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Recombinant interleukin 2 therapy in severe combined immunodeficiency disease

(T-cell growth factor/primary immunodeficiency disease/immunotherapy)

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ABSTRACT **Severe combined immunodeficiency disease (SCID) is a congenital disorder of severe B- and T-lymphocyte dysfunction in which several pathogenic mechanisms have been identified. The present study describes a female child with SCID who had a primary defect in the ability of T cells to secrete interleukin 2 (IL-2). B- and T-cell numbers were normal, but their functions were severely deficient. Mitogen and antigen-driven lymphoproliferative responses were diminished but were correctable *in vitro* with recombinant IL-2 (rIL-2). The patient's phytohemagglutinin-stimulated lymphocytes expressed IL-2 receptors normally. Despite the presence of the gene for IL-2, the patient's cells were grossly deficient in messenger RNA for IL-2 and endogenous IL-2 production. Pokeweed mitogen-driven B-cell differentiation was decreased and was not corrected by the addition of normal T cells to the B cells. Two attempts at immune reconstitution by haploidentical bone marrow transplantation failed. Therapy with rIL-2 (30,000 units/kg, given daily i.v.) resulted in marked clinical improvement as well in improved T-cell functions. The child, now 3 yr old, has been on rIL-2 therapy for 2 yr and receives rIL-2 (30,000 units/kg) three times weekly at home. This case study points to a new direction in the treatment of such disorders with rIL-2.**

Severe combined immunodeficiency disease (SCID) is a congenital disorder of immune dysfunction involving the B- and T-cell systems. The condition is uniformly fatal if untreated. The pathogenic mechanisms involved in the evolution of the SCID syndromes are varied, the classical form being that of a "stem cell" defect (1). A multitude of other possible defects, usually linked to arrested T-cell differentiation (2–5), have been described to explain the pathogenesis of this disease. In this communication, we describe a female child with SCID whose disease could be attributed to a deficiency in synthesis and secretion of interleukin 2 (IL-2).

The initiation of T-cell proliferation involves a cascade of biochemical events culminating in induction of IL-2 receptor (IL-2R) expression and endogenous IL-2 production (6–11). The T-lymphocyte antigen–receptor complex (CD3Ti) recognizes processed antigen in association with major histocompatibility complex II determinants on the antigen-presenting cell (12). This recognition is transduced into intracellular biochemical events that result in a biologic response. The inability to synthesize adequate amounts of IL-2 has been reported to cause several types of T-cell dysfunction, including SCID (13–20). Successful treatment of SCID has thus far been possible only with bone marrow transplantation (BMT). Thus, the trial reported here supports the view that SCID represents several different diseases and demonstrates the potential usefulness of recombinant IL-2 (rIL-2) in the treatment of primary defects of T-cell function secondary to a deficiency of production of IL-2.

MATERIALS AND METHODS

Isolation of Lymphocytes. Mononuclear cells were isolated from heparinized peripheral blood of healthy volunteers or from the patient by centrifugation on Ficoll/metrizoate (Lymphoprep; Nyegaard, Oslo) gradients and designated peripheral blood lymphocytes (PBLs). To isolate B and T cells, double rosetting of PBLs with neuraminidase-treated sheep erythrocytes was performed as described (21). Rosette-forming cells were designated T cells; non-rosetting cells, depleted of adherent cells on plastic Petri dishes for 30 min, were considered B cells.

Phenotypic Analysis of Lymphocytes. T and B lymphocytes and T-cell subsets were quantified in whole blood using monoclonal antibodies (mAbs) (Ortho-immune, Coulter clone, and Becton Dickinson reagents) by flow cytometry (22).

Detection of IL-2R. PBLs of the patient and a healthy control were cultured with and without phytohemagglutinin (PHA, 20 μg/ml) or concanavalin A (Con A, 8 μg/ml) for 24–48 hr and expression of IL-2R was examined by flow cytometry using anti CD-25 mAb (Becton Dickinson).

