Effect of Stem Cell Factor on In Vitro Erythropoiesis in Patients With Bone Marrow Failure Syndromes

By Blanche P. Alter, Mary Ellen Knobloch, Liya He, Alfred P. Gillio, Richard J. O'Reilly, Laura K. Reilly, and Rona S. Weinberg

Stem cell factor (SCF) enhances normal hematopoiesis. We examined its effect in vitro on bone marrow and blood progenitors from patients with inherited bone marrow failure syndromes, including 17 patients each with Diamond-Blackfan anemia (DBA) and Fanconi’s anemia (FA), 3 with dyskeratosis congenita (DC), and 1 each with amegakaryocytic thrombocytopenia (ameg) and transient erythroblastopenia of childhood (TEC). Mononuclear cells were cultured with erythropoietin (Ep) alone or combined with SCF or other factors. SCF increased the growth of erythroid progenitors in cultures from 50% of normal controls, 90% of DBA, 70% of FA, 30% of DC, and the amega and TEC patients; normal numbers were reached in 25% of DBA studies. Improved in vitro erythropoiesis with SCF in all types of inherited marrow failure syndromes does not suggest a common defect involving kit or SCF, but implies that SCF may be helpful in the treatment of hematopoietic defects of varied etiologies.

SPECIFIC AND EFFECTIVE therapy for aplastic anemia is not available for most patients with inherited bone marrow (BM) failure syndromes who do not have a donor for marrow transplantation. The most common of these rare disorders, Fanconi’s anemia (FA; pancytopenia), Diamond-Blackfan anemia (DBA; pure red blood cell aplasia), and dyskeratosis congenita (DC; pancytopenia), are treated with a variety of steroids (androgens for FA and DC, and corticosteroids for DBA) with hematologic responses in more than half, but with significant side effects, and often subsequent relapses.1 So far, only Kostmann’s syndrome (KS; genetic agranulocytosis) has been treated effectively with a recombinant hematopoietic growth factor (HGF), granulocyte colony-stimulating factor (G-CSF).2 However, the focus of current research in hematopoiesis is on HGFs, and it is anticipated that several of these factors may be effective in patients with impaired hematopoiesis. There are already clinical trials of interleukin-3 (IL-3)3 and granulocyte-macrophage-CSF (GM-CSF)4 for patients with inherited marrow failure syndromes.

We wished to determine whether the recently described HGF, stem cell factor (SCF), was effective in the stimulation of erythropoiesis in cultures from marrow and blood progenitors from patients with these syndromes. The patients in our study had DBA, FA, DC, amegakaryocytic thrombocytopenia (ameg), and transient erythroblastopenia of childhood (TEC). Previous in vitro studies of DBA found decreased numbers of erythroid progenitors, with a requirement for higher than normal concentrations of erythropoietin (Ep), burst-promoting activities (BPA), and IL-3,5,6 Patients with FA were also noted to have decreased numbers of progenitors, with slightly improved growth in reduced oxygen and with high concentrations of Ep; these responses were seen only in those patients whose hematologic status was close to or essentially normal.7 DC patients also have reduced numbers of progenitors; GM-CSF and IL-3 increased the number of colonies in one study.8 Megakaryocyte progenitors were decreased in ameg,9 whereas myeloid and erythroid progenitors were low only after aplastic anemia (AA) developed.10 In contrast, erythroid progenitors are usually normal in TEC patients, who are often recovering by the time they are studied.11 The new growth factor that was examined in depth is called SCF, mast cell growth factor (MGF), steel factor (SF), or kit ligand (KL).12-15 The gene for this factor is mutant in Steel (SI) mice, and the gene for its receptor, kit, is mutant in W mice. Homozygotes for W or SI have macrocytic anemia, hair pigmentation abnormalities, mast cell deficiency, and sterility.16 W has defective hematopoietic stem cells (abnormal kit tyrosine kinase receptor), whereas SI has a defective hematopoietic microenvironment that is unable to synthesize the ligand for kit. In humans, kit maps to chromosome 4q11-4q127 and SCF maps to 12q14.3 to qter.18 DBA may be a candidate disease for mutations of either kit or SCF, although the fact that DBA can be cured by marrow transplantation19 suggests that the microenvironment (ie, SCF) is not defective, and recent reports indicate that one disease associated with mutations in kit in humans is piebaldism.20,21 In addition, both the c-kit and SCF genes are not grossly deleted or rearranged in DBA.22,23 The primary defect in FA is presumably neither kit nor SCF, because the disease is probably due to an as yet unidentified abnormality in DNA repair, and one of the genes for FA may be on chromosome 20q, whereas other FA genes are on other chromosomes,24 including the recently mapped FACC gene on 9q.25 Patients with DC have ectodermal dysplasia with characteristic reticular pigimentary changes and there is no evidence to implicate kit or SCF. Thus, mutations in kit or SCF may not be the
cause of any of the inherited BM failure syndromes. However, because SCF has significant hematopoietic effects in vitro on normal progenitors\textsuperscript{26-29} and those from DBA patients\textsuperscript{30,31} and in vivo in rodents and primates,\textsuperscript{32-34} we examined its efficacy in cultures. SCF was a potent stimulator of erythropoiesis in cultures from most patients with any type of inherited marrow failure syndrome, leading to normal colony numbers in many.

