The Second-Class Disease: Pediatric Cancer

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"Tommy" was a fit and happy boy who loved baseball and dinosaurs. At the age of six, he began feeling tired all the time and developed a persistent cough that just would not quit. His pediatrician, labeling Tommy's symptoms "allergy-like" and diagnosing him with a nasal drip, assured his family that he would get better soon. Unfortunately, he didn't. Unlike other boys his age, between Cub Scout meetings and Little League games, for nearly one year of his short life he also unsuccessfully traversed the world of medical specialists, with expert after expert unable to identify why Tommy was sick. Eventually, with a worsening cough and the appearance of stomach pains and uncontrolled, erratic blinking, Tommy was referred to an otolaryngologist who then suggested a consultation with an allergy specialist. With eosinophil counts in the hundreds of thousands, he was next referred to a hematologist, who finally discovered a 13-centimeter abdominal tumor. The diagnosis of stage IV Hodgkin's lymphoma was finally made.

Pediatric malignancy is a far-reaching problem. Nearly 11,000 children between the ages of 1 and 15 are diagnosed with cancer yearly (What is childhood cancer? 2009). More than a third of all boys and girls under the age of 20 will develop cancer, and over the past three decades incidence rates have slowly been rising (Ries et al. 1999).

Pediatric malignancy is also a devastating diagnosis. For this age group, it is the leading cause of death from disease (What is childhood cancer? 2009). Indeed, despite great advances in the medical management of pediatric cancers, the five-year mortality rate is 20% (What is childhood cancer? 2009). For those who live past childhood, 30 years after diagnosis the cumulative incidence of chronic health conditions is nearly 73.4%, with a 42.4% incidence of death or severe, disabling, or life-threatening conditions (Oeffinger et al. 2006). Often, because these diseases affect multiple systems (Morris-Jones and Craft 1990), the child is relegated to a life of perpetual medical treatment. Subsequently, the physical, social, and psychological effects on an entire family are massive (Cohen 1999).

Despite its extensive reach and the reported poor outcomes, pediatric malignancy is severely underfunded. The National Cancer Institute (NCI), a branch of the National Institutes of Health (NIH) and the federal government's principal cancer research and development agency (NIH 2010), had 2006 and 2007 budgets of $4.75 and $4.79 billion, respectively (NIH 2009a). Strikingly, its investment in pediatric cancer research was only $179.6 million in 2006, and this figure decreased to $172.7 million in 2007 (NIH 2008). Additionally, considering that in 2003 its pediatric cancer research allocation was $152.8 million, after adjusting for inflation using the Consumer Price Index, we realize that from 2003 to 2007 there was a mere $726,633 increase in pediatric funding, in contrast to a $40 million increase in the total NCI budget. The medical profession's frustration about underfunded pediatric cancer research is captured in the words of Gregory Reaman, M.D., chair of the Children's Oncology Group: "Each day that pediatric cancer research goes under-funded, the road to discovering new treatments and cures become[s] longer, and more children are put at risk" (Hope Street kids join CureSearch 2005). In the case of Tommy and many like him, this lack of funding manifests itself in two perceptible forms: poor early detection, and a dearth of safe and effective treatment options.

One reason for the delay in Tommy's diagnosis may be the typically asymptomatic initial clinical presentation of Hodgkin's lymphoma. Due to the indolent nature of the disease course, persistent painless supraclavicular or cervical lymphadenopathy is the most common symptom. In some cases of pediatric malignancy, because children commonly undergo cervical lymph node enlargement due to normal reactive processes, it is only the presence of supraclavicular nodes—rather than cervical nodes—that is indicative of the presence of the disease. In cases of intrathoracic Hodgkin's lymphoma, associated findings include cough, dyspnea, chest pain, and superior vena cava syndrome. Axillary and inguinal lymphadenopathies are uncommon, and infradiaphragmatic nodal involvement is found in fewer than 5 percent of cases. In addition to lymphadenopathy, due to an increase in the number of stimulating cytokines, lymphocytosis is present in some patients (Weinstein et al. 2007). Constitutional B symptoms such as fever, night sweats, and weight loss manifest in approximately 28.4% of patients. Tommy's initial presentation of persistent flulike symptoms, which failed to resolve for more than a year, is consistent with a more common and less dramatic presentation of Hodgkin's lymphoma; this may also be why Tommy and his family were forced to spend nearly a year seeking guidance from medical specialists who didn't have definitive answers.

Unfortunately, even after his diagnosis, Tommy's tribulations due to the inadequate medical management of Hodgkin's lymphoma were not yet over. Development of new therapies for childhood cancers has been lagging. From 1948 to 2003, the FDA approved 120 new cancer therapies for adults. Of those, during the same time span, only 15

gained approval for pediatric use (Hirschfeld et al. 2003; DHHS 2003a). Inadequate funding of pediatric cancer research and development can be traced to a number of factors. Self-advocacy is not possible for children, and—as is evident in the decreasing federal funding for all pediatric cancers, which is now less than 3.59% of the $4.8 billion NCI budget—without political clout, pediatric cancers are not prioritized on Capitol Hill when new budgets are drawn up. Children's cancers are also widely non-environmental and are not lifestyle-related, compared to those of adults (DHHS 2003b), and there are significantly more cases of adult cancer than there are of children's cancer (Alunedin et al. 2009). Accordingly, it is understandable that more funding is allocated for adult cancers, but should it be at the cost of a defenseless population?

Current treatment for Hodgkin's lymphoma consists of variable-length cycles of chemotherapy plus low-dose, involved field radiation (15-25 gy). Modern antiemetics have allowed for easier administration of the chemotherapy and radiation therapy, but deleterious effects remain. The most common dose-limiting factor in treatment is myelosuppression, which, although it can be ameliorated with the use of granulocyte colony–stimulating factors, still poses a significant risk. Also, the use of various vinca alkaloid compounds during treatment may be the cause of peripheral neuropathies. Patients taking bleomycin may undergo relatively severe pulmonary toxicity, and patients taking doxorubicin have been known (although rarely) to suffer from acute cardiac toxicity. With patients who have cervical involvement, side effects such as alopecia, dysphagia, xerostomia, and taste alteration may result from the local effects of radiation therapy. A handful of patients may even experience a rare, transient myelopathy known as Lhermitte's syndrome, in which an electric shock radiates down the patient's back during neck flexion. Additionally, although certain treatments have achieved five-year survival rates that have approached 90%, this has not been without consequences (Fermé et al. 2007). The use of radiation therapy has increased the long-term risks of other malignancies for these patients, and the morbidity of modern chