Pediat. Res. *11:* 65 (1977)

# I. Introduction

RUSSELL J. BLATTNER

*Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston, Texas, USA*

Infants born with SCID rarely survive the first year of life because of their severely impaired ability to resist infection. The most effective method for correcting the deficiency in the human has been bone marrow transplantation. Bone marrow transplants from sibling donors matched at the HLA and MLC loci have been successful in restoring both humoral and cellular immunity in patients with SCID. Graft vs. host (GVH) disease has been a serious and frequently fatal complication (8, 55) and has necessitated refinements in this and other procedures for successful reconstitution of immune deficient patients. Yet in all cases of SCID there is a danger of death from infection before reconstitution can be achieved. Moreover, in some cases where reconstitution is successfully established without serious damage from GVH, death may occur from a pre-existing viral, protozoan, or bacterial infection. An approach to this problem was attempted in two children in Germany, nonidentical twins with a primary combined immune deficiency, lymphopenic hypo-γ-globulinemia (49). After diagnosis of their deficiency they were decontaminated and, at age 6 weeks, were placed in protective isolation to prevent reinfection. They survived in the isolators and, surprisingly, showed a slow maturation of the immune responses so that, at 30 and 32 months, respectively, they could be released into the unprotected environment.

The case to be presented here is that of a boy with SCID who has been reared from birth in strict reverse isolation to the age of 4 years. The possibility of an immune deficiency disorder was anticipated before birth in this case because of a brother who had SCID. The child was placed in the isolator at birth to prevent infection until a bone marrow transplant could be made. Unfortunately, no nonreactive donor for bone marrow transplantation has been found for him. Therefore, he has been maintained in a simplified and specially constructed plastic isolator system. This is a completely closed system which the child never leaves and which the attendants never enter but which allows the child and attendants to see each other clearly at all times.

The survival and continuing excellent health of a child with SCID for such a long time and under such unusual circumstances has provided a unique opportunity for observation and study. A number of interesting and unexpected findings have led to more intensive research into various aspects of his developmental progress as well as into the nature of his immunologic defect. The present report, therefore, includes a comprehensive survey of his care and development, along with related research studies during his life to the age of 4 years under the conditions of strict reverse isolation.

 *Printed in U.S.A.*

Pediat. Res. *11:* 56 (1977)

# II. Family Background, Early History, and Diagnosis

JOHN R. MONTGOMERY, MARY ANN SOUTH, RAPHAEL WILSON, AND ROSALINDA SORIANO

*Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston, Texas, USA*

The parents are from the upper middle income bracket and are in good mental and physical health. They have had two other children, including a girl who is 3 years older than the patient and who appears to be normal in every respect, and a boy who died at 7 months with SCID. There is no evidence of immune deficiency in either parent or in the genetic background on the maternal side. Three male children of a brother of the mother's father may have had immune deficiencies. Two had been treated during childhood for γ-globulin deficiency but the treatment had been discontinued and the two grew to be teenagers with no apparent problems. Another died suddenly at 8 months, reportedly with "Asian influenza." At autopsy, however, lymph nodes in this infant appeared to be normal with abundant lymphocytes.

The deceased older brother of the patient had been under the care of one of us (Dr. J. R. Montgomery) and had been diagnosed to have SCID in infancy. This first son had received a

bone marrow transplant from his sister who was histocompatible with him. The child died a week after transplant, but autopsy showed no evidence of engraftment or GVH disease within that time limit. Autopsy findings showed *Pneumocystis carinii* pneumonia to be the direct cause of death and contributed to the diagnosis of SCID. The findings were hypoplasia of lymphoid tissue, including Peyer's patches and lymph nodes. Only one lymph node was found in the entire autopsy material. This was predominantly sinusoidal with few collections of lymphocytes and no peripheral follicular organization. The thymus was approximately that of a 6-week embryo, *i.e.*, it was epithelial, without lymphoid population, and showed no Hassal's corpuscles. The spleen consisted of sinusoidal tissue with small Malpighian corpuscles without germinal centers. There were no plasma cells in the intestinal lamina propria. The hypoplasia of lymphoid tissue with, however, a few lymphocytes present, is consistent with the diagnosis of X-linked SCID rather than with the recessive autosomal type of SCID according to the criteria of Hoyer *et al.* (23).

After the birth of the first defective child there were several possibilities to consider in estimating the chances that there might be other children with SCID. Statistically, about one-third of the cases are without a positive family history. The histology in such cases may resemble either the X-linked or the autosomal recessive type of SCID. The first case could have been the result of a new mutation in the mother or in the child. If the first case was the result of a new mutation in the child there would be a 1/10,000 chance for the parents to have another child with SCID, the same chance as with the first child. If the first child's disorder was familial, *i.e.*, the result of a mutation in a past generation, there would be a 25% chance for a child to be affected in future pregnancies. This would increase to 50% for a male child if the SCID were the X-linked type. There would be a 50% chance for a child of either sex being a carrier in autosomal recessive SCID. The first boy in the present family was diagnosed as having X-linked SCID on the basis of histologic findings, according to the criteria of Hoyer *et al.* (23). There was, at that time, no certain way to differentiate between sporadic (new mutation) and genetic types of SCID or between X-linked and autosomal recessive types of SCID except on the basis of family history.

