogen.

Table 1. Proliferative response to PHA, TT, and monilia

Subject	cpm of [^{3}H]thymidine incorporated in cultures stimulated with							
		Mitogen			Antigen			
					TT			
	No stimulation	PHA	Con A	PWM	Pre	Post	Monilia	DT
Patient	1332 ± 281	64,894 ± 9,643	25,552 ± 5,488	23,758 ± 6,975	967 ± 769	769 ± 156	1087 ± 270	1,616 ± 645
Mother	512 ± 58	183,427 ± 6,502			706 ± 124	72,155 ± 8362	5107 ± 603	706 ± 261
Normal control (n = 9)	753 ± 236	238,342 ± 52,475	137,533 ± 41,320	105,094 ± 33,853	—	21,250 ± 8639	8458 ± 3910	11,892 ± 6485

PHA was added at a concentration of 1 μg/ml, TT and diphtheria toxoid (DT, Massachusetts Biological Laboratories, Jamaica Plain, MA) were added at a concentration of 20 μg/ml, and monilia antigen (Hollister Stier, Spokane, WA) was added at a dilution of 1:500. Values represent mean ± SEM of triplicate cultures. Mitogen-stimulated cultures were harvested at 3 days and the remainder at 6 days. The background for unstimulated 6-day cultures is shown and was not significantly different from the background for 3-day cultures, which is not shown. Normal subjects ranged in age from 7 to 25 years. TT pre and post indicate before and after immunization, respectively, with TT.

gen assay (12, 13), in which one rabbit pyrogen dose is the amount of IL-1/LP that when injected intravenously in a rabbit causes an elevation of 0.6–0.9°C in body temperature within 1 hr.

Thymocyte Costimulator Assay. This was performed as described in ref. 13.

RESULTS

Response to Mitogens and Antigens. PBMC from the patient had a diminished proliferative response (<3 SD below the mean of normal controls) to PHA, Con A, and pokeweed mitogen (PWM) and an absent response to TT, diphtheria toxoid, and monilia antigens (Table 1). Subsequently, the patient and his mother, who was not immune to TT, were given a series of three immunizations with TT antigen (5 limit flocculation units each) over a 2-month period. Following this, PBMC from the patient remained unresponsive to TT, whereas PBMC from his healthy mother proliferated vigorously to TT (Table 1). After immunization, the delayed hypersensitivity skin test with TT remained negative in the patient but converted to positive in the mother.

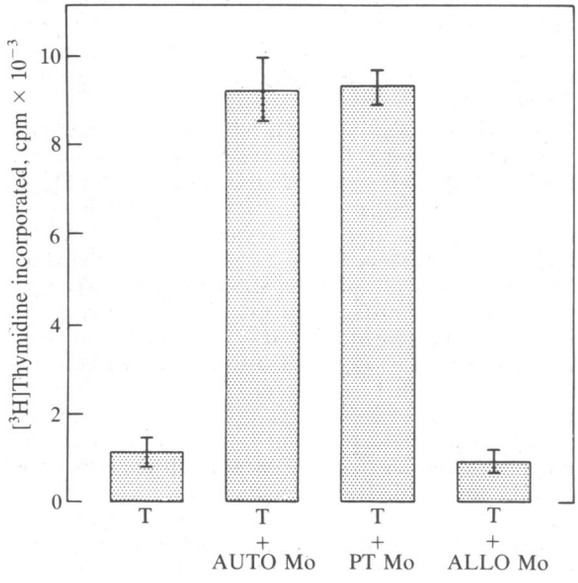

FIG. 1. Proliferative responses of maternal TT-specific T-cell blasts (T) to TT presented by Mo. Cultures contained 4 × 10^4 T cells and 4 × 10^4 irradiated (5000 rads) Mo with or without soluble TT at 40 μg/ml. AUTO, autologous; PT, patient; ALLO, allogeneic. Values represent mean ± SEM of triplicate cultures. Cultures containing T-cell blasts and accessory cells always incorporated <1300 cpm of [^{3}H]thymidine into DNA.