MATERIALS AND METHODS

Blood and BM samples were obtained according to protocols approved by the Institutional Review Boards at Mount Sinai Medical Center, Memorial Sloan Kettering Cancer Center, and Rockefeller University Hospital. The diagnosis of FA depended on finding increased chromosome breakage after culture of peripheral blood (PB) lymphocytes with diepoxybutane (performed by the laboratory of Arleen Auerbach, PhD, Rockefeller University, New York, NY). The other syndromes were diagnosed according to accepted clinical criteria.\textsuperscript{35} PB and BM cultures were performed in six normals, 17 patients with DBA, 17 with FA, three with DC, and one each with amega and TEC. Details regarding the patients' sex, age, blood counts, and treatment at the time of our studies are provided in Table 1. The clinical groups were defined elsewhere in this study.8 In brief, group 1 has severe transfusions; group 2 has also severe AA, but on androgens; group 3 has severe AA responding to androgens; group 4 has just developing severe AA; group 5 has moderate hematologic signs without treatment; and group 6 has essentially normal blood counts (rarely macrocytosis and/or slightly increased hemoglobin [Hb] F).

Erythroid cultures were performed as described previously.\textsuperscript{26} Ten to 30 mL of blood was collected in heparinized vacutainer blood collection tubes (sodium heparin; Becton Dickinson, Rutherford, NJ) and 1 to 3 mL of BM was drawn into a heparinized syringe and then added directly to 5 mL of medium containing 50 U/mL heparin (Liquemins; Organon Inc, West Orange, NJ), transported in the syringe (\textless 2 hours), or shipped overnight at room temperature in 10 mL of medium containing 10% fetal calf serum. Shipped samples were from two DBA, one FA, one amega, and one TEC patient (Table 1). Mononuclear cells were recovered after centrifugation on Ficoll-hypaque (Pharmacia Fine Chemicals, Piscataway, NJ) with 300,000 mononuclear cells plated per milliliter in 0.8% methyl cellulose and divided into triplicate 0.3 mL minwells (Nunc, Intermed, Roskilde, Denmark). Recombinant human Ep, kindly provided by Amgen Biologicals (Thousand Oaks, CA), was used at 2 and 8 U/mL. Additions to cultures that contained Ep at 2 U/mL included hemin (H) at 100 \textmu mol/L (Sigma Chemical Co, St Louis, MO), IL-3 (I) at 50 U/mL, GM-CSF (G) at 50 U/mL, and SCF (S) at 10 to 500 ng/mL (all kind gifts of Dr K. Zsebo at Amgen Biologicals). Factors were tested individually and in several combinations with Ep at 2 U/mL. When SCF was combined with other factors plus Ep, the concentration of SCF was 100 ng/mL. Because the BM cell yield was very low and did not increase with any combinations of SCF, the numbers of BM CFU-E with Ep alone were increased 1.4-fold with SCF. Day 7 marrow BFU-E were below normal with Ep, but more than doubled and reached the normal range with SCF. Marrow CFU-E and BFU-E numbers did not increase with additives other than SCF (Table 2). Blood BFU-E were very low and did not increase with any combinations of factors.

TEC. Marrow CFU-E were high normal (>100/10\textsuperscript{5} cells) and doubled with SCF (Fig 1). Day 7 marrow BFU-E reached 21/10\textsuperscript{5} cells with Ep + SCF in low oxygen. Day 13 marrow BFU-E were below normal with Ep, but not more than doubled and reached the normal range with SCF. Marrow CFU-E and BFU-E numbers did not increase with additives other than SCF (Table 2). Blood BFU-E were very low and did not increase with any combinations of factors.

RESULTS

Normals. SCF dose response curves are shown in Fig 1. With Ep at 2 U/mL, normal BM had 50 to 350 CFU-E/10\textsuperscript{5} mononuclear cells. The addition of SCF led to a significant increase in colony numbers in three of six cultures. SCF accelerated the appearance of marrow BFU-E-derived colonies, which were apparent by day 7 in all plates that contained SCF, and were usually in higher numbers in the plates that both contained SCF and were in low oxygen. Without SCF, there were 0 to 8 BFU-E in room air, and 0 to 4 in low oxygen, but these increased to 3 to 46 in room air, and 6 to 80/10\textsuperscript{5} cells plated in low oxygen (data not shown).

On day 13, the usual day for counting BFU-E-derived colonies, there were 18 to 90/10\textsuperscript{5} colonies in room air with Ep alone. SCF increased the numbers of BFU-E in two studies 1.6- and 2.7-fold in room air (Fig 1 and Table 2). Despite the early appearance of BFU-E with SCF noted above, maximal colony growth was still usually on day 13.

There were 1 to 30 (mean, 17) BFU-E/10\textsuperscript{5} cells with Ep alone; SCF led to increases of 1.4- to 2.4-fold in five of nine studies (Fig 1). Blood BFU-E were not seen on day 7, although they did begin to appear by day 10. The day of maximal growth usually remained day 13 in cultures with SCF.

Table 2 summarizes the marrow BFU-E results for Ep combined with other factors. Ep at 8 U/mL led to higher numbers of CFU-E– and BFU-E–derived colonies in only one marrow. The combination of SCF with GM-CSF in addition to Ep did produce higher numbers of colonies in one more study. The largest sized colonies were in those plates that had SCF, Ep, and hemin, or those factors plus GM-CSF and IL-3 (not shown).

Amega. There was one patient with amega, who had thrombocytopenia, macrocytosis, and increased Hb F, but no anemia. Normal numbers of marrow CFU-E in Ep alone were increased 1.4-fold with SCF (Fig 1). Day 7 marrow BFU-E reached 21/10\textsuperscript{5} cells with Ep + SCF in low oxygen. Day 13 marrow BFU-E were below normal with Ep, but more than doubled and reached the normal range with SCF. Marrow BFU-E and CFU-E numbers did not increase with additives other than SCF (Table 2). Blood BFU-E were very low and did not increase with any combinations of factors.

TEC. Marrow CFU-E were high normal (>100/10\textsuperscript{5} cells) and doubled with SCF (Fig 1). Day 7 BFU-E increased from 0 to 14 with SCF in low oxygen. Day 13 marrow BFU-E were normal in number (42/10\textsuperscript{5} with Ep) and increased 1.4-fold with SCF. Blood BFU-E were also normal with Ep and doubled with SCF. Other factors did not produce further increases in colony numbers (Table 2). 

DBA. The numbers of BM CFU-E with Ep alone were below normal, ranging from 0 to 37 in room air and up to 58
SCF increased the number of CFU-E in 15 of 16 studies from 1.3- to 8.4-fold in air and up to 18-fold in low oxygen (Fig 2). The number of CFU-E reached normal levels (at least 50/10^5 cells) in 4 of 16 when SCF was present. The only patient whose CFU-E did not increase in low oxygen. SCF increased the number of CFU-E in 15 of 16 studies from 1.3- to 8.4-fold in air and up to 18-fold in low oxygen (Fig 2). The number of CFU-E reached normal levels (at least 50/10^5 cells) in 4 of 16 when SCF was present. The only patient whose CFU-E did not increase in low oxygen. SCF increased the number of CFU-E in 15 of 16 studies from 1.3- to 8.4-fold in air and up to 18-fold in low oxygen (Fig 2). The number of CFU-E reached normal levels (at least 50/10^5 cells) in 4 of 16 when SCF was present. The only patient whose CFU-E did not increase in low oxygen. SCF increased the number of CFU-E in 15 of 16 studies from 1.3- to 8.4-fold in air and up to 18-fold in low oxygen (Fig 2). The number of CFU-E reached normal levels (at least 50/10^5 cells) in 4 of 16 when SCF was present. The only patient whose CFU-E did not increase in low oxygen. SCF increased the number of CFU-E in 15 of 16 studies from 1.3- to 8.4-fold in air and up to 18-fold in low oxygen (Fig 2). The number of CFU-E reached normal levels (at least 50/10^5 cells) in 4 of 16 when SCF was present. The only patient whose CFU-E did not increase in low oxygen. SCF increased the number of CFU-E in 15 of 16 studies from 1.3- to 8.4-fold in air and up to 18-fold in low oxygen (Fig 2). The number of CFU-E reached normal levels (at least 50/10^5 cells) in 4 of 16 when SCF was present. The only patient whose CFU-E did not increase in low oxygen. SCF increased the number of CFU-E in 15 of 16 studies from 1.3- to 8.4-fold in air and up to 18-fold in low oxygen (Fig 2). The number of CFU-E reached normal levels (at least 50/10^5 cells) in 4 of 16 when SCF was present. The only patient whose CFU-E did not increase in low oxygen.
compared with 10 to 40 in normals). The day of maximal growth for blood BFU-E was approximately 16, compared with day 13 for normals.

