Severe Combined Immunodeficiency among the Navajo. I. Characterization of Phenotypes, Epidemiology, and Population Genetics

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Abstract Previous studies have identified a high incidence of severe combined immunodeficiency (SCID) among the Navajo Native American population. To determine the incidence and population genetics of this condition, we reviewed the death certificates of all children who died between 1969 and 1982, established the cases that met criteria identified in previously investigated cases, and interviewed the selected children's families. SCID cases were distributed spatially and temporally. Segregation parameter estimates of 0.27–0.38 were obtained from data from 24 interviewed families, suggesting an estimated gene frequency of 2.1% (arguing against a multifactorial inheritance). SCID cases referred to specialty centers lacked T and B cells in their blood, and their serum immunoglobulins ranged from absent to near normal.

Severe combined immunodeficiency (SCID) describes a group of conditions in which there is a failure of antibody responses and of cell-mediated immunity (WHO Scientific Group 1986). Most cases are congenital, and approximately 25% of cases are the consequence of adenosine deaminase deficiency. The etiology of the remaining 75% of cases is poorly understood, and for clinical purposes these cases are divided into those with X-linked inheritance (incidence estimated at 1 in 1,000,000 live births) (Gatti and O'Reilly 1979) and those with autosomal recessive inheritance (incidence estimated at 1 in 1,000,000 births) (O'Reilly 1979). Nothing is known of the underlying biochemical abnormality in these cases, and immunologic tests point to further heterogeneity. For example, approximately 60% of cases have circulating B cells and no T cells and 20% have neither T cells nor B cells in the blood. The

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occasional engraftment of maternal lymphocytes in scid patients (Pollack et al. 1982; Flomenberg, Dupont et al. 1983) confuses the classification of scid by lymphocyte phenotype, and the rarity of the condition makes further investigation difficult.

In 1980 we reported five cases of scid in a population of Athapaskan-speaking Navajo (Murphy et al. 1980). The incidence of scid at that time was estimated to be 50 per 100,000 live births. There were no obvious etiologic factors, although we found that serum from affected children contained sufficient interferon to inhibit proliferative responses by mitogen-stimulated lymphocytes (Jones et al. 1983).

We now report the results of an epidemiologic study undertaken to determine as completely as possible the distribution among the Navajo of scid cases in space, time, and pedigree. We also report the results of immunologic tests undertaken on affected infants who were diagnosed in time for referral to tertiary care centers to define the phenotypic heterogeneity of scid among the Navajo.

Materials and Methods

Population and Geographic Distribution. The Navajo are a relatively endogamous population of American Indians of Athapaskan descent who have a restricted repertoire in the histocompatibility (HLA) (Troup et al. 1982) and GM (Williams et al. 1985) systems and whose HLA antigens resemble those of other native North American populations (Williams et al. 1981; Kostyu and Amos 1981). The majority live in scattered rural settlements on the Navajo Reservation, which covers approximately 25,000 square miles of northern Arizona and New Mexico and southern Utah. Although the availability of health care has improved in recent decades (Broudy and May 1981), infectious disease continues to be a major health problem.

Clinical and Immunologic Studies. The World Health Organization (WHO) classification (WHO Scientific Group 1986) of scid states that this category of disease should be restricted to infants with severe and potentially fatal defects in cell-mediated immunity and antibody production. Subcategorization is based on enzymatic abnormalities, mode of inheritance, or level of faulty cellular development. Some children have low levels of T cells and B cells, whereas others have a low level of T cells and a normal amount of B cells. Thus the overall clinical and laboratory patterns allow assignment of this diagnostic label only to severely ill children.

Laboratory criteria for the diagnosis of scid in this study at a tertiary care center were (1) lack of normal levels of T cells in blood and (2) immunoglobulin deficiency or, where immunoglobulins were present,
abnormalities in their electrophoretic mobility together with antibody deficiency. Supportive clinical criteria were absence of the thymus (determined by chest X-ray), opportunistic infections, and diarrhea. Criteria at autopsy were absence of the thymus and small lymph nodes with abnormal architecture.