Antigen-Presenting Function of Mo. T-cell proliferation to antigen is dependent on antigen presentation by Ia^+/DR^+ accessory Mo and on the secretion of IL-1 by the Mo. In two separate experiments, 77% and 75% of the patient's PBMC that adhered to plastic plates (i.e., Mo) were found to express Ia antigen compared to 82% ± 14% in five normal controls.

To examine the antigen-presenting function of the patient's Mo and because no HLA identical siblings were available, we examined the capacity of his Mo to support the proliferation of a TT-specific T-cell line derived from his HLA haploidentical mother. The results of this experiment are shown in Fig. 1. Mo from the patient and from the mother supported T-cell proliferation of the maternal T-cell line in the presence of TT. Mo from an HLA-DR unrelated donor failed to support the proliferation of the maternal T-cell line in the presence of TT.

We next examined the capacity of the patient's Mo to generate IL-1 and found it to be normal. Table 2 shows that normal immune T cells proliferated in response to TT-pulsed autologous Mo but not in response to autologous TT-pulsed UV-irradiated Mo. This response was reconstituted by the addition of supernatants from Con A-stimulated Mo derived from both the patient and a normal donor. This effect was not due to residual Con A in the Mo supernatants because addition of these supernatants alone did not cause proliferation of T cells and Mo.

IL-2 Production and Response. Fig. 2*A* shows that the patient's PBMC were severely deficient in their capacity to generate IL-2 for the normal IL-2-dependent T-cell line. Although the patient's PBMC failed to generate IL-2, Con A-induced blasts from the patient were able to respond to IL-2, as shown in Fig. 2*B*, but not to supernatants of his own PHA-stimulated PBMC. Thus, it appears that the T cells of the patient respond normally to IL-2, even though his PBMC were unable to generate it. Mixing experiments failed to de-

Table 2. Reconstitution of the T-cell response to UV-irradiated antigen-pulsed Mo (Mo_{TT}/UV) by supernatants of Con A-stimulated adherent cells

Cells in culture	Source of Con A-stimulated Mo supernatant	[^{3}H]Thymidine incorporated per culture, cpm
T + Mo_{TT}	—	37,784 ± 3753
T + Mo_{TT}/UV	—	964 ± 188
T + Mo_{TT}/UV	Normal	46,896 ± 4903
T + Mo_{TT}/UV	Patient	44,168 ± 2150
T alone	Normal	620 ± 144

Mo_{TT}, autologous Mo pulsed with TT (50 μg/ml) for 18 hr. Mo_{TT}/UV, TT-pulsed Mo irradiated with UV light. T cells and Mo were obtained from a normal subject. Values represent mean ± SEM.

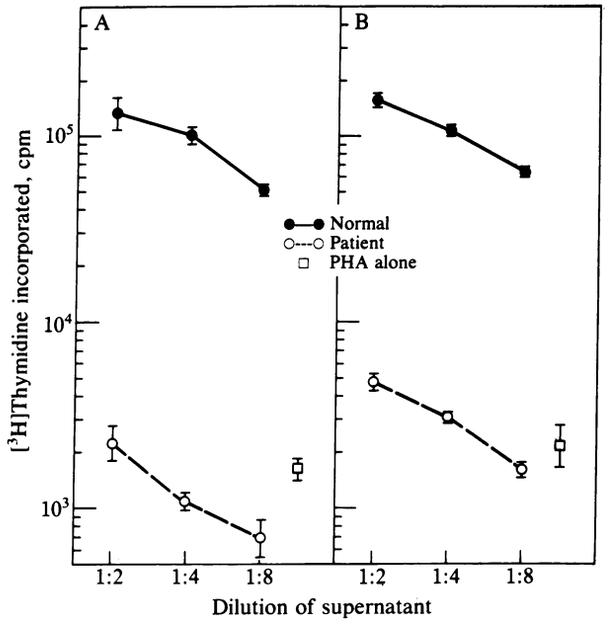

FIG. 2. (*A*) Response of normal Con A-induced T-cell blasts to supernatants of PHA-stimulated PBMC from a normal subject (——) and from the patient (----). (*B*) Response of the patient's Con A-induced T-cell blasts to supernatants of PHA-stimulated PBMC from a normal subject (——) and from the patient (----). Numbers represent cpm. Values represent mean cpm ± SD of [^{3}H]thymidine incorporated in triplicate cultures of 4×10^4 blasts.

tect the presence of an inhibitor of IL-2 activity in supernatants of the patient's PHA-stimulated PBMC (data not shown).