In the current studies, Ep at 8 U/mL was more effective than Ep at 2 U/mL for marrow BFU-E growth in three cultures (Table 3). IL-3 also increased erythroid colony growth, although only in four of our studies and not as effectively as SCF. Combinations of SCF + Ep that also had hemin were more potent than SCF + Ep alone in more than half of the patients. The hemin effect was noted even in low oxygen and thus was not solely acting as an oxygen free radical scavenger. Normal numbers of marrow CFU-E were reached with Ep at 8 U/mL or with added hemin in three studies, whereas normal marrow BFU-E were observed in only one with high Ep and one with IL-3. Combinations including SCF led to normal CFU-E numbers in two and in an additional two with hemin as well as SCF. Marrow BFU-E were normalized with Ep plus SCF in four, but with SCF plus other factors in an additional five. More blood BFU-E reached the normal range when IL-3 and hemin were included with SCF than in SCF alone. On average, colony numbers were somewhat higher in the low oxygen incubator (not shown).

FA. BM CFU-E were present in 13 of 16 FA marrows with Ep alone, ranging from 0.5 to 100/10⁵, but were in the normal range in only patients 1 and 2 (Table 1), who were in groups 5 and 6, respectively. SCF increased CFU-E in 11 of 15 cultures from 1.3-fold to 2.7-fold in air (Fig 3), but only one more culture achieved the normal range with SCF than the two that were normal with Ep alone. Thus, SCF increased marrow CFU-E from FA patients from very low levels to levels usually still below normal. SCF was effective in all clinical groups, although the numbers of colonies were higher in cultures from patients in groups 5 and 6.

As noted above in the normal and DBA cultures, SCF + Ep + low oxygen led to the appearance of marrow BFU-E by day 7 in 9 of 14 FA cultures, ranging from 2 to 34/10⁵ cells. The patients were in groups 3 through 6. In air, there were marrow BFU-E on day 13 in only three cultures, whereas in 5% oxygen marrow BFU-E were seen in nine; the numbers were all below the normal range (Fig 3 and Table 4). SCF was effective in 10 cultures from patients in groups 3 through 6, increasing BFU-E up to threefold. The effect of SCF was thus clearly evident albeit somewhat less impressive in FA than in DBA cultures. The peak remained on day 13.

Blood BFU-E were usually absent with Ep alone, as we have noted previously. Only two patients had 2 and 3 BFU-E/10⁵ cells and only in low oxygen. SCF led to similar low numbers of BFU-E in room air cultures from 10 patients and had no effect on BFU-E from blood cultured in 5% oxygen.

Fig 1. SCF dose-response curves in normal, amega, and TEC cultures. Data are numbers of CFU-E- and BFU-E-derived colonies/10⁵ mononuclear cells in response to SCF at 0 to 200 ng/mL. (A) BM CFU-E on day 7. (B) BM BFU-E on day 13. (C) PB BFU-E on day 13. (○) Normal; (×) amega; (■) TEC.

### Table 2. Normal BM BFU-E

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<th>+SCF</th>
<th>SCF Concentration</th>
<th>+Best Combination</th>
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<td>134*</td>
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<td>37</td>
<td>69*</td>
<td>20</td>
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*Data are BFU-E-derived colonies/100,000 cells plated. See Materials and Methods for abbreviations of factors.