Lymphoproliferative Responses. The functional capacity of the patient's PBLs was assessed by measuring their proliferative responses to phytomitogens—namely, PHA, Con A, and pokeweed mitogen (PWM)—or common antigens (23). In certain experiments, a number of agents that are known to activate T cells (mAbs anti-CD2, anti-CD28, and anti-CD3; phorbol esters; and ionomycin) were used alone or in combination (24–30); rIL-2 was also used in an effort to augment responses. Responses were determined by measuring incorporation of [^{3}H]thymidine or [^{14}C]thymidine (New England Nuclear).

Assay for IL-2 Activity. PBLs (1×10^6) from the patient or a healthy control were cultured with or without PHA (20 μg/ml) or Con A (8 μg/ml) for 24–48 hr in culture medium with 10% fetal calf serum and 50 μM 2-mercaptoethanol in 5% CO_2/95% air. Supernatants were removed, filtered, and

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Abbreviations: BMT, bone marrow transplantation; SCID, severe combined immunodeficiency disease; EBV, Esptein–Barr virus; IL-2, interleukin 2; IL-2R, IL-2 receptor(s); ISC, immunoglobulin-secreting cell(s); MLC, mixed lymphocyte culture; mAb, monoclonal antibody; PBL, peripheral blood lymphocyte; PHA, phytohemagglutinin; PMA, phorbol 12-myristate 13-acetate; PWM, pokeweed mitogen; rIL-2, recombinant human IL-2.

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frozen at −20°C until used for IL-2 assays. IL-2 activity in the supernatant was assayed by quantifying proliferation of cells of a murine IL-2-dependent cell line (HT-2). HT-2 cells were cultured with test supernatants for 24 hr, and 1.0 mCi of [^{3}H]thymidine (1 Ci = 37 GBq) was added for the last 4 hr of culture. Cells were harvested to determine uptake of [^{3}H]-thymidine as described by Gillis (31) and Azoqui *et al.* (32).

Generation of Immunoglobulin Secreting Cells (ISC) *in Vitro*. Cultures consisting of 5×10^4 PBLs in 0.1 ml of RPMI 1640 medium supplemented with antibiotics and 15% fetal calf serum were set up in triplicate in round-bottomed microtiter plates (Costar). The cells were cultured for 7 days at 37°C in 5% CO_2/95% air in the presence or absence of the following stimuli: PWM, 10 μl/ml; heat-killed formalin-treated *Staphylococcus aureus* Cowan strain, 0.0015%; and Epstein–Barr virus (EBV)-containing culture supernatants derived from an infected B95-8 marmoset cell line, 150 μl/ml, as described (33). At the end of the culture period, cells were washed and assayed for ISC by reverse hemolytic plaque assay using protein A-coated sheep erythrocytes as targets and rabbit anti-human immunoglobulin as a developing serum.

Study Subject. Patient R.D. was born by caesarean section in December 1985, to a 30-yr-old white female after a 37-wk gestation. Birth weight was 2300 g. At age 2 mo, the patient presented with a diarrheal illness. Immediately thereafter, she developed vesicular lesions on the head, shoulders, and back after exposure to a sibling with chicken pox. Because the vesicular lesions persisted, R.D. was treated with acyclovir i.v. for 2 wk and recovered. Investigations to rule out immune deficiency showed a normal leukocyte count with no lymphopenia. Immunoglobulin levels in serum were low (IgG, 170 mg/dl, n = 196–558; IgA, <1 mg/dl, n = 4–73; IgM, 12 mg/dl, n = 27–101), and the patient failed to make adequate anti-varicella antibodies after onset of lesions characteristic of varicella. Although T- and B-cell numbers were normal, the patient had impaired B- and T-cell function *in vitro*. An enzymatic basis for immune deficiency was ruled out when adenosine deaminase and purine nucleoside phosphorylase were shown to be normal. A diagnosis of SCID was considered, and treatment with i.v. immunoglobulin was begun. The patient then developed *Pneumocytosis carinii* pneumonia, diagnosed by open lung biopsy, which was successfully treated with i.v. pentamidine after i.v. trimethoprim sulfamethoxizole failed to reverse the pulmonary disease. *S. aureus* cultured from a pustular infection of the thoracotomy site responded to oral dicloxacillin therapy. At 4 mo of age, the patient exhibited persistent thrush, which required continuous treatment with nystatin. She also exhibited failure to thrive, and at age 6 mo she was transferred to All Children's Hospital (Saint Petersburg, FL) for efforts to achieve immune reconstitution.