Addition of exogenous IL-2 on day 0 to PHA-stimulated cultures of the patient's PBMC reconstituted the proliferative response after 3 days in culture to normal. Furthermore, unlike the situation in normal subjects, the patient's PBMC proliferative response to PHA was not sustained for 6 days of culture but was reconstituted to the normal level by addition of exogenous IL-2 at day 3 of culture (Table 3). In contrast to the effect of IL-2 on the PHA response, addition of PHA-free IL-2 to cultures for the patient's PBMC stimulated with TT did not result in cell proliferation (data not shown). Addition of purified IL-1 to the patient's PBMC did not correct their defective proliferative responses (data not shown).

Response to Phorbol 12-Myristate 13-Acetate (PMA). We next considered the possibility that the failure of the patient's T cells to make IL-2 was due to their failure to respond to IL-1. In an effort to bypass the IL-1 requirement for lectin-induced IL-2 production, we examined the capacity of the patient's PBMC to produce IL-2 activity when stimulated with PHA in the presence of the phorbol ester PMA. Table 4 shows that when the patient's PBMC were stimulated with both PHA and PMA they released substantial amounts of IL-2 activity into their supernatants. Stimulation of the patient's PBMC with either PHA or PMA alone did not result in the release of significant IL-2 activity as assessed by blast proliferation (Table 4). The blast proliferation induced by supernatants of PBMC stimulated with PMA and PHA was not due to the action of these agents together on the blasts used for the assay (Table 4). PMA induced a negligible increment or no increment in the production of IL-2 by PHA-stimulated normal T cells (data not shown).

We next examined the capacity of T-cell blasts from the patient and from a normal subject to absorb IL-1 activity. Con A-induced T-cell blasts from normal individuals and from the patient were propagated in culture for 4 weeks by the addition of IL-2. No differences could be discerned in their response to IL-2. Fig. 3 depicts the activity of purified IL-1 in a mouse thymocyte stimulator assay following its absorption with Con A-induced T-cell blasts from the patient and a normal control. IL-1 activity was absorbed by normal T-cell blasts but not by the patient's T-cell blasts. T-cell blasts from both patient and a normal control completely absorbed IL-2 activity from IL-2-containing supernatants (data not shown).

DISCUSSION

The present study describes a defective T-cell response to the monokine IL-1 in a child with immunodeficiency. This was supported by the following three findings. (*i*) Despite the production of normal IL-1 activity by the patient's Mo, the IL-1-dependent induction of IL-2 by PHA was severely deficient (Fig. 2). (*ii*) The failure to produce IL-2 following stimulation with PHA was corrected by the addition of an agent that mimics the effect of IL-1 (Table 4). (*iii*) T-cell blasts from the patient, in contrast to normal T-cell blasts, failed to absorb IL-1 activity from a preparation of purified IL-1 (Fig. 3).

Mitogen-induced IL-2 production has been shown to require IL-1 (14–16). Failure to produce IL-2 in the face of normal IL-1 production in our patient suggested that his T cells either were unable to respond to IL-1 or were intrinsically unable to produce IL-2. The latter possibility was ruled out by demonstrating normal IL-2 production in the presence of PHA and PMA, which can act as an IL-1 analogue in the activation of Mo/macrophage-depleted T lymphocytes (7, 17, 18). Although PMA also enhances IL-1 secretion (19, 20), it is unlikely that its effect of the patient's cells was mediated by this mechanism because the patient's Mo produced IL-1 normally. Thus, it appeared that our patient's T cells failed to respond normally to IL-1. This could have resulted from defective binding of IL-1 to T cells, which was supported by the observation that the patient's T cells exhibited a decreased capacity to absorb IL-1 when compared to normal T cells (Fig. 3). Absorption of IL-1 by T-cell blasts has been demonstrated in the mouse by Gillis and Mizel (21). In agreement with their findings, we had to use large numbers of normal T-cell blasts to absorb IL-1. This suggests that the affinity of the T cell for IL-1 is low.

