Severe Combined Immune Deficiency Presenting with Cyclic Hematopoiesis

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At age 2 months a male infant presented with a cyclic clinical syndrome every 14–21 days that included pharyngeal aphthous ulcers, high fever, lymphadenopathy, pallor, and malaise. Serial blood studies indicated cycling of all blood cell elements, compatible with a diagnosis of cyclic hematopoiesis (CH). He also manifested a progressively severe immune deficiency, not described before in human CH. When first studied at age 5 months, he was hypogammaglobulinaemic with normal B lymphocyte numbers. By 6.5 months, he was agammaglobulinemic. At age 8 months, he developed severe pneumocystis carinii pneumonia, and studies showed a state of severe combined immune deficiency. The patient received a bone marrow transplant from his HLA-identical sister with no preconditioning therapy. Subsequently, normal immune function developed and the cyclic hematopoiesis resolved. The majority of lymphocytes is of donor origin. Persistence of erythrocytes and neutrophils of recipient origin suggests that the hematopoietic stem cells were not abnormal. We speculate that this patient had a primary deficiency of a differentiation factor affecting maturation of lymphoid and myeloid progenitor cells.

KEY WORDS: Immune deficiency; cyclic neutropenia; bone marrow transplantation.

INTRODUCTION

Severe combined immune deficiency (SCID) can result from a variety of genetic defects. Through study of children with SCID, much has been learned about normal lymphocyte development. Cyclic neutropenia is a relatively rare blood disorder characterized by regular cycling of neutrophil numbers and an associated periodic clinical syndrome of malaise, fever, mucosal ulcerations, infections, and lymphadenopathy (1, 2). In some human cases (1–4) and in the gray collie dog, a naturally occurring animal model (5), other peripheral blood cell elements also cycle, prompting the term cyclic hematopoiesis (CH). Cycles occur with striking regularity between 14 and 30 days apart but are usually constant for an affected individual. About 25% of human cases have a genetic origin, with an autosomal recessive or dominant trait, and onset can be in infancy.

CH has been attributed to a regulatory abnormality affecting the pluripotent bone marrow stem cell. Examination of serial bone marrow specimens shows a characteristic wave-like progression of myelopoiesis occurring through a cycle (3). With bone marrow transplantation, canine CH can be introduced or corrected (5), and human CH has been transferred from an affected woman to her sister (6). Bone marrow transplantation to correct this blood dyscrasia in humans has not been undertaken. Although fatal complications have been described in CH, the majority of affected humans experience a relatively benign clinical course, which may even improve with age (1, 2). This is unlike the situation for the gray collie dog, which manifests associated immune dysfunction and experiences progressive depletion of lymphoid tissue (7).

We report the presentation, treatment, and follow-up of an infant with a heretofore undescribed “experiment of nature” who presented with cyclic hematopoiesis and developed a severe progressive immune deficiency.
CASE REPORT

This male infant was the second child of healthy nonconsanguineous parents. He was well until age 8 weeks, when he became acutely febrile (38°C), was pale and irritable, fed poorly, seemed uncomfortable swallowing, and appeared to have crampy abdominal pain. Pharyngeal aphthous ulcers were noted by his father, who is a physician. The child was treated symptomatically with antipyretics and, after 3 days, was much improved, although the ulcers took about 10 days to entirely resolve. Sixteen days after onset of this first episode, the clinical syndrome and mouth ulcers recurred, then recurred again 14, then 21, days later. These episodes were not obviously associated with infections. While the mouth ulcers were present, occasional flecks of blood were noted in the stools. Immunofluorescence assay for herpes simplex virus and virus cultures of the ulcers were negative. At 4.5 months, the child developed a moderately severe laryngotracheobronchitis and was hospitalized for 10 days. A general physical examination, including detailed ophthalmologic exam, was negative. Tonsils, adenoids, and lymph glands were present, and the child had no dysmorphic features.