*P < .05 by paired t-test for colonies with Ep + factor versus Ep alone.
Fig 2. SCF dose-response curves in DBA cultures. See Fig 1 for details. (□) Recently diagnosed; (●) on prednisone; (△) on transfusions; (◇) on transfusions and prednisone; (○) on transfusions and desferral; (○) on IL-3 for 3 weeks at 0.5 μg/kg for 3 weeks, followed by 3 weeks off treatment.

Table 3. DBA BM BFU-E

<table>
<thead>
<tr>
<th>Category</th>
<th>Patient No.</th>
<th>Ep 2</th>
<th>Ep 8</th>
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<th>SCF Conc.</th>
<th>+Best Combination</th>
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<td>72*</td>
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<td>5</td>
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<td>1</td>
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<td>10</td>
<td>18*</td>
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<tr>
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<td>1</td>
<td>3</td>
<td>22*</td>
<td>10</td>
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<td>0</td>
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<td>P</td>
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See Tables 1 and 2 for abbreviations.

*P < .05 by paired t-test for colonies with Ep + factor versus Ep alone.
†Increased above normal mean - 1 SD (ie, above 33 colonies/10^5 cells plated).

DISCUSSION

SCF is one of several newly identified HGFs that acts early in hematopoiesis. It presumably acts directly on cells that have the c-kit receptor, producing more mature committed progenitors.\(^{28,29}\) Combinations of SCF with factors that act later in hematopoiesis, such as Ep, GM-CSF, or IL-3,
SCF AND MARROW FAILURE SYNDROMES

![Graphs of SCF dose-response curves in FA cultures. See Fig 1 for details.](Image)

SCF AND MARROW FAILURE SYNDROMES

are then required to detect large numbers of colonies in in vitro assays.

Our studies were directed at the determination of whether SCF might have a role in in vitro erythropoiesis from patients with inherited BM failure syndromes, in whom hematopoiesis is impaired in vivo. We found that SCF plus Ep was generally more effective than Ep alone, and that the provision of growth factors in addition to SCF and Ep was of further benefit in some studies.

Normals. The response of normal erythroid progenitors to SCF plus Ep is confirmed here, although we did not observe this in all cultures. We used marrow and blood mononuclear cells that were not further fractionated, on the premise that agents of potential therapeutic use should be investigated in the milieu of the total marrow. SCF did have an effect on erythropoiesis in this assay. The increase in CFU-E as well as BFU-E-derived colonies suggests that both early and late progenitors may have the c-kit receptor, although the role of accessory cells was not examined.

**DBA.** DBA might be due to a mutation in kit or SCF; perhaps in a different region of kit than in piebald spotting. More detailed molecular investigations of larger numbers of patients are needed to exclude these genes completely. Many cases of DBA are apparently sporadic, with less than 25% autosomal recessive or dominant, and the syndrome is probably due to more than a single mutation. Despite this apparent genetic heterogeneity, the in vitro erythroid response to SCF was remarkably uniform.

SCF was relatively more effective in erythroid cultures from DBA than from normals or any of the other marrow failure syndromes, and produced significant increases in 90% of the DBA studies. Because the erythroid progenitor cell is presumably defective in DBA, it is tempting to conclude that SCF is able to overcome the defect, either by providing a missing factor (unlikely, because marrow transplant is successful, as discussed above) or by saturating the kit receptor, or perhaps by improving binding of Ep to its receptor, through receptor cross-communication. We did observe that addition of SCF to low Ep concentrations (0.5 U/mL) resulted in erythroid colony growth equivalent to Ep at 8 U/mL without SCF (data not shown). The addition of other factors, particularly hemin, led to a further increase in the number and size of the colonies. This is consistent with a model whereby SCF directly increases growth of CFU-E and BFU-E (or does so indirectly through accessory cells), which are then further stimulated by Ep, hemin, or other late-acting factors. SCF might also have stimulated production of BFU-E from earlier progenitors.

There have been several recent reports of small numbers of DBA patients in which SCF was effective in vitro.
Abkowitz et al.\textsuperscript{30} suggested that patients who responded to low concentrations of SCF were distinct from those who required high concentrations; the former might be mutant at SCF, and the latter at \textit{c-kit}. However, that study included only four BMs and six other PB cultures. Olivieri et al.\textsuperscript{32} found that 4 of 10 patients had good marrow BFU-E growth with SCF, two had a moderate response, and four had essentially none, concluding that DBA is a heterogenous condition and that some of these patients might benefit from SCF treatment. Our studies comprise a larger number of cases with a better overall response rate. Four normalized with SCF in vitro, another nine had at least half normal growth, one had moderate growth, and only two had no SCF effect. Only five of our cases required high concentrations of SCF (\(\geq 50\) ng/mL). We found that the effective SCF concentration in marrow and blood was not always consistent, and conclude that variability in technical components of the cultures might be as relevant to the SCF peak concentration as patient heterogeneity. We do agree that DBA patients seem to be segregating into good, moderate, and poor responders to SCF, and would like to be able to correlate the in vitro with in vivo effects.