The findings in the present study have important implica-

Table 3. Effect of IL-2 on the PHA response of PBMC

Source of PBMC	[^{3}H]Thymidine incorporated per culture, cpm			
	3-day culture		6-day culture	
	PHA	PHA and IL-2	PHA	PHA and IL-2
Patient	67,585 ± 5,360	180,373 ± 36,491	1,952 ± 544	165,400 ± 3,435
Normal subject				
1	270,250 ± 13,748	275,167 ± 23,356	207,770 ± 5,147	247,330 ± 19,682
2	263,330 ± 40,581	223,070 ± 12,509	100,995 ± 54,012	104,565 ± 21,588

IL-2-containing supernatants were added at a 1:4 dilution. Values represent mean ± SEM of triplicate cultures.

Table 4. PMA stimulation of IL-2 production by the patient's PBMC

Stimulation for generation of supernatants	cpm of [^{3}H]thymidine incorporated in the presence of supernatants used at dilutions of			
	1:2	1:4	1:8	1:16
PBMC + PHA-M	563 ± 52	493 ± 39	424 ± 44	463 ± 151
PBMC + PMA	5,306 ± 205	4,915 ± 109	1,736 ± 109	456 ± 44
PBMC + PHA-M + PMA	93,137 ± 5344	95,048 ± 5028	55,424 ± 3202	18,799 ± 6334
No cells + PHA-M + PMA	9,016 ± 2600	116 ± 16	127 ± 44	186 ± 67

Values represent mean ± SEM of triplicate cultures. T-cell blasts were derived from a Con A-stimulated T-cell line obtained from a normal subject. PMA was used at 20 ng/ml and PHA-M was used at a 1:100 dilution.

tions for the mechanism of immunodeficiency in this patient as well as for the understanding of human T cell–Mo interactions. The PHA proliferative response of the patient's PBMC to PHA was abnormal. It was decreased to 40% of normal when measured after 3 days of culture and was absent when measured after 6 days in culture. These abnormalities were associated with a severe deficiency in IL-2 secretion but with normal capacity to respond to IL-2 because addition of exogenous IL-2 corrected the PHA responses measured both at day 3 and day 6 of culture. The early 3-day proliferative response of the patient's T cells to PHA in the face of severely diminished IL-2 secretion suggests that IL-1 may not be required for T-cell proliferation to PHA but is required for IL-2 secretion. Alternatively, a minimal response of the patient's T cells to IL-1 could have been sufficient to initiate T-cell proliferation and expression of IL-2 receptors but insufficient to induce the synthesis and secretion of normal amounts of IL-2. The requirement for IL-1 in T-cell responses to PHA is not well established. Highly purified T cells do not proliferate to PHA and this is corrected by the addition of IL-1 (15, 16, 18). Lipsky *et al.* have shown that a relative excess antibody to IL-1 does not inhibit the proliferative response of PBMC to PHA (5). However, even a relative excess of anti-IL-1 may not have an effect on the PHA response if only very small amounts of IL-1 are needed for this response. Such small amounts of IL-1 could be delivered by direct cell-to-cell contact and may not be accessible to anti-IL-1 antibody. It remains to be determined whether accessory cell-derived signals other than IL-1 could support the proliferation of T cells to PHA. In this regard, recent experiments in our laboratory indicate that Epstein–Barr virus-transformed B cells free of Mo can support the proliferation of highly purified T cells to PHA despite the inability of the Epstein–Barr virus B cells to secrete measurable amounts of IL-1.