With the above facts and considerations in mind, the parents received genetic counseling after the death of their first son. They understood the risk, yet they decided to have another child.

In the early part of the seventh month of the mother's third pregnancy, a karyotype study (11) of the amniotic fluid cells indicated a male child. There is no method available to make the diagnosis of SCID *in utero*. If the first child's defect were, indeed, familial, there was a 50% chance that this second boy would have SCID. On September 21, 1971, at term, a cesarian section was performed. This was an ordinary cesarian with extraordinary precautions to eliminate air contamination of the delivery room. The details of this successful germ-free birth have been published (32).

The infant (*DV*) was placed immediately in the isolator. He appeared normal on gross examination except for the absence of palpable lymph nodes. The Apgar score at 1 min and at 5 min was 9. The weight was estimated to be 6.5–7 lbs. Chest x-rays, taken at birth and in the weeks following, appeared to be normal except for a narrowed mediastinum and no thymic shadow (Fig. 1). The results of laboratory tests were as follows: urinalysis, normal; serum calcium, 8.4 mg/100 ml; glucose, 112 mg/100 ml; maximum bilirubin total 8.5 mg/100 ml, direct 0.9 mg/100 ml; follow-up bilirubin total 4.2 mg/100 ml, direct 0.7 mg/100 ml; Coombs' direct and indirect, negative; blood-urea-nitrogen, 8 mg/100 ml; phenylketonuria, negative. His electrophoretic pattern for total serum protein was normal. His blood group was ABO group A and he was $Rh_0$ (D) positive. His blood count at birth was normal except that his absolute lymphocyte count ranged from 300–440/mm$^3$ and the lymphocytes showed no proliferative response to PHA.

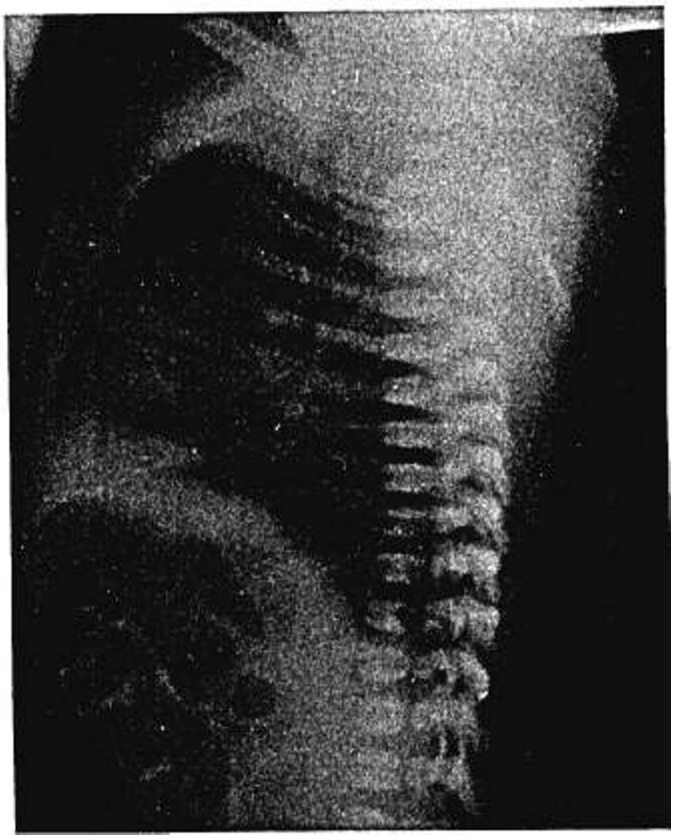

Fig. 1. Chest x-ray of severe combined immune deficiency patient taken at birth shows no thymic shadow.

In the months after birth the patient continued to thrive in the isolator but specific tests showed both the antibody-producing immune system (B cells) and the cell-mediated immune system (T cells) to be severely defective (47). Deficiency of the B-cell system was demonstrated as follows: IgG progressively decreased to zero, IgM was low and IgA was absent; antibody responses to specific antigens were negative; isohemagglutinin titers were negative. Deficiency of the T-cell system was demonstrated as follows: stimulation of lymphocytes in mixed lymphocyte culture or by many types of mitogens was always low in comparison with controls; delayed hypersensitivity tests were negative; a skin graft from an unrelated donor was not rejected. On the basis of these tests and the family history, the patient was diagnosed as having the X-linked type of severe combined immune deficiency.

Tissue typing of the patient showed phenotype A1 B7/Aw31 B14. Histocompatibility HLA testing of the father, mother sister, and paternal grandparents showed none with the same phenotype. The patient's lymphocytes, used as stimulating cells in MLC, elicited positive responses by lymphocytes from the father, mother, and sister. Subsequent search for HLA-matched donors in the national and international tissue typing laboratories (56) has shown four HLA matches for *DV* but none of these has been nonreactive with his cells in MLC. Therefore, this patient has not received a transplant and he has remained in strict reverse isolation to the present, when he is 4 years old.



*Printed in U.S.A.*