RESULTS

Immunological Assessment. *Phenotypic analysis of lymphocytes.* At age 6 mo, the patient had 84% CD3$^+$ lymphocytes (T cells) and 9.8% CD20$^+$ lymphocytes (B cells). Absolute numbers of T and B cells and the ratio of CD4$^+$ T cells to CD8$^+$ cells (T4/T8 ratio) were normal.

Lymphoproliferative responses and effect of exogenous IL-2. T-cell function assessed by thymidine uptake showed depressed lymphoproliferative response to PHA at various concentrations, but responses to Con A and PWM were within normal range. Lymphoproliferative responses to common antigens (*Candida* and tetanus) were markedly depressed (data not shown). Mixed lymphocyte culture (MLC) reactivity against three unrelated donors demonstrated 25% of the response seen with controls (data not shown).

To determine whether a lack of IL-2 might account for the unresponsiveness of the patient's PBLs to mitogens or to allogeneic cells, PBLs from the patient and from a healthy control were cultured with optimal concentrations of PHA, Con A, and PWM in the presence of rIL-2. As shown in Table 1, the patient's depressed responses to PHA were augmented by the addition of as little as 1 unit of exogenous rIL-2 per ml. rIL-2 also enhanced the responses of patient cells in MLC reactions (data not shown).

The functional defect in T-cell lymphoproliferation was further investigated by activating patient T cells with mAb directed against CD3 and CD2 receptors (24–30) and with a combination of phorbol 12-myristate 13-acetate (PMA) and ionomycin (30). Depressed lymphoproliferative responses to anti-CD2 and anti-CD3 mAbs were augmented by the addition of rIL-2 to the cultures. The patient's cells also proliferated when cultured with a combination of PMA and ionomycin or with PMA and anti-CD2 mAb.

Induction of IL-2R and IL-2 secretion. When the patient's PBLs were cultured with PHA or Con A, expression of IL-2R increased from <1% to 12% and 20%, respectively. However, the patient's cells failed to secrete IL-2 after stimulation with PHA or Con A (Fig. 1). In another set of experiments, the patient's cells secreted low amounts of IL-2 in response to a combination of PMA and ionomycin (data not shown).

Analysis of DNA and mRNA for IL-2. Although the IL-2 gene was normal in Southern blot analysis, induction of mRNA for IL-2 was absent, suggesting that the abnormality in IL-2 secretion was linked to a failure of IL-2 gene transcription (34, 35).

In vitro *studies of B-cell differentiation.* The patient's B cells showed poor ISC response to three stimuli (PWM, EBV, and *S. aureus* Cowan strain) as compared to normal controls (data not shown). That the patient's B cells were intrinsically defective is suggested by the observation (Table 2) that purified patient B cells failed to respond to EBV or to PWM in the presence of normal T cells. Surprisingly, the patient's T cells could provide adequate help to normal B cells in their differentiation response to PWM. Exogenous IL-2 failed to significantly influence ISC response of patient or control PBLs to any stimuli (data not shown).

Clinical Course and Treatment. *Treatment with BMT.* At age 6 mo, the child was hospitalized, isolated by laminar air flow, and given oral nonabsorbable antibiotics and total

Table 1. Lymphoproliferative responses, IL-2R expression, and *in vitro* effect of rIL-2

	Patient			Control		
	Lymphoproliferative responses		IL-2R expression	Lymphoproliferative responses		IL-2R expression
Stimulus	Cells	Cells + IL-2	% positive	Cells	Cells + IL-2	% positive
PHA	1735	38,547	12.0	21,041	25,603	32.6
Con A	3989	23,579	20.8	4,710	8,753	38.1
PWM	4978	5,171	ND	4,501	4,695	ND
Medium	177	571	0.1	353	1,246	0.2

Lymphoproliferative responses were measured by ^{14}C uptake (cpm). After patient or control PBLs were cultured with rIL-2 (Cetus; 1 unit/ml) for 40 hr, they were stained with anti-IL-2 receptor antibody (Becton Dickinson). ND, not done.