\textit{FA.} The genetic defect in FA is clearly inherited as an autosomal recessive, although there appears to be more than one mutated gene by cellular and molecular complementation analyses\textsuperscript{36,37} and analysis of restriction enzyme polymorphisms.\textsuperscript{25} Despite the genetic and clinical heterogeneity of FA, more than 90\% will probably develop AA.\textsuperscript{1} The primary defect in FA probably involves one or more enzymes in the DNA repair pathway, and the hematologic problem may reflect the evolution of hematopoietic clones with limited capacity for self-renewal or differentiation. Because the hematopoietic defects might therefore be heterogeneous, it is unlikely that they would be specific to either \textit{kit} or SCF.

The response to SCF that we saw in three-quarters of the FA marrow cultures probably reflects a general hematopoietic response to an effective growth factor. Our studies in FA patients do not provide insight into mechanisms. Indeed, because the marrow cellularity is often low in FA, it may be difficult to perform the appropriate enrichment of stem cells to do direct assays of receptors. The mechanism in FA may be different from that in DBA, and may be unique in each FA patient due to clonal hematopoietic selection and marrow expansion from a very small number of stem cells.\textsuperscript{38}

Low oxygen was beneficial in all studies, but no more so in FA (which has been suggested to be defective in removal of toxicity from oxygen free radicals) than in the other disorders. It did increase numbers of BFU-E-derived colonies more than colonies from CFU-E, but this was also seen in all studies, and thus the role of oxygen toxicity in FA remains unclear.

\textit{DC.} The inheritance of DC is X-linked, autosomal recessive, and autosomal dominant, and thus presumably involves at least three different mutations.\textsuperscript{39} Certainly for the X-linked majority, neither \textit{kit} nor SCF is the primary defect. SCF was effective in erythroid cultures from one of the three male patients whom we studied. GM-CSF was also effective in the only study in which it was examined, similar to a previous report.\textsuperscript{9}

\textit{Amegs.} This rare condition is usually inherited as an X-linked recessive; however, our one patient was female. The pattern of response to factors resembled the normal pattern, including incremental erythroid growth in the presence of SCF + Ep.

### Table 5. DC BM BFU-E

<table>
<thead>
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<th>Category</th>
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See Tables 1 and 2 for abbreviations.

\* \(P < .05\) by paired \(t\)-test for colonies with Ep + factor versus Ep alone.
SCF AND MARROW FAILURE SYNDROMES

TEC. TEC is not inherited, but is an acquired disorder in young children, often apparently after a viral illness. This patient is included because the preliminary diagnosis was in fact DBA, and only the normal growth in vitro led to the consideration of the correct diagnosis, discontinuation of steroid treatment, and maintenance of normal blood counts. TEC is not necessarily clonal, and the in vitro effectiveness of SCF and other factors most likely speaks to the hematopoietic potency of SCF, and not to specific defects in the receptor or the in vivo levels of SCF.

SCF increased in vitro erythropoiesis in cultures from normals, as well as from patients with all types of BM failure syndromes. Although one of these diseases (DBA) might be a candidate for mutations of either kit or SCF, the other disorders, both inherited (FA, DC, and amegakaryocytic anemia), and acquired (TEC), are quite unlikely to be due to mutations in either of those genes. The SCF-related increases in CFU-E and BFU-E-derived colonies that we observed in our studies of patients with all types of BM failure syndromes suggest that differentiated erythroid progenitors have c-kit receptors even during compromised hematopoiesis. Immature progenitors from these patients may also have receptors for SCF, and may have matured into BFU-E in our assay. Further studies are required to ascertain whether the SCF effects are directly on progenitors, or indirectly through accessory cells, and whether the mechanism is the same in all of the BM failure syndromes.

Our results with SCF do not identify the specific hematopoietic defect in any of the syndromes, but the effectiveness of SCF in cultures from patients with these disorders suggests that clinical trials with SCF should be considered.

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Effect of stem cell factor on in vitro erythropoiesis in patients with bone marrow failure syndromes

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