Investigations indicated abnormal blood counts. Fifteen sequential cell counts performed over a 2-month period revealed regular oscillation of blood cells, compatible with a diagnosis of cyclic hematopoiesis (Fig. 1). Over this period, the child had four clinical "attacks" and significant problems with mouth ulcers but no obvious infection. Neutrophil counts were documented to be low at 0.611, 0.744, and 1.440 × 10⁹/L, with clinical "attacks" on days 1, 18, and 38 respectively, while monocyte counts reciprocally peaked at 1.645, 0.720, and 1.209 × 10⁹/L (Fig. 1). Reticulocyte (not shown), eosinophil, and platelet counts followed a pattern with increases at neutrophil cell peaks. As shown in Fig. 1, neutrophil peak counts of 5.184, 4.212, 3.965, and 6.360 × 10⁹/L on days 9, 22, 43, and 64 were associated with elevated peak platelet counts of 949, 599, 577, and 1110 × 10⁹/L. Following the neutrophil nadirs, myelocytes and metamyelocytes appeared in peripheral blood for 2–5 days.

Serum immunoglobulin levels were determined to be low, prompting a more extensive immune workup, detailed in Table I and described under Results. Prophylactic immunoglobulin therapy (0.6 ml/kg/3 weeks im) was commenced. The infant remained apparently infection-free but continued to

Fig. 1. Peripheral blood-cell counts at the time of diagnosis on the patient showing cyclic changes. Clinical attacks are indicated by the arrowheads.
### Table I. Immune Studies Before and After Bone Marrow Transplantation

| Study                        | Normal range | Age Pretransplant (months)* | ↓ BMT | Months posttransplant |
|------------------------------|--------------|-----------------------------|-------|-----------------------|
| Neutrophil count             | 2-7.5        | 0.744 1.000 1.000 4.234     | 2.900 1.100 1.065 |
| (cells x 10^9/L)             |              |                             |       |                       |
| Lymphocyte count             | 2-8          | 2.046 0.500 1.200 0.580     | 0.630 2.000 1.395 |
| (cells x 10^9/L)             |              |                             |       |                       |
| Lymphocyte subset            |              |                             |       |                       |
| B                            | 0.180-0.520  | 0.194 0.045 0.115 0.012     | 0.038 0.020 0.976 |
| OKT11(CD2)                   | 1.350-2.480  | 0.859 0.120 1.056 0.087     | 0.447 0.920 1.028 |
| OKT3(CD3)                    | 1.270-2.530  | 0.041 0.010 0.996 0.002     | 0.233 1.300 0.949 |
| OKT4(CD4)                    | 0.880-1.760  | 0.122 ND 0.576 0.023       | 0.239 1.140 0.781 |
| OKT8(CD8)                    | 0.280-0.790  | 0.839 ND 0.456 0.075       | 0.151 0.280 0.237 |
| Proliferative response (cpm) |              |                             |       |                       |
| No mitogen                   | 1,559        | 3,019 7,475                 | 2,135 1,457 509  |
| PHA                          | ND           | 53,588 27,491               | 86,115 278,428 144,734 |
| ConA                         | ND           | 125,228 27,491              | ND     ND     ND      |
| PWM                          | ND           | 69,048 2,423                | 157,554 159,715 119,027 |
| SAC                          | ND           | ND ND ND                    | 5,711 16,973 20,362 |
| Immunoglobulin level         |              |                             |       |                       |
| IgG                          | 3.73-14.6    | 1.04 ND 1.85^a ND           | 4.75^a 9.12 5.62 |
| IgA                          | 0-1.0        | 0.04 ND <0.03 ND            | <0.03 0.49 0.50 |
| IgM                          | 0-2.2        | 0.10 ND <0.03 ND            | 0.41 3.71 1.84 |

*For reference to Figure 1, ages 5 and 6 months correspond to days 18 and 45.

*On immunoglobulin therapy: im, PreTransplant; IVlg, Post-Transplant.

have regular clinical "attacks" every 13 to 18 days, unaffected in length or severity by the immunoglobulin therapy. At age 6.5 months, he had become agammaglobulinemic.

At age 8 months, the patient developed grunting respirations during a cyclic "attack," and this worsened over the next weeks, prompting hospital admission. Blood studies on admission showed a white-cell count of 5,800 cells × 10^9/L with only 0.580 lymphocytes × 10^9/L (normal, 2.300-8.000 × 10^9/L). A chest roentgenogram showed widespread patchy bronchopneumonia, predominately involving the left lung. He was commenced on antibiotics. His condition deteriorated over a week, prompting a lung biopsy. Microscopic examination of alveolar tissue showed little polymorphonuclear response and an absence of plasma cells. Silver stains showed numerous *Pneumocystis carinii* organisms. No other opportunistic infections were identified, and all other lung cultures for viruses, bacteria, mycobacteria, and fungi were negative. A stool culture was positive for enterovirus, subsequently identified as poliovirus, likely persisting from the child's first and only oral immunization 5 months earlier. Administration of intravenous gammaglobulin (400 mg/kg/dose) every 2 days for 2 weeks failed to eradicate the enteral poliovirus infection.