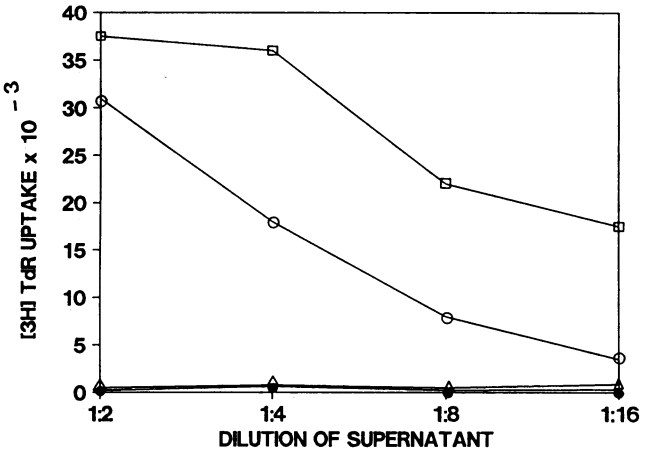

FIG. 1. PBLs (1×10^6) from patient R.D. and from a healthy control were stimulated with PHA (10 μg/ml) (●, patient; □, control) or Con A (△, patient; ○, control) for 48 hr. As measured by [^{3}H]thymidine uptake, the patient's cells failed to secrete IL-2 in response to stimulation.

parenteral nutrition. Since an HLA-identical MLC-nonreactive matched sibling donor was not available, an attempt was made to correct the patient's immunodeficiency disease by a T-depleted bone marrow graft from a haploidentical paternal donor. BMT was done after extensive myeloablation with busulfan (4 mg·kg^{-1}·day^{-1} for 4 days) and immunosuppression with Cytoxan (cyclophosphamide) (50 mg·kg^{-1}·day^{-1} for 4 days). Initially the graft was accepted, but subsequently it failed or was rejected 50 days after BMT. A second T-cell-depleted BMT given as a booster 81 days later also was rejected.

Treatment rIL-2. After failure of the BMT, the long-term prognosis for this patient was very poor. Since studies had revealed normal expression of IL-2R but deficiencies of IL-2 production by R.D.'s T lymphocytes, a therapeutic trial was undertaken to administer rIL-2 in incremental doses (Fig. 2). Therapy began on day 339 of hospitalization, with 10,000 units·kg^{-1}·day^{-1} of rIL-2 administered by continuous i.v. infusion over a period of 6 hr. After 2 wk, the dose was increased to 20,000 units·kg^{-1}·day^{-1} for 7 days and then to 30,000 units·kg^{-1}·day^{-1} i.v. for 2 wk. The child tolerated these infusions well. Dosage was then increased to 40,000 units·kg^{-1}·day^{-1} i.v., to be infused over a 6-hr period. With the first infusion at this dose, the patient exhibited hypertension (blood pressure, 140/94 mmHg) and tachycardia (heart rate, 140–160 beats per min). The infusion was stopped, and blood pressure and pulse stabilized within 8 hr. When the same high dose was administered the next day, a similar hemodynamic reaction occurred. This reaction was deemed a side effect of the rIL-2 therapy, and thus the dosage was reduced to 30,000 units·kg^{-1}·day^{-1}. On day 441 of hospitalization, this dosage was reduced in frequency to three times weekly (Monday, Wednesday, and Friday) by i.v. infusion over a period of 1 hr. The patient tolerated this regimen well and was discharged from the hospital on day 464.

Table 2. Evidence for an intrinsic B-cell defect in patient R.D.