The following case study is illustrative. Patient 16 weighed 8 lbs., 15 oz. at birth. He was the first child of healthy unrelated Navajo parents from the Cameron area. At 1 month of age he was admitted to the hospital with a cough and cyanosis and was treated for chlamydia pneumonia for 8 days. When he was discharged, he had an oral ulcer (noma), which progressed to a 1 × 2 cm lesion over the next 4 days. He was admitted to the hospital again and treated with Pediazole for 10 days, during which time he developed oral candidiasis, diarrhea, and fever. No thymus was seen on the chest X-ray. The oral ulcer healed slowly over the next 6 weeks. At age 2 months he developed fever and cyanosis. His blood count showed 9800 white blood cells per square millimeter, 94% segmented neutrophils, 4% lymphocytes, and 2% metamyelocytes, and he had pneumococci and Klebsiella species in a tracheal aspirate. The pneumonia worsened despite antibiotic treatment, and tests for respiratory syncytial virus pneumonia were positive. Lymphocyte phenotyping of blood mononuclear cells (MNC) showed 0% T3, 0% T4, 0% T8, 57% Leu 11, 0% B, and 7% Ia; there were no proliferative responses to phytohemagglutinin (PHA) or in mixed lymphocyte culture. He died before he could be given a bone marrow graft.

**Immunologic Methods.** Blood T lymphocytes were stained with monoclonal antibodies (OKT3, OKT4, OKT8, Ortho Reagents, Raritan, NJ), either directly conjugated or unconjugated, and then with fluorescein conjugated goat-anti-mouse IgG. B cells were identified by surface IgM, and pre-B cells by cytoplasmic u chains and lack of surface IgM (Hayward 1978). Natural killer cells were identified with anti-CD16 monoclonal antibodies (Becton-Dickinson, Mountain View, CA) by indirect immunofluorescence. Serum immunoglobulins were measured by nephelometry. Lymphocytes were cultured in RPMI 1640 with 10% human serum; PHA cultures were stimulated for 3 days with a 4-hour \(^3\)H thymidine pulse, and mixed lymphocyte cultures for 6 days with an 8-hour \(^3\)H thymidine pulse [methods are further described by Hayward and Harbeck (1983)]. Blood mononuclear cells were HLA typed with NIH extended or Terasaki trays by standard microcytotoxicity tests.

**Epidemiologic and Population Genetic Studies**

**Death Records.** Initially, the death records of all Native Americans who had died in Arizona between the years 1969 and 1978 were reviewed. Children who died between the ages of 1 and 24 months were catego-
rized as having a death associated with an infectious disease or for other reasons (i.e., trauma or congenital abnormalities). Analysis of this review suggested differences between Navajo and non-Navajo children (see Figure 1). Subsequently, additional death records were obtained and the 1969–1982 death records of all Navajo children who died in Arizona and New Mexico between 1 and 24 months of age were evaluated in further detail. Criteria for possible immunodeficiency and thus inclusion in further record searches included (1) definitive diagnosis of SCID, (2) infectious disease (including pneumonia, diarrhea, and encephalitis), (3) failure to thrive or malnutrition, and (4) unknown causes (including sudden infant death syndrome). Excluded were cases of trauma, congenital malformation, and death within 2 weeks of birth. Three hundred deaths that fit these criteria were chosen for further investigation.

Hospital Chart Review. Attempts were made to locate all hospital and clinic charts on all 300 cases: charts for 248 cases were found and reviewed. Charts were initially sought at the hospital or clinic where the death was certified. Additional records were obtained from the homes of the parents, the birth site, or clinics mentioned in other charts. All retrievable charts were examined at each hospital and clinic identified. For many children it became possible to follow in some detail the entire illness history. Information recorded from each chart included nature and duration of illness; X-ray or autopsy data on presence of thymus; white blood cell count, differential, absolute number, and appearance of leukocytes; serum immunoglobulin levels; skin rashes, candidiasis, and mucocutaneous ulcers; presence or absence of lymphoid tissue; failure to thrive; comments on liver or spleen size and consistency; and unusual infectious agents or those associated with depressed immune function (such as pseudomonas species).