Following his lung biopsy, the child was admitted to the ICU, intubated, and started on high-dose cotrimoxazole. Pentamidine and empiric amphotericin B therapy were added 5 days later as his condition deteriorated. Progressive nodular enlargement of the liver and spleen developed and was felt to be extramedullary hematopoiesis. The chest roentgenogram picture of severe ARDS (adult respiratory distress syndrome) developed and he had repeated pneumothoraces, requiring a total of five chest tubes. Maximal ventilation with 100% inspired oxygen was required for over 3 weeks to maintain adequate oxygenation.

Over the first week of this hospitalization, the child's lymphocyte counts had progressively dropped. By the time he was admitted to the ICU, counts remained <0.100 cells × 10^9/ml. Lymphocyte phenotyping and blastogenic assays on peripheral blood confirmed a state of severe combined immune deficiency (Table I, age 8 months). Studies performed on the family revealed the infant's healthy 2-year-old sister was HLA-identical, with HLA type A 3/24, B 7/27, CW1, DR2. There were insufficient patient cells for DR typing or mixed leukocyte cultures. Because of the infant's critical condition, a peripheral venous infusion of his sister's peripheral blood lymphocytes (10^8 cells from

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100 ml venous blood) was given, followed 2 days later with $5.3 \times 10^9$ bone marrow cells ($3 \times 10^9$ cells/kg). Erythrocytes were depleted from the donor (group B) mononuclear peripheral blood and bone marrow preparations because the recipient had a significant anti-B titer as a result of the IV Ig infusions. No preconditioning myeloablative therapy was given. Methotrexate was given every 3 days for 2 weeks posttransplant.

Five days posttransplant (day 20, Fig. 2), when the child was felt to be preterminal, methylprednisolone was begun in an empiric attempt to manage his lung disease. The next day, a maculopapular skin rash characteristic of graft-versus-host disease (GVHD) began to develop over the child's trunk. This became generalized and intense (grades II–III), then abated after 18 days. There was no coincident diarrhea or increase in liver enzymes. Twelve days posttransplant (day 27, Fig. 2), as the rash worsened, cyclosporin (1 mg/kg iv every 12 hr) was started. Coincident with the appearance of features of GVHD, the child began a gradual but dramatic recovery. He was finally extubated after 32 days on the respirator. His liver and spleen size normalized. Lymphocyte counts increased, and other blood cell elements gradually stopped oscillating (Fig. 2). One month posttransplant, the phenotype and blastogenic responses of peripheral blood lymphocytes were normal (Table I). Engraftment of donor cells was confirmed by chromosome analysis of bone marrow and peripheral blood lymphocytes. Four months posttransplant, 88% of bone marrow cells were female. By 7 months posttransplant, 100% of cells cultured 3 days with phytohemagglutinin (PHA) were of donor female origin. Studies with unstimulated cells stained with quinacrine showed no Y-bearing cells among 25 Q-banded metaphase cells or 50 interphase nuclei. Studies performed 3 years posttransplant indicating his chimeric state are detailed in Table II.

Because stool cultures had been repeatedly positive for poliovirus, 1 month after transplant a 2-week course of oral gamma-globulin therapy was given (5 ml/dose at 165 mg/ml every 3 days) (Connaught Novo Ltd.; preservative-free preparation for im use). Subsequent stool cultures were negative. The child had received intravenous gammaglobulin up to 3 days prior to transplantation, and infusions 3 and 5 weeks after.

At the present time, 4 years posttransplant, the child is in excellent health and has suffered only occasional, minor upper respiratory infections with-

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**Fig. 2.** Peripheral blood-cell counts on the patient around the time of bone marrow transplantation. Arrowheads indicate the times when prednisone and cyclosporine were commenced.