Culture	ISC × 10^{-3} per 10^6 cultured cells
PWM stimulation	
Patient B + patient T	7.5
Patient B + patient T*	10.2
Patient B + patient T	3.8
Patient B + control T	13.4
Control B + control T	71.8
Control B + patient T	58.5
Control B + patient T*	62.2
Control B + patient T	38.2
EBV stimulation	
Patient B	7.8
Control B	47.5

Purified B cells from patient R.D. failed to respond to stimulation with EBV or PWM in the presence of either patient or control T cells, suggesting an intrinsic B-cell defect. Additions of B and T cells were done at a 1:1 ratio; final cell concentration, 5×10^4 cells per well. Background ISC counts of B or T cells cultured alone were <0.1.
*Irradiated T cells (2000 rads; 1 rad = 0.01 Gy).

Effect of therapy on lymphoproliferative responses. Fig. 2 shows the lymphoproliferative responses to PHA, Con A, and PWM during the course of BMT and subsequent IL-2 therapy. On day 0 (date of hospitalization), the patient showed depressed proliferative responses to PHA but normal responses to Con A and PWM. The first BMT was done on day 159 of hospitalization; the second was done on day 240. After BMT, the lymphoproliferative responses to PHA, Con A, and PWM were extremely low from day 159 to day 339. When IL-2 therapy was begun, proliferative responses increased exponentially and became maximal at a dose of 30,000 units/kg. After rIL-2 therapy was temporarily discontinued on day 397 for 3 wk, proliferative responses to PHA, Con A, and PWM decreased by >50% within a week. When therapy was resumed on day 422, proliferative responses to Con A and PWM normalized, and PHA responses were frequently, but not always, within the normal range.

Effect of therapy on lymphocyte phenotypes. Upon admission (day 0) at age 6 mo, the patient had normal proportions and numbers of T (84.0%) and B (9.8%) cells. After BMT, from days 159–308 of hospitalization, the percentage of T cells became low, ranging from 4% to 20%, and the number of B cells increased, ranging from 3% to 54%. After initiation of rIL-2 therapy (day 339), the percentage of T cells gradually increased from 37.5% to 84.0%, and the proportion of B cells decreased from 34.0% to 11.0%. These results indicate that *in vivo* rIL-2 therapy served to normalize the total numbers and proportions of T and B cells.

Current clinical status. Since her discharge from the hospital in September 1987, the patient has been receiving rIL-2 therapy at home at a dosage of 30,000 units/kg i.v. three times weekly via a broviac catheter. She remains free of serious infections and has not required hospitalization. At age 3 yr, she is just below the 50th percentile for height and weight.

DISCUSSION

In this study, we describe a patient with a primary defect in IL-2 secretion who has been managed successfully with rIL-2 therapy. The clinical illness was compatible with a diagnosis of SCID featured by persistent thrush, recurrent infections, persistent viral infections, and opportunistic infection with *P. carinii* pneumonia. The patient had phenotypically normal T- and B-lymphocyte distribution, but studies on T-lymphocyte activation via lectins demonstrated defective lymphoproliferative responses to PHA and responses at the low part of the normal range to Con A and PWM. Defective lymphoproliferative responses to allogeneic cells, common antigens, and anti-CD3 and anti-CD2 mAbs were also observed. Exogenous IL-2 consistently augmented lymphoproliferative responses to PHA, PMA, and anti-CD2 and anti-CD3 mAbs.

