Correspondence

To the editor:

Lessened severe graft-versus-host after “minitransplantations”

We greatly appreciate Dr Brian Abbott’s commentary1 on the publication by Diaconescu et al,2 which compared toxicities and non-relapse mortality in patients undergoing HLA-matched related hematopoietic cell transplantation (HCT) following either nonablative or ablative conditioning, and we would like to make 3 points in response to his cautionary notes. First, we recently published very similar observations in patients given unrelated HCT.3 All nonablative patients in that study received 2 Gy total body irradiation preceded by 3 doses of fludarabine, 30 mg/m²/d for 3 days. Even though nonablative patients had significantly higher pretransplantation comorbidity scores, were older, and had more often failed preceding ablative HCT and cytotoxic chemotherapies, they experienced fewer grades III-IV toxicities than ablative patients. The 1-year nonrelapse mortality was 20% in nonablative compared with 32% in ablative patients, a difference that was significant after adjusting for pretransplantation differences between the 2 groups of patients (P = .04).

Second, while we agree that no long-term follow-up data on disease control are available as yet, early results in patients with multiple myeloma, non-Hodgkin lymphoma, chronic lymphocytic leukemia, and acute myelocytic leukemia look encouraging.4-7

Third, the graft-versus-host disease (GVHD) incidence among nonablative recipients was lower than that among their ablative counterparts,3,8 and this was most pronounced for grades III-IV acute GVHD among unrelated recipients (Figure 1).

Finally, we share Dr Abbott’s enthusiasm for the use of the Charlson Comorbidity Index (CCI) to evaluate patients before HCT. Patients with CCI scores of 1 or higher might benefit from undergoing nonablative HCT, regardless of their age.

Mohamed Sorror, Michael Maris, Razvan Diaconescu, and Rainer Storb

Correspondence: Rainer Storb, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave North, D1-100, PO Box 19024, Seattle, WA 98109-1024; e-mail: rstorb@fhcrc.org.

References

To the editor:

Down syndrome in Down House: trisomy 21, GATA1 mutations, and Charles Darwin

At the outer edge of the leafy southeastern London suburbs lies the small village of Downe, nestled in the rolling hills of Kent just 16 miles from the city. The chief attraction of Downe for nonresidents is Down House (the customary spelling for the estate is different from that of the village), the family home of the man who was arguably England’s most important contribution to the biological sciences: the great naturalist Charles Robert Darwin (1809-1882). In recent years, Down House has been extensively restored, and the property is now maintained in the public trust by English Heritage. The site is an increasingly popular pilgrimage destination for biologists and others with an interest in the history of the natural sciences.

During a recent visit to Downe, my daughter and I were fascinated by the Darwin family photos scattered about the 19th-century rooms on the ground floor of Down House. I was prompted to read the sensitive and engaging account of Darwin’s family life published by his great-great-grandson, Randal Keynes.1 By all accounts, Darwin and his wife (and first cousin) Emma Wedgewood enjoyed a close, warm, and generally happy domestic existence, limited by Charles’ poorly defined chronic ailments—possibly sequelae of Chagas disease contracted during the voyage of the Beagle—and broken by the premature deaths of 3 of their 10 children.
Keynes’ book focuses on the death of 10-year-old Annie Darwin in 1851 after a long illness, probably tuberculosis, and he speculates that the pain of those events shaded Charles’ ideas during the period of intellectual turmoil when he was formulating and refining the theories that underpin *The Origin of Species* (1859). Another Darwin daughter, Mary, died at 3 weeks of age in 1842; the Darwins also lost their youngest child, Charles Waring, who was born in December of 1856 when Emma was 48 years old.\(^1\)\(^{(p\,246)}\)