Abnormal objective values included length and weight less than the 10th percentile for age, less than 1500 lymphocytes/mm³, serum IgG levels below 2 standard deviations below age mean, absent thymic shadow on chest X-ray, and absence of lymphoid tissue on physical examination.

Cases were assigned on the basis of these data to one of four patient groups:

1. Known immunodeficiency: definitive diagnosis from a tertiary care center (see Table 1).
2. Probable immunodeficiency: (a) recurrent infections, failure to thrive, and abnormal laboratory results; (b) recurrent infections, including skin lesions and failure to thrive, with no available laboratory data; (c) recurrent infections, including skin lesions and failure to thrive, with normal laboratory findings.
3. Possible immunodeficiency: death at 2 months of age or less with first respiratory or gastro-intestinal (GI) infection and abnormal laboratory findings.

4. Questionable immunodeficiency: death at 24 months or less with first major GI or respiratory infection but no abnormal laboratory findings or evidence of failure to thrive.

**Demographic Information.** Families of known and probable cases were located with the help of local public health nurses and asked for interviews. Informed consent and interview data were collected with the assistance of a Navajo interpreter who had already lost two affected SCID children. Interview data included places of residence and work during the life of each parent; type of work; fertility history of the mother, including offspring of all partners; health status of all offspring; and details of each parental sibship (including members who had died, their age at death, and the cause if known; and the number, sex, and health status of offspring of each sibling). For families initially identified in the chart review process, additional information on the course of the illness of the affected child was obtained by interview. This additional information was included in the final designation of status. Children for whom the natural history of the disease was consistent with SCID were designated “clinical SCID” and were included with the cases in all subsequent analyses. (For example, several children in this category had other siblings who died of similar conditions before our study period; still others were siblings of children who developed SCID as determined in a tertiary care center after 1982.) Children with medical data suggesting SCID but whose families could not be located were not included as cases.

**Segregation Analysis.** Segregation analysis for single-gene Mendelian inheritance was performed on the family data using standard methods (Morton 1962). Maximum likelihood estimates of the ascertainment probability (π), the segregation ratio (p), and the proportion of sporadic cases (X) were obtained under a model of segregation with incomplete ascertainment, a mixture of sporadic cases, and a uniform segregation frequency in a sample of nuclear families. An alternative model is the multifactorial threshold model described for birth defects and other apparently non-Mendelian traits (Carter et al. 1982). Under a multifactorial threshold model, expression of a trait depends on the additive effects of several minor genes and environmental factors. That model was tested for goodness of fit (Gladstien et al. 1978). The test is applicable to disorders showing different incidence rates in males and females and involves a comparison of the observed number of nuclear families having at least two affected offspring with the expected distribution for such families under the multifactorial threshold model. The computation of the ex-
Table 1. Clinical Findings and Outcomes