In the case of resting T cells, macrophages and/or IL-2 are essential for the initial responsiveness of CD3Ti receptor triggering (CD3 pathway) and to phytomitogens (36), whereas IL-1 and/or monocytes are not required for activation of the T cells via the CD2 pathway (30, 37). In this patient, IL-1 or normal irradiated monocytes failed to reconstitute the patient's low lymphoproliferative responses to phytomitogens

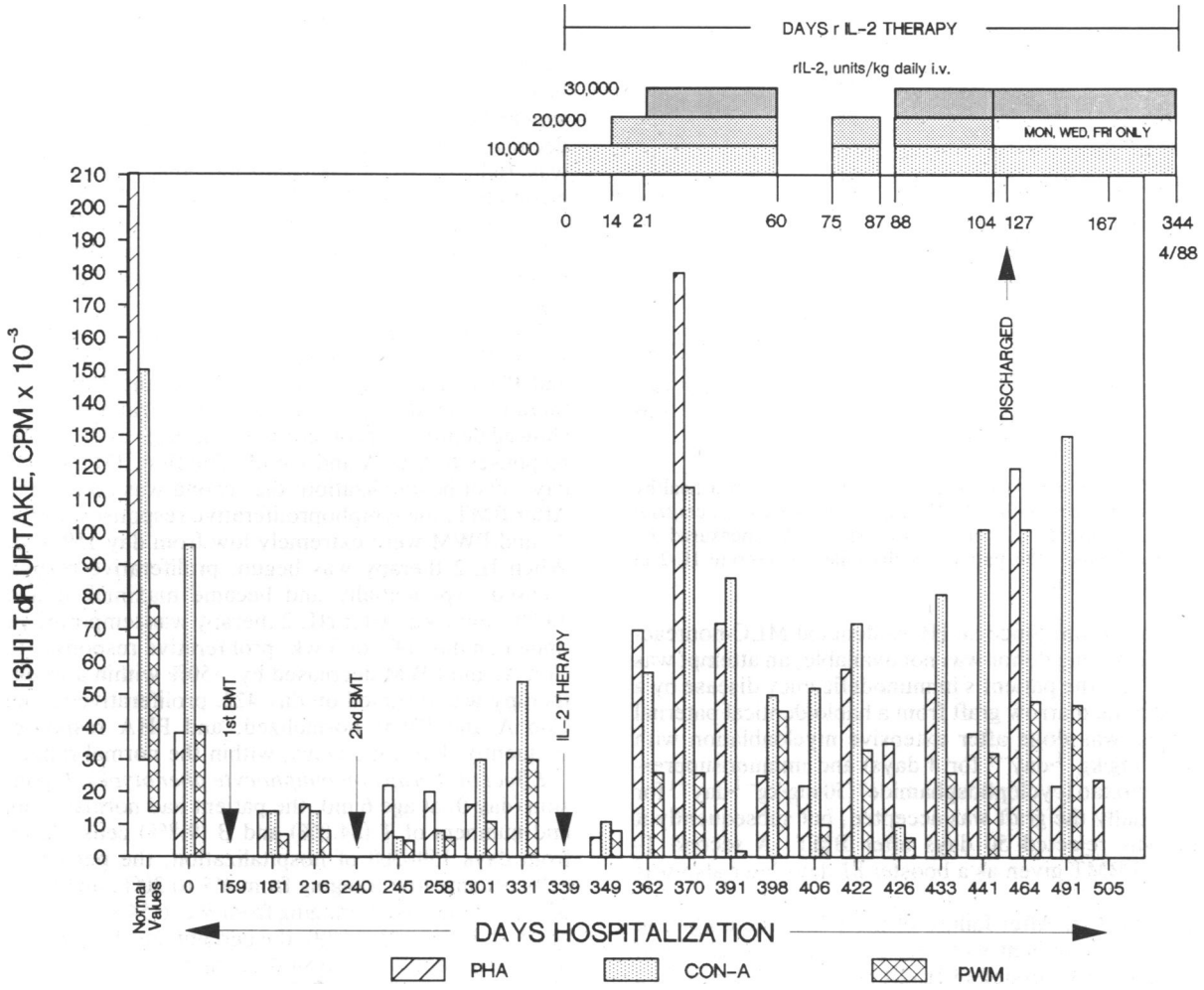

FIG. 2. Clinical course and lymphoproliferative responses. Vertical bars represent lymphoproliferative responses to phytomitogens. Horizontal bars indicate periods of IL-2 therapy at the doses indicated.