From early on, it was clear that the Darwin’s last infant was not normal. There was no name yet in 1856 for the baby’s condition. John Langdon Haydon Down had not yet been employed by the Earlswood Asylum in Surrey, and Down would not publish his first paper on what he and others would call “mongolism” (the result of a wildly erroneous Victorian-era racial theory) for another 10 years.\(^2\) The only extant photograph of Charles Waring (Figure 1) was taken by the eldest Darwin son, William (Figure 2), with a camera that William received for his 17th birthday. The image is grainy and underdeveloped but reveals suggestive facial features. Darwin *père*, always a careful observer, took meticulous notes on the development of all of his children; several of the descriptions of Charles Waring are potentially consistent with an infant with trisomy 21: “He was small for his age and backward in walking and talking... He was of a remarkable sweet, placid and joyful disposition, but had not high spirits. ... He often made strange grimaces and shivered, when excited... He would lie for a long time placidly on my lap looking with a steady and pleased expression at my face... making nice little bubbling noises as I moved his chin.”\(^1\)\(^{(p\,246)}\)

In addition to the baby’s facial features and placid disposition, Emma’s advanced maternal age also supports a retrospective diagnosis of Down syndrome. For a woman older than 45 years, the risk of giving birth to an infant with Down syndrome exceeds 1 in 30.\(^3\)

In the summer of 1858, when Charles Waring was 19 months old, an epidemic of scarlet fever swept through the region surrounding the village of Downe. The Darwin’s oldest surviving daughter, Henrietta, had been chronically unwell since a bout with diphtheria the year before, and her parents were anxious about her vulnerability. But in the end it was the baby who became seriously ill. On June 25, 1858, Darwin shared his growing concern about his youngest child’s condition in a letter to a friend, the geologist Charles Lyell—a letter chiefly written to ask Lyell for advice about asserting intellectual priority over Alfred Russel Wallace on the mechanism of evolution: “I fear we have a case of scarlet fever in House with Baby. Etty [Henrietta] is weak but is recovering. My dear good friend forgive me. This is a trumpery letter influenced by trumpery feelings.”\(^4\)\(^{(p\,474)}\)

On July 1, 1858, when the Linnean Society in London heard the sensational first announcement of Darwin’s (and Wallace’s) theory of natural selection, Darwin was not in attendance. He was at the funeral of his youngest son, who had died on June 28.\(^1\)

Mel Greaves and others interested in the new field of evolutionary or “Darwinian” medicine argue convincingly that human neoplasia and many other diseases may be best understood within an evolutionary framework.\(^5\) As Greaves summarizes: “Cancer doesn’t just parody evolution, it is a form of evolution played by the same Darwinian ground rules as apply to evolution in general and particularly for asexually propagating species. The essential game plan is progressive genetic diversification by mutation within a clone, coupled with selection of individual cells on the basis of reproductive and survival fitness, endorsed by their particular mutant gene set. It’s evolution in the fast track.”\(^5\)\(^{(p\,39)}\)

The usual model cited for cellular “natural selection” and clonal evolution in the setting of malignancy is the work of Vogelstein on the accumulation of somatic mutations in colonic mucosa cells as they progress through adenomatous stages to form carcinoma in situ and eventually frankly invasive cancer. Recent exciting developments have demonstrated that the transient myeloproliferative disorder (TMD) and megakaryoblastic leukemia (AML-M7)
that frequently complicate Down syndrome are another excellent example of this process in action (recently reviewed in Blood by Gurbuxani, Vyas, and Crispino.6)

Hematopoietic cells that acquire a point mutation in the key X-encoded transcription factor GATA1 in the setting of trisomy 21 gain a proliferative advantage that appears to be dependent on a permissive environment, probably the fetal liver. Clonally restricted GATA1 mutations are exceptionally common in neonates with TMD, and have been detected prenatally and at birth.7 Additional molecular events allow one of these GATA1 mutant clones to obtain a postnatal growth advantage and avoid the usual path of extinction—most cases of TMD spontaneously remit, and as with species extinction, this is probably related to changes in the environment. When extinction of the clone does not occur, leukemia develops. The additional molecular lesions required for overt leukemia are unknown at present, but are likely reflected in the more complex karyotypes observed in AML-M7 cells compared with TMD clones.6