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out complications. Subsequent chest roentgenograms have been normal. He has had no recurrence of clinical “attacks.” The integrity of this graft has been documented by maintenance of adequate neutrophil and lymphocyte numbers, normal numbers and proportions of B and T cells and T-cell subpopulations, and normal proliferative responses to mitogens (Table I, +7 and +21 months) and specific antigens including candida and CMV. He has maintained normal immunoglobulin levels and developed good antibody responses to immunizations given posttransplant, which included diphtheria, tetanus, polioviruses (Salk), hemophilus influenzae, and live-attenuated measles, mumps, and rubella viruses. Red blood cells remain recipient (group O, Rh +, E +, M -, N +, S-) 3 years posttransplant, and it is interesting that antibodies have developed to blood group antigens including group B, which was the donor red blood-cell type (group B, Rh -, E -, M +, N -, S +).

Leukocyte counts remained low for several months until cyclosporin and prophylactic septra therapy were discontinued. Neutropenia with counts 0.594-0.746 × 10^9 was noted on several occasions when the patient was recovering from an apparent viral infection. Neutropenia (1.836 cells × 10^9), which had been detected on an initial pretransplant blood count from the donor sister when she was recovering from an apparent viral infection, and this had risen to 2.501 × 10^9 by the time of the marrow donation 3 days later. Subsequent family studies showed that the parents had normal sequential blood cell counts over a 1-month study period. The donor sister developed neutropenia during a mild, likely viral, upper respiratory infection (Fig. 3). She shows no cycling of any cell elements, has no lymphopenia, and has had normal immune studies including T- and B-cell enumeration, proliferative responses to mitogens and specific antigens, and normal serum immunoglobulin levels and documented antibody responses to infections and immunizations.

METHODS AND RESULTS

Immunologic Studies

Lymphocyte subpopulations were enumerated on heparinized peripheral blood and bone marrow samples by flow cytometry (EPIC-C, Coulter, Burlington, CA) using polyclonal anti-Ig (Zymed Dimension Labs, Missisauga, ON, Canada), and monoclonal antibodies directed against lymphocyte surface antigens including OKT₃, pan T; OKT₄, CD4, helper; OKT₅, CD8, suppressor/cytotoxic (Ortho Diagnostics, Raritan, NJ); and B₄, unique B (Coulter Immunology, Hialeah, FL). For functional assays, mononuclear cells were separated from heparinized peripheral venous blood samples by density-gradient centrifugation using Ficoll–Hypaque, washed, and resuspended in minimum essential medium (MEM; Gibco/BRL, Burlington, ON, Canada) with 100 µl/ml penicillin and 100 µg/ml streptomycin. Lymphocyte proliferative responses were determined by ^3H-thymidine incorporation of 5 × 10⁴ cells after 5

### Table II. Studies of Posttransplant Engraftment

| Cell tested | Cytogenetic analysis | Protein A stimulation | PCR for Y chromosome | VNTR analysis* |
|-------------|----------------------|-----------------------|----------------------|----------------|
|             | Metaphase: 3 δ, 100 γ cells | Metaphase: 20 δ, 100 γ cells | Positive |
| Recipient PBMC | Interphase: 4 δ, 97 γ cells | Interphase: 12 δ, 101 γ cells | B⁷/C/D |
| Recipient T cells | Interphase: 7 δ, 244 γ cells | NT | NT |
| Recipient B cells | NT | Failed | NT |
| Recipient PMN | NT | Positive |
| Donor PBMC | B⁷/C/D | A/B⁷/C |
| Mother PBMC | A/C | B/C | NT |
| Father PBMC | B/D | A/C | NT |

*Allele-specific analysis for variable number of tandem repeat (VNTR) segments utilizing three probes as detailed under Methods and Results. Allele designations are arbitrary and the superscript (W) indicates a weak band.
Lymphocyte profiles are detailed in Table I and show that this patient never manifested a normal distribution of cells. Initial lymphocyte studies, at age 5 months, when the child was ill during an "attack," showed an acceptable lymphocyte count and normal numbers of B lymphocytes but an abnormally low number of cells expressing markers of mature T cells. There was a deficiency of cells with a T-helper phenotype and an increased proportion of cells with a T-suppressor phenotype. Tests repeated when he was clinically recovered showed a low lymphocyte count and low numbers of T lymphocytes but normal in vitro proliferative responses of lymphocytes to mitogen activators. Studies at 6.5 months of age showed acceptable numbers and proportions of B and T lymphocytes and T-cell subpopulations but deficient responses to mitogens. Because of the high background uptake, these were interpreted at the time to indicate in vivo activation, resulting in nonresponse to in vitro activators.