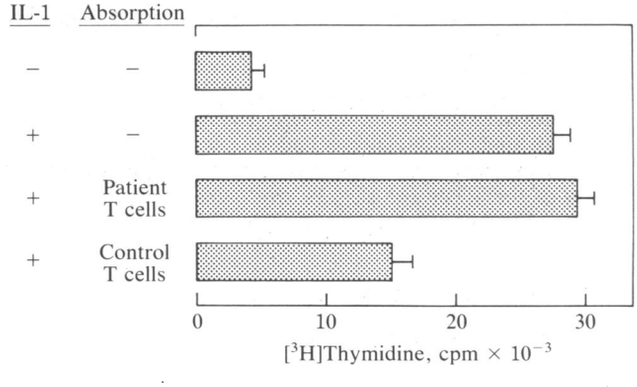

FIG. 3. One-half milliliter of partially purified IL-1/LP (25 × 10^{-2} rabbit pyrogen dose per ml) was absorbed at 4°C for 2 hr with 5 × 10^7 Con A-induced T-cell blasts and the absorption was done twice. IL-1/LP was then added at a 1:5 dilution to mouse thymocytes stimulated with PHA. The cultures were assayed for DNA synthesis after 3 days. Values represent mean ± SD of [^{3}H]thymidine incorporated in triplicate cultures. Mouse thymocytes alone incorporated <300 cpm of [^{3}H]thymidine per culture.

Our patient had absence of delayed hypersensitivity responses to antigens *in vivo* and his PBMC failed to proliferate to antigens *in vitro*, including TT antigen with which he was repeatedly immunized. The failure of our patient's PBMC to proliferate to TT could have resulted from his defective response to IL-1. Indeed, we and others have demonstrated a requirement for IL-1 in the proliferative response of human T cells to antigen (2, 3, 22). In particular, antibody to human IL-1 markedly inhibits the response of human PBMC to TT antigen (3). In contrast to the situation with PHA, IL-2 did not correct the failure of the patient's PBMC to respond to TT antigen. This may be related to the fact that initial proliferation occurred with PHA that allowed a subsequent response to exogenous IL-2, while no proliferation at all occurred with TT antigen. In addition, it is possible that in the presence of a defective response to IL-1 the expansion of TT-immune T cells *in vivo* did not occur. Because PMA was mitogenic for resting human lymphocytes, including our patient's, we could not use PMA to substitute for the IL-1 signal in antigen-driven responses.

Inability to produce normal amounts of IL-2 in the face of normal or increased capacity to generate IL-1 has been described in nude mice. Peritoneal macrophages from these mice produce supranormal amounts of lymphocyte-activating factor, subsequently termed IL-1 (23). Their thymocytes fail to proliferate and to generate IL-2 after mitogen stimulation. Addition of both mitogen and a source of exogenous IL-2 induces normal proliferative responses (24). The findings in the nude mouse are analogous to those made in our patient and suggest that he may have suffered from a T-cell maturation defect. In this regard, a number of T-cell leukemias are unable to produce IL-2 in the presence of PHA and normal Mo as a source of IL-1 but do so in the presence of added phorbol ester (25). Inasmuch as T-cell leukemias represent malignant transformation of T cells frozen at a particular stage in their differentiation, these observations also suggest that our patient suffered from a T-cell maturation defect. The history of three siblings having died in infancy with recurrent infections raises the possibility that the defect in our patient was inherited. Because of geographic constraints only one of the patient's five healthy siblings was studied and was found to be normal.

The authors thank Mr. Mark Tedesco and Miss Marianne Lareau for technical assistance and Miss Melissa Smith for secretarial assistance. This research was supported by U.S. Public Health Service Grants RR-02172, AM31925, AI20373, AI-21163, AI-07167, AI17833, and AI15614 and grants from the National Foundation–March of Dimes. R.S.G. is recipient of Allergic Diseases Academic Award K07AI0440. E.T.C. is recipient of Fellowship Immunology Training Grant 5T332AI07167. C.A.D. is a recipient of a Career Development Award from the National Institute of Allergy and Infectious Diseases.

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