<table>
<thead>
<tr>
<th>Year of Birth</th>
<th>Age at Presentation</th>
<th>Main Symptoms</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>birth</td>
<td>Diarrhea, pneumonia</td>
<td>Marrow</td>
<td>Died, GVH</td>
</tr>
<tr>
<td>2</td>
<td>birth</td>
<td>None</td>
<td>TEG</td>
<td>Died, Candida sepsis</td>
</tr>
<tr>
<td>3</td>
<td>2 wk</td>
<td>Diarrhea, pneumonia</td>
<td>None</td>
<td>Died, RSV</td>
</tr>
<tr>
<td>4</td>
<td>2 mos.</td>
<td>Diarrhea, noma</td>
<td>TEG</td>
<td>Died, renal failure</td>
</tr>
<tr>
<td>5</td>
<td>2 mos.</td>
<td>CMV, pneumonia</td>
<td>None</td>
<td>Died, CMV</td>
</tr>
<tr>
<td>6</td>
<td>3 mos.</td>
<td>Diarrhea, pneumonia</td>
<td>TEG</td>
<td>Died, sepsis</td>
</tr>
<tr>
<td>7</td>
<td>15 mos.</td>
<td>Staph skin sepsis</td>
<td>Grafted</td>
<td>Died, bronchiectasis</td>
</tr>
<tr>
<td>8</td>
<td>8 mos.</td>
<td>Diarrhea, thrush</td>
<td>Grafted</td>
<td>Reconstituted</td>
</tr>
<tr>
<td>9</td>
<td>4 mos.</td>
<td>Diarrhea, GVH</td>
<td>Grafted</td>
<td>Died, antibody deficiency</td>
</tr>
<tr>
<td>10</td>
<td>1 mo.</td>
<td>Diarrhea, ulcers</td>
<td>Grafted</td>
<td>Reconstituted</td>
</tr>
<tr>
<td>11</td>
<td>13 mos.</td>
<td>Oral ulcers</td>
<td>Grafted</td>
<td>Died, noma</td>
</tr>
<tr>
<td>12</td>
<td>8 mos.</td>
<td>URTI, ulcers</td>
<td>None</td>
<td>Died, meningitis</td>
</tr>
<tr>
<td>13</td>
<td>5 mos.</td>
<td>Diarrhea</td>
<td>None</td>
<td>Died, GVH</td>
</tr>
<tr>
<td>14</td>
<td>4 mos.</td>
<td>Diarrhea, pneumonia</td>
<td>Grafted</td>
<td>Died, EBV hepatitis</td>
</tr>
<tr>
<td>15</td>
<td>4 mos.</td>
<td>Pneumonia, ulcers</td>
<td>None</td>
<td>Died, CMV hepatitis</td>
</tr>
<tr>
<td>16</td>
<td>4 mos.</td>
<td>Pneumonia, ulcers</td>
<td>None</td>
<td>Died, RSV pneumonia</td>
</tr>
<tr>
<td>17</td>
<td>2 mos.</td>
<td>Diarrhea, ulcers</td>
<td>Grafted</td>
<td>Died, EBV hepatitis</td>
</tr>
<tr>
<td>18</td>
<td>9 mos.</td>
<td>Meningitis, UTI</td>
<td>Grafted</td>
<td>Died, interstitial pneumonia</td>
</tr>
</tbody>
</table>

a. URTI, upper respiratory tract infections; GVH, graft versus host disease; EBV, Epstein-Barr virus; CMV, cytomegalovirus; RSV, respiratory syncytial virus; TEG, thymic epithelial graft.
b. Age at presentation is the subjects age when the principal symptoms first appeared.
c. From nonirradiated blood transfusion in neonatal period.

Expected distribution is conditioned on several family-dependent variables, including parental status, numbers of sons and daughters, and whether each family was ascertained through only affected males or through at least one affected female. The probabilities of observing the data are derived for a range of heritabilities and ascertainment probabilities.

Results

Clinical Findings. Clinical data on the cases referred to tertiary centers are summarized in Table 1. Cases identified after 1982 and therefore after the study period are included to demonstrate the narrow range of clinical findings. Significant findings include the occurrence of oral mucosal ulceration in four of the nine cases seen since 1982; in three of these, the lesions were severe enough to be described as noma or cancrum oris. The high frequency of diarrhea is expected.
Table 2. Immunologic Findings

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Lymphocytes (1600-5480 mm³)</th>
<th>CD4 (29-63)</th>
<th>CD8 (18-44)</th>
<th>CD16 (4-16)</th>
<th>B (3-12)</th>
<th>IgG c</th>
<th>IgM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Birth</td>
<td>720</td>
<td>ND</td>
<td>0</td>
<td>1000 b</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Birth</td>
<td>450</td>
<td>20% ER</td>
<td>ND</td>
<td>200</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>2 wk</td>
<td>700</td>
<td>5% ER</td>
<td>0</td>
<td>80</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>2 mos.</td>
<td>700</td>
<td>7% ER</td>
<td>0</td>
<td>135</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>2 mos.</td>
<td>1000</td>
<td>55% ER</td>
<td>ND</td>
<td>158</td>
<td>91</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>3 mos.</td>
<td>1500</td>
<td>17% ER</td>
<td>0</td>
<td>143</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>15 mos.</td>
<td>2210</td>
<td>3% ER</td>
<td>0</td>
<td>48</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>8 mos.</td>
<td>3840</td>
<td>2% ER</td>
<td>52</td>
<td>561</td>
<td>10</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>4 mos.</td>
<td>4320</td>
<td>7% ER</td>
<td>0</td>
<td>7</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>1 mo.</td>
<td>1606</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>ND</td>
<td>0</td>
<td>1050</td>
</tr>
<tr>
<td>11</td>
<td>13 mos.</td>
<td>2600</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>22</td>
<td>0</td>
<td>248</td>
</tr>
<tr>
<td>12</td>
<td>8 mos.</td>
<td>4320</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>ND</td>
<td>0</td>
<td>59</td>
</tr>
<tr>
<td>13</td>
<td>5 mos.</td>
<td>740</td>
<td>0</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>14</td>
<td>4 mos.</td>
<td>1410</td>
<td>4</td>
<td>0</td>
<td>5</td>
<td>47</td>
<td>0</td>
<td>147</td>
</tr>
<tr>
<td>15</td>
<td>4 mos.</td>
<td>1960</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>ND</td>
<td>0</td>
<td>131</td>
</tr>
<tr>
<td>16</td>
<td>4 mos.</td>
<td>392</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>57</td>
<td>0</td>
<td>364</td>
</tr>
<tr>
<td>17</td>
<td>2 mos.</td>
<td>376</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>409</td>
</tr>
<tr>
<td>18</td>
<td>9 mos.</td>
<td>330</td>
<td>0.5</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>0.5</td>
<td>951</td>
</tr>
</tbody>
</table>

a. ER, E-rosette-forming cells; B, B cells, IgG, IgA, and IgM are serum level (mg/dl).
Patients 1–9 were evaluated before the availability of monoclonal antibodies; therefore only ER data were available. Patients 10–18 did not have ER studies.
b. Range of values in healthy siblings (n = 8) of Navajo patients (percent); no Ig isotype values for Navajos are available.
c. When IgG is present alone, it is probably mostly maternal. Subjects 10 and 16 had received intravenous IgG before levels were measured. Serum samples from subjects 16, 17, and 18 were measured by high-resolution electrophoresis; in each case one or more monoclonal bands were seen in IgG and IgM.

Immunologic Studies. In the earlier cases (pre-1982), T cells were identified only by the sheep red blood cell rosette test because monoclonal antibodies were not yet available. The findings on the later cases (numbers 10–18), described in Table 1, indicate a consistent lack of T cells with the CD3 antigen in all the subjects except case 14, who had active graft versus host disease when examined (Table 2).

PHA did not stimulate cells from any of the patients. Lymphocytes from an occasional patient did respond in mixed lymphocyte culture (MLC) reaction with parent or sibling stimulator cells.

The HLA typing data shows that the A2, A24, B15, B27, and B35 antigens were often found, as is generally the case with the Navajo (Trup et al. 1982).
Epidemiology. Figure 1 illustrates the distribution of early childhood deaths among Navajo and non-Native Americans in Arizona born between 1969 and 1978. Noninfectious deaths vary from year to year in both groups, with no clear trend over time. In contrast, the frequency of infectious deaths dropped precipitously among the non-Navajo tribes, whereas it remained high among the Navajo. This overall decrease in infectious diseases among Native Americans correlates with the increased availability of medical care and improved nutrition (Broidy and May 1981). The distribution by sex of cases and noncases was calculated from the 248 individuals whose charts were located. Cases were those with definitive diagnoses and those classified as clinical cases by the criteria given earlier. Among the cases 52% were male; among noncases 58% were male. SCID among the Navajo appears to show no differential distribution by sex.

The geographic distribution of on-reservation clinical cases from 1968 to 1981 (Arizona and New Mexico) was analyzed based on the service unit in which the parents resided at the time of the child's death. In all but two cases this was the same service unit in which the child was born. The distribution of cases was found to be homogeneous throughout the reservation, not including the Tuba City Service Unit (chi-square value for non-Tuba City service units = 3.645, d.f. = 5, p = 0.6041). SCID represents 5.56% of all deaths to children under 24 months in 6 of the 7 service units; in Tuba City SCID was responsible for 14.5% of deaths (difference of Tuba City from the rest of the reservation, one-sided binomial test, p = 0.0171). The risk ratio of Tuba City to the remainder of the reservation was 2.60 (90% confidence interval 1.46–4.66).

The minimum incidence rate was calculated from these data. From 1969 to 1981 there were approximately 54,000 live births on the entire Navajo Reservation. The 28 on-reservation cases represents an incidence of 52 per 100,000. The year-to-year variation in total number of cases of SCID was compared to the total number of deaths for each year. The greatest number of deaths from SCID was in 1976: almost 10% of all deaths of Navajo children below 24 months of age. Over the entire period SCID deaths represented 7% of all Navajo deaths in the 1–24 months age group.

Population Genetics. Segregation analysis was performed on data from 24 interviewed families, using only data on the full sibships of the probands. Four separate analyses were run, omitting or including as cases those apparently affected children not found in our chart reviews (e.g., those born outside the study period). Segregation parameter estimates ranged from 0.27 to 0.38. In this maximum likelihood estimation procedure, with the small number of families, neither recessive nor dominant models of inheritance could be rejected with significant chi-square values. It was possible, however, to reject the multifactorial threshold model...
Figure 1. Number of deaths in Native American children, age 1–24 months, in Arizona 1969–1978. (A) Navajo; (B) non-Navajo. Deaths attributed to infectious diseases are depicted in dotted columns and deaths attributed to noninfectious causes are in hatched columns. Data for 1978 is only partial.
for a wide range of heritabilities and ascertainment probabilities because there were statistically too many affected individuals in the families.

An evaluation of pedigrees was possible among families in the western region of the reservation. Figure 2 presents a pedigree from that area, which accounted for a large proportion of the excess cases in the Tuba City Service Unit; it includes several cases outside the 1969–1982 study period for statistical analysis. Affected families are related to each other horizontally; a potential common ancestor has been determined for only two families, relating affected children as third cousins. In one family both the mother and the father of the probands are related to other parents of probands; in three families both members of a grandparent pair are related to other parents or grandparents of probands.

These results are all consistent with an autosomal recessive disease. Given the incidence of scid of 52 per 100,000, the estimated gene frequency would be 22.5 per 1000 (2.25%). Families (both affected and unaffected) are represented multiple times in these pooled data. Therefore we also calculated the average of the gene frequency estimates for each year in the period 1968–1981, because any particular family is represented only once in a calendar year. The average gene frequency estimate is 21 per 1000 (2.1%). Because of the high likelihood under ascertainment of scid, this estimate is probably conservative.

Discussion

Immunologic Characteristics. Our subjects differ from classical descriptions of scid in several ways. Only 3 cases were clearly lymphopenic when symptoms appeared (cases 16, 17, and 18), although cases 10 and
14 were low in comparison with age-matched controls. Many of the subjects had substantial amounts of serum IgG when diagnosed. In most cases these subjects were young enough for this IgG to be derived from their mothers. Six of the 18 cases had readily measurable amounts of IgM (values of <9 mg/dL are disregarded because the rate nephelometry method is generally unable to distinguish between these low levels and complete absence of IgM). In patient 14 the presence of near-normal amounts of IgM led to considerable delay in diagnosis, and it was only in subsequent patients that serum immunoglobulins, when present, were analyzed by high-resolution electrophoresis. Both the subsequent cases with detectable IgM (17 and 18) had monoclonal IgM bands. None of the subjects had B lymphocytes detected in the blood by immunofluorescence for surface immunoglobulin, even when serum immunoglobulin was present. This finding suggests that the immunoglobulin that was made did not arise following the normal development of the B cell series.

Monoclonal antibody phenotyping of blood MNC for T cells gave negative results except for one patient (case 14) who had a mild skin rash 2 months following an unirradiated blood transfusion. When tested by us or at referring hospitals, many of the patients had a low level (<10%) of E-rosette-forming cells. The E rosette receptor (CD2) is expressed on natural killer cells and on T cells. Because all the tested patients had normal or high numbers of natural killer cells with the CD16 (Leu 11a) antigen (Lanier et al. 1983), it seems likely that these cells were responsible for the rosetting. Patients 2, 3, and 4 had numerous cell-containing parallel tubular arrays (Payne et al. 1977). This organelle was subsequently found to be a marker of NK cells (Payne and Glasser 1981). The lack of cells with T cell antigens is consistent with the uniform lack of response to PHA we observed and supports a severe T cell deficiency.

Proliferation in MLC was detected with several patients' lymphocytes, as has previously been reported in other SCID patients. In each case the subjects' lymphocytes failed to proliferate in PHA stimulated cultures, although they did proliferate in the presence of IL2, whether PHA was added or not. The phenotype of the cells that proliferated in the presence of IL2 is unknown, although natural killer cells would seem possible candidates. These cells are known to be capable of expressing IL2 receptors, they are present in the subjects' MNC preparations, and they proliferate in cultures containing IL2 (Flomenberg, Welte et al. 1983). The similarity among HLA types in patients and North American Indians in general and the occurrence in several families of HLA matched but healthy siblings argue against the presence of the Navajo SCID gene on chromosome 6.

Epidemiology and Genetics. Because oral ulceration is uncommon in infants, its presence was useful in facilitating epidemiologic studies, such
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as this one, that rely on retrospective data collection. The mother of one child identified by chart review as having SCID reported that she had had four children die of the same conditions, with the skin lesions being, for her, the most characteristic feature (Rotbart et al. 1986).

With high rates of infectious disease and malnutrition common among the Navajo into the 1970s, the presence of SCID was unlikely to be detected. Deaths from SCID have been occurring at least since the 1950s according to our interviews, but such deaths were routinely attributed to infectious diseases or malnutrition. It has only been with the substantial improvements in the availability of medical care that such children have become identifiable.

The most likely genetic model is a recessive one. None of the Navajo children evaluated at tertiary care centers had abnormalities in the purine nucleotide enzyme pathway, as seen in some cases of SCID with autosomal recessive inheritance patterns. The estimated segregation parameters are higher than the expected 0.25, but not significantly so, and may be due to sampling error in this small sample. The gene frequency estimated for Navajo SCID as a genetic recessive is comparable to that for cystic fibrosis in the US white population or slightly higher than the prevalence of Tay-Sachs disease among the Ashkenazim (1 per 1500). However, it is clear for the clusters in the Tuba City area that the gene frequency in the western reservation is higher.

In researching Navajo pedigrees in the later phases of data collection, it became clear that much of the information becomes blurred at the time of the Long Walk to Fort Sumner, New Mexico, in 1868. This historical event resulted in major population reduction, an event commonly associated with increased frequencies of recessive alleles. The pedigree data are remarkable for the lack of common ancestors identified. This is consistent with Navajo marriage rules, which tend to maximize nonconsanguineous matings in the face of tribal and regional endogamy through rules prohibiting marriage into either the mother’s or the father’s clan or to members of related clans. In the one pedigree presented, it is notable that the linkage requires kinship through males and thus is consistent with the marriage rules. The pedigrees suggest that, rather than the increased homozygosity expected in association with inbreeding, there may be excess heterozygosity associated with maximized outbreeding. In that case the gene frequency estimates based on random mating at genetic equilibrium would underestimate the true frequency.

Two cases of SCID in Native Americans in this geographic area have now been diagnosed outside the Navajo population. One was among the Jicarilla Apache in northern New Mexico and the other among the San Carlos Apache in central Arizona. Both tribes are Athapaskan speakers, closely related genetically to the Navajo (Williams et al. 1985; Kostyu and
Amos 1981). The Jicarilla Apache were interred at Fort Sumner with the Navajo. The other Apache patient has a Navajo father.

With continuing improvements in health status for Navajo children, SCID will probably come to account for an increasing share of early mortality in that population. Successful treatment by bone marrow transplants continues to depend on the speed of diagnosis and referral and the availability of a suitable donor. Although we allude to differences in immunologic function between Navajo children and the classic presentation of SCID in other populations and although there is remarkable similarity among the Navajo cases, it is premature to consider Navajo SCID as a separate entity. With the rapid rate of advancement of understanding of the molecular genetics of human immunodeficiency diseases (Puck et al. 1989), however, additional information regarding this population will be forthcoming in the near future.

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