Plasma and erythrocyte purine and pyrimidine nucleotide assays were generously performed by Dr. Michael Hershfield on samples taken when the child was clinically ill and well and were normal.

**Bone Marrow Studies**

Samples were taken at the time of the child's lung biopsy, a week before bone marrow transplantation. Bone marrow aspirate and Jamshidi biopsy showed normal bony architecture and development. There was normal overall cellularity and a normal M:E ratio. Normal granulocytic and erythroid maturation and normal megakaryocyte numbers and morphology were noted. There was profound lymphopenia, but lymphocytes present were morphologically normal. There were no abnormal infiltrates and granuloma formation was not seen. Special stains for fungi and tubercle bacilli were negative. Cytogenetic analysis showed a normal male karyotype at the 300-band level resolution and no existence of another cell line or cytogenetic abnormality.

**Posttransplant Cytogenetic and Molecular Genetic Studies**

Cytogenetic studies utilized heparinized whole blood and fractions of peripheral blood mononuclear cells isolated by density-gradient centrifugation with Ficoll-Hypaque, then centrifugation after...
incubation with AET-treated sheep red blood cells to separate B (interphase) and T (E-rosette pelleted) lymphocytes. Phytohemagglutinin was utilized to stimulate T lymphocytes, and protein A to stimulate B lymphocytes. Interphase and metaphase cells were analyzed by staining with quinacrine for the Y chromosome after a 3-day incubation with mitogens.

Polymerase chain reaction amplification was utilized to generate product for subsequent analysis by Southern blotting using probes for SRY (Y chromosome) and allele-specific analysis of variable number of tandem repeat (VNTR) segments using the probes YNZ22 (HGM locus D17S30), ApoB, and D1S80. Conditions were similar to those previously published (8). Band intensity indicated a greater donor contribution to mononuclear-cell than to PMN-cell preparations. (Data not shown)

DISCUSSION

This child presented with strikingly periodic clinical signs and symptoms, and serial blood studies revealed oscillation of all cells, prompting an initial diagnosis of cyclic hematopoiesis. Less characteristic and disturbing aspects of his disease included a less regular periodicity, with attacks occurring 13–21 days apart, and quite severe and prolonged clinical attacks. However, in CH the lack of association between the duration and extent of neutropenia and the severity of clinical symptoms has been well documented (1), and the absolute relationship of these has been questioned. Family studies and long-term follow-up of affected patients indicates that some individuals can have regular neutrophil cycles but remain free of clinical symptoms (1). Also, a clinical recovery, but no effect on neutrophil cycles, has been observed in patients treated with steroids (1, 9), lithium (10, 11), or G-CSF (12). These findings have raised the possibility that the clinical signs and symptoms are related to something other than neutropenia.

The development of increasingly severe immune deficiency has not been described before in cases of human CH. This patient was noted to be hypogammaglobulinemic with normal B lymphocyte numbers when first studied at 5 months of age. The presence of some detectable IgM and IgA at this time indicates that he had some earlier function of these cells. By 6.5 months of age, he was agammaglobulinemic. When he returned to hospital at age 8 months with severe *Pneumocystis carinii* pneumonia, studies indicated a state of severe combined immune deficiency.

This patient does not fit into any of the previously described syndromes of primary immune deficiency. Cases associating hypogammaglobulinemia and neutropenia (13–15), or cyclic neutropenia (9), have been reported but there is little record of outcome in these patients. In some, there has been resolution of neutropenia with exogenous gammaglobulin therapy (13, 14) but this had no effect on our patient. In other disorders of acquired or congenital neutropenia, affected children do not periodically develop the mouth ulcers that characterize CH and were a prominent feature of this child's disorder. Reticular dysgenesis, a severe immune deficiency with agranulocytosis, was ruled out by the presence of lymphoid tissue and bone marrow granulocyte precursors (16). The documentation of normal numbers of functional T lymphocytes (albeit, periodically) initially ruled out a classic disorder of SCID. Moreover, this course was atypical from previously described cases of SCID, and to our knowledge, children with SCID have not been described with CH or mouth ulcers. The milder Nezelof variant (T-cell deficiency with immunoglobulins) was negated by the agammaglobulinemia. This patient did show relative increases in T-suppressor cells; patients with hematopoietic inhibitory T cells have been identified (17) and this can be associated with cyclic neutropenia (11). However, we feel that this was not the etiology of our patient’s blood dyscrasia because lymphocytes were virtually absent in bone marrow and blood prior to transplantation. This deficiency may have facilitated engraftment without prior chemotherapy.