(data not shown). Furthermore, the patient's irradiated monocytes could support the proliferative responses of normal T cells, ruling out a primary defect of either monocyte-supportive function or IL-1 production. The observed enhancement of lymphoproliferative responses with exogenous rIL-2 suggested that the abnormalities observed in this patient might be linked to expression of IL-2R or to IL-2 production. The patient's cells failed to secrete IL-2 after stimulation with different lectins, but the cells did secrete a minimal amount of IL-2 after combined stimulation with PMA and ionomycin. Analysis at the molecular level showed no mRNA for IL-2 in a sample from the patient after PHA stimulation, suggesting that this patient's deficient expression of mRNA was linked to a failure to transcribe DNA that encoded secretion of IL-2 (T.C., E. Castigalli, R.P., R.A.G., and R.G., unpublished data).

Recent work (38, 39) suggests that IL-2 production depends on two early activation signals that are initiated by T-cell membrane perturbation: an increase in intracellular Ca^{2+} and activation of protein kinase C. The activation of CD3Ti receptors results in the cleavage of phosphatidylinositol 4,5-bisphosphate to inositol 1,4,5-trisphosphate ($InsP_3$) and diacylglycerol. $InsP_3$ causes release of Ca^{2+} from intracellular stores, while diacylglycerol activates protein kinase C. These two signals then synergize to initiate transcription of the IL-2 gene. Given that IL-2 mRNA was absent in our patient, it is possible that the patient's cellular defect may reside in inositol phospholipid metabolism leading to unresponsiveness of the T cells; such could be the case even though some T-cell activation events could occur—e.g., partial IL-2R and some degree of response to Con A and PWM (38, 39). Alternatively, T-cell proliferation in this patient may have been possible via an interleukin-independent pathway for lymphocyte activation (40).

The patient described here also appears to have an intrinsic defect of the B lymphocytes, as demonstrated by a defect in the differentiation of B cells into ISC. This abnormality, which occurs commonly in patients with SCID, was not corrected by addition of normal T cells and/or by exposure of B cells to exogenous IL-2. It is interesting to note that the patient's T cells could provide adequate help to normal B cells. Since production of IL-2, IL-4, and IL-6 is independently regulated (41), and since each is important in B-cell differentiation and immune response, it may be that production of the latter two factors is intact in this patient.

Recently, several patients with the SCID phenotype who have a defect in T-lymphocyte activation have been described. Such defects include the absence of IL-1 production (42) and defects of IL-2R expression and of IL-2 production (13–20). IL-2 receptors are expressed by activated T lymphocytes, and the binding of this receptor to its ligand is required for T-cell proliferation. Our findings imply that defective IL-2 secretion also results in one form of the SCID phenotype, which as reported herein has several distinct features. Such patients may have normal numbers of T and B cells based on surface markers and may manifest various degrees of deficiency in the T-cell activation pathways related to CD2 and CD3 stimulation and diminished prolifera-

tive responses to mitogens and antigens, all of which can be consistently augmented *in vitro* by rIL-2. In the patient described here, appropriately stimulated lymphocytes expressed the 55-kDa chain of the IL-2R but did not secrete IL-2. It is not known whether the patient could express the 75-kDa chain of the IL-2R. A likely defect in this patient's cells is a defect at the mRNA level, which is responsible for transcription of DNA that encodes IL-2 (T.C., E. Castigalli, R.P., R.A.G., and R.G., unpublished data).

In efforts to treat patient R.D., two haploidentical BMTs were unsuccessful. It is possible that engraftment of IL-2-producing donor cells allowed residual recipient T lymphocytes to proliferate and destroy the histoincompatible donor cells. With the failure of BMT, the long-term prognosis for this patient appeared very poor. At this point, treatment was initiated with rIL-2 (10,000 units/kg) given daily i.v. and was gradually increased to 30,000 units/kg i.v. This dosage of rIL-2 was well tolerated, as documented by clinical and laboratory analyses. The success of this new therapeutic approach underscores the need to establish the etiology of SCID in each affected patient and points to another direction for treatment by using rIL-2 for certain SCID patients.

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