question whether haptotaxis is a special case of chemotaxis cannot as yet be answered. But the results show that chemotaxis is not a special case of haptotaxis. They also indicate that it is premature to conclude that any increased cell accumulation as measured in the filter assay is the result of chemotaxis.

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Changes in beta-2 adrenergic receptor sensitivity with maturation of erythroid progenitor cells[1]

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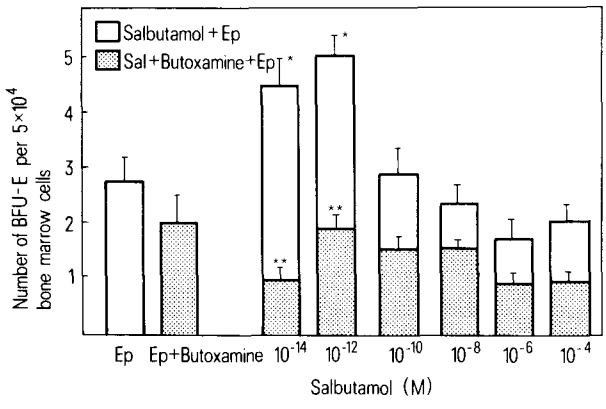
Summary. Erythroid burst forming units (BFU-E) were much more sensitive to the beta-2 selective adrenergic drug, salbutamol, than erythroid colony forming units (CFU-E) in an in vitro study of erythroid progenitor cells.

2 broad classes of erythroid progenitor cells have been described[2,3]. The 1st class, designated as CFU-E (colony forming unit erythroid), forms small erythrocytic colonies consisting of 8–32 cells after 2 days in culture and is considered to be a late stage of progenitor cell development[4]. The 2nd class, BFU-E (burst forming unit erythroid), is recognized by its ability to form large, macroscopic clusters of colonies termed 'bursts' due to their unique morphology. Burst forming units (BFU-E) are thought to be an earlier stage of erythroid progenitor cell development than CFU-E[3,4].

Pluripotent stem cell colonies (CFU-S) and the late stage erythroid progenitor cell colonies (CFU-E) are known to be sensitive to certain drugs and hormones that stimulate the adenylate cyclase-cyclic AMP system such as beta-adrenergic drugs[5–7], growth hormones[8], thyroid hormones[9] and hormones that are independent of cyclic AMP such as steroids[10–12]. Very few studies[13,14] have investigated the responsiveness of the BFU-E compartment to hormones or drugs. Since the BFU-E compartment is intermediate between CFU-S and CFU-E, it might be expected to also be sensitive to those agents which affect CFU-S and CFU-E. Experiments described here further characterize the effects of beta-adrenergic agents on erythroid progenitor cell proliferation by comparing their effects on BFU-E and CFU-E.

Methods. The method of McLeod et al.[15] was modified as described previously[6] for the culture of BFU-E. Briefly, a cell suspension containing 500,000 cells in 0.1 ml of culture medium was dispersed in 0.9 ml NCTC-109 medium containing 20% fetal calf serum, 10% beef embryo extract, 10% L-asparagine, 0.5 units erythropoietin, 10% bovine citrated plasma and the drug to be tested. 0.1 ml of this mixture was pipetted into wells of sterile microtiter plates. The mixture was then allowed to clot and microtiter plates were incubated in sterile 100-mm petri dishes in a humidified atmosphere of 95% air and 5% CO_2 for 10 days at 37 °C. The contents of each well were placed on a microscope slide, blotted gently and fixed with 5% gluteraldehyde. BFU-E colonies were scored if they contained 1000 or more benzidine-positive cells. The Dunnett's multiple range test[16] was employed for statistical analyses.

Results and discussion. The numbers of BFU-E were significantly ($p < 0.05$) increased in the presence of salbutamol, a selective beta-2 agonist. The greatest enhancement was seen at 10^{-12} M salbutamol. In the presence of butoxamine (10^{-8} M), a selective beta-2 antagonist, the salbutamol effect was blocked. In an earlier study[6] we found that erythropoietin-dependent CFU-E formation was enhanced by salbutamol with a peak effect at 10^{-8} M. Butoxamine



Effect of salbutamol, erythropoietin and butoxamine on erythroid burst colony (BFU-E) formation in rabbit bone marrow. Open bars represent the mean ± SE of 5 separate experiments while the stippled bars represent n = 3. * Significantly different from control with Ep alone ($p < 0.05$) using the Dunnett's multiple range test. ** Significantly different ($p < 0.05$) from salbutamol + Ep at same concentration.

also blocked the CFU-E enhancement. The present study provides the first demonstration that BFU-E proliferation is enhanced by beta-2 adrenergic drugs. Of perhaps greater importance is the observation that the BFU-E compartment appears to be more sensitive to beta-2 agonists than the CFU-E compartment as demonstrated with our dose response data for salbutamol. Byron's report[7] that the pluripotent stem cell (CFU-S) can be triggered into DNA synthesis with concentrations of isoproterenol as low as 10^{-14} M suggests that the CFU-S may be exquisitely sensitive to catecholamines, as well as to drugs such as prostaglandins, carbamylcholine, and certain steroids. Gregory[4] recently provided evidence that a decline in proliferative capacity of cells may be associated with a progressive increase in erythropoietin responsiveness as primitive erythroid progenitors move from a position close to pluripotent stem cells through several differentiation steps of the erythroid progenitor cell compartment until they reach a stage just prior to the onset of hemoglobin synthesis. On the basis of the data presented here and the findings of Byron[7,10] and Gregory[3,4], it is postulated that pluripotent stem cells have a variety of hormone and drug receptors on their membrane surfaces which when triggered can determine the future pathway of their differentiation. The possibility that the concentration of a ligand can regulate the number and/or binding properties of its own receptors on the surface of target cells has gained considerable support in recent years[17]. Our present data suggest that beta-2 receptors may decrease during maturation while those receptors necessary for further differentiation increase, i.e., erythropoietin receptors. The observed increases in both BFU-E and CFU-E seen with salbutamol suggest that an increase in recruitment of erythropoietin responsive cells can be mediated by a beta-2 adrenergic mechanism. These data may be useful in designing therapy in certain clinical refractory anemias.

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Increased incidence of lymphomas in survivors of the host-versus-graft syndrome[1]

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Summary. When $(SB)F_1$ spleen cells were injected into perinatal parental B strain mice a lethal runting syndrome was induced. The survivors showed a significantly increased incidence of lymphomas in old age. The tumors occurred much later and less frequently than in the reverse reaction, $B \rightarrow (SB)F_1$ GVHD.

When F_1 lymphoid cells are injected into neonatal mice of the parental (P) strain, a lethal runting syndrome ensues in certain combinations of strains[2]. Recently I reported an increased incidence of lymphomas in a mild sublethal form of this disease, designated low dose host-versus-graft disease (HVGD)[3]. The present report confirms and extends this finding by providing evidence of the maximal tumor induction potential of this model, by use of a highly vigorous form of this disease (high dose HVGD).

Spleen cells from young adult (SJL/J X C57BL/1)F_1 ($(SB)F_1$) were injected i.p. into nursing parental B strain mice. 2 or 3 doses of cells were given at weekly intervals, with the 1st dose within a few days of birth (see table, footnote). Each cell dose consisted of 30–50 million cells. The mortality from HVGD in this group of 94 mice up to 90 days of age was 64%. Thereafter gradual recovery occurred. The 34 surviving mice form the basis of this report. These mice were observed 3 times weekly up to 18 months of age for tumor development. Mice which were moribund from tumor were autopsied. At 18 months, all remaining mice were sacrificed. Control B mice which received the same dose of B strain spleen cells or which were left uninjected were also sacrificed at 18 months.

The results are summarized in the table. In low dose HVGD, cumulative lymphoma incidence was 12 of 23 or 52%. In high dose HVGD, the incidence was 22 of 34 or 65%. The difference is not significant. In both groups tumor incidence was significantly higher than in $B \rightarrow B$ ($p < 0.05$, $p < 0.001$ respectively) and in uninjected normal B controls ($p < 0.001$ for both). The tumors were reticulum cell sarcomas or lymphosarcomas or a mixture of these. In low dose HVGD 6 of 12 tumors were detected clinically up to 18 months, the 1st one at 12.5 months. In high dose HVGD, 8 of 22 tumors were detected clinically up to 18 months, 3 of the 8 in the 1st year, at ages 7.5, 9 and 11 months. Thus, despite maximally vigorous HVGD, tumors appeared much later and in lower incidence than in the reverse model, $B \rightarrow (SB)F_1$ GVHD (see Cornelius[3], table 4). The tumor induction potential of HVGD therefore appears more limited than in the reverse model, GVHD. In contrast to low dose HVGD, in which injection of the initial dose of $(SB)F_1$ cells into perinatal B mice within 24 h of birth was essential for tumor development, in high dose HVGD an initial injection of $(SB)F_1$ cells into B mice at 24–48 h of age was as effective in inducing tumors (9 tumors in 15 mice) as an initial injection in the period 0–24 h (9 tumors in 14 mice).

6 lymphomas were transplanted into 3-week-old B, $(SB)F_1$, S, and AKR mice. 1 tumor did not grow in any hosts. 5 tumors grew in B and $(SB)F_1$ hosts but not in S and AKR