The possibility of progressive marrow destruction by engrafted cells was raised, but he had not been transfused, and he lacked other clinical features of this disorder, such as failure to thrive, rash, diarrhea, or organ dysfunction. Intrauterine engraftment of maternal lymphocytes was ruled out initially by cytogenetic and HLA studies, and not supported by results of allele-specific analysis of lymphocytes posttransplant (Table II). An acquired immune deficiency due to a virus was considered. However, multiple cultures of the patient for viruses were negative, and the parents and his donor sibling were HIV seronegative. We question whether the bone marrow transplant would have been so successful, in light of the common failure of these in AIDS patients (18).
The interrelationship of lymphoid cells and hematopoiesis has been the focus of intense investigation in recent years. The importance of T cells in the normal regulation of hematopoiesis has been recognized through case reports of patients with disturbed hematopoiesis and T-cell deficiency (19, 20) or CD 4/8 inversion (21). The results of T-depleted bone marrow transplant, where there can be failure or marked delay in engraftment (22), suggest the importance of lymphocytes in promoting normal hematopoiesis.

Although rare, cycling of lymphocytes and periodic immune dysfunction has been described in human cyclic hematopoiesis (3, 4, 10). Unlike two patients described by Bakowsky et al. (10), who developed T-cell lymphopenia and reduced PHA proliferative responses during neutrophil nadirs, this child had discordant results for lymphocyte numbers and function, and no clear-cut relationship of this with his neutrophil counts. In this respect, his disorder most closely resembled that of the gray collie dog, which also develops progressive lymphoid depletion (7). We were unable to demonstrate any change in plasma or erythrocyte ADA or NP levels, as has been determined during canine and some human cycles (23).

It is currently thought that all hematopoietic cell types originate from a common ancestral cell which early on gives rise to lymphoid progenitors and stem cells which become committed to other blood cell types under the influence of specific humoral factors (24). In CH, since all cell lines are involved, this indicates a very early progenitor cell is affected. Prevailing theories of CH include periodic defective stem cell production, competition by stimulatory factors for a limited number of stem cells, and oscillation in production of or response to regulatory factors (25).

We speculate that our patient had a primary disorder affecting generation of lymphoid progenitor cells. Retrospective review of his lymphocyte profiles detailed in Table I shows that he never manifested a normal distribution of cells. Progressive immune dysfunction could have occurred through failure to generate mature, functional T cells. Cycling of other blood cell elements might have resulted if periodic failure to generate lymphoid progenitors led to a periodic fluctuation in response of stem cells to other lineage specific early differentiation factors. The marked rise in numbers of other blood cells in the absence of lymphocytes prior to transplantation supports this possibility. No metabolic defect was demonstrated in this patient's cells. His erythrocytes and a proportion of his neutrophils and lymphocytes have remained of recipient origin posttransplant. It is interesting that no recipient-derived lymphocytes were detected by cytogenetic analysis of 75 cells at 7 months posttransplant, compared to detection of 5% recipient-origin cells at 3 years posttransplant. It may be that not enough cells were counted earlier, although possible that there has been expansion of recipient cell clones over the years since transplant. We feel that these studies rule out a primary defect of the pluripotent stem cell and raise the possibility that this patient was deficient in a growth factor influencing the very early differentiation of lymphoid cells. Initially, he showed partial immune function and produced IgM and IgA prior to becoming agammaglobulinemic, then developed combined immune deficiency. We wonder if this indicates the existence of a transplacentally derived maternal hematopoietic factor capable of acting on the bone marrow stem cell. Experience with G-CSF therapy has indicated that it is possible for peripherally infused hematopoietic factors to correct cyclic neutropenia (12).

In summary, we have described an unusual new "experiment of nature." This is the first report to show that in humans, as for the gray collie dog, it is possible to correct the disorder of cyclic hematopoiesis with bone marrow transplantation.

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