Charles Waring Darwin quite probably had Down syndrome; we have no way of knowing whether his fatal bout with “scarlet fever” was in fact a hematologic disorder such as leukemia, which had only been described in 1845. Much later, Charles Darwin Sr—ever attentive to the workings of biological principles in his own family—worried about to what extent the fact that he and Emma were first cousins had predisposed his deceased children to their illnesses. He publicly advocated collecting such data as part of the British National Census for 1871, a suggestion that was rejected because of concerns over privacy.1(p230) There was growing awarenessness in the late 19th century that “inbreeding” contributed to the development of certain ailments. Darwin had proposed natural selection as the mechanism of evolution, but he had no mechanistic insights into the potential problems of consanguinity, because the rediscovery of Mendel’s work had not yet occurred and there was no clear concept of genetics. If Annie Darwin died of tuberculosis and Charles Waring had Down syndrome, these illnesses indeed started “at home,” but not for the reasons Darwin envisioned. There is no evidence that consanguineous partnerships predispose to either condition.

The tremendous advances in cellular and molecular biology in the century and a half since the publication of Origin of Species have highlighted the analogy between the development of cancer clones and the evolution of new species. Only very recently has it been demonstrated that one of the clearest examples involves GATA1 mutations arising in infants with the very illness that likely afflicted the great naturalist’s youngest son. What would Darwin have thought?

David P. Steensma

Correspondence: David P. Steensma, Division of Hematology, Department of Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905; e-mail: steensma.david@mayo.edu.

References


To the editor:

Clinical significance of intrahepatic hepatitis B virus covalently closed circular DNA in chronic hepatitis B patients who received cytotoxic chemotherapy

Hepatitis B virus (HBV) reactivation is a well-recognized complication associated with cytotoxic therapy.1 Despite its clinical importance, data on the risk factors for HBV reactivation after chemotherapy are limited.2 As the hepatitis is preceded by enhanced HBV viral replication3 and intrahepatically closed circular DNA (cccDNA) is a key intermediate in the replication of the virus,4 we investigated the association of intrahepatic HBV cccDNA and HBV-related hepatitis after chemotherapy.

Thirty-five hepatitis B surface antigen (HBsAg)-positive lymphoma patients treated at the Department of Medicine, Queen Mary Hospital, Hong Kong Special Administrative Region (SAR), between January 2000 and March 2003 were included into this prospective study if they fulfilled the following criteria: (1) had nucleoside analogs or were chemotherapy naive; (2) were treated with intensive chemotherapy regimen; and (3) had no evidence of liver cirrhosis histologically. Thirteen patients were excluded due to previous chemotherapy (n = 20) and pre-existing liver cirrhosis (n = 1). Of the 22 patients included in the study, 15 patients had participated in a previous study.2

Serum alanine transaminase (ALT) and serological testing for hepatitis B e antigen (HBeAg), hepatitis B e antibody, and serum HBV DNA by Digene Hybrid Capture II assay (Digene Diagnostics, Beltsville, MD) were performed at the initiation of chemotherapy and then prospectively every 2 weeks until the end of chemotherapy. A percutaneous liver biopsy was performed on all patients 2 weeks before chemotherapy and the level of intrahepatic viral cccDNA was quantitated using selective HBV cccDNA primers by real-time polymerase chain reaction (PCR).5 HBV reactivation induced by chemotherapy was defined according to previously published criteria.6

Statistical analyses were performed using the SAS Release 8.02 system (SAS, Cary, NC). Independent factors in Table 1 were individually examined in relationship to hepatitis due to HBV reactivation in simple Cox proportional hazards regression analysis. Important determinants among these factors were also explored by a Cox proportional hazards regression model together with a forward stepwise variable selection procedure. P
Down syndrome in Down House: trisomy 21, GATA1 mutations, and Charles Darwin

David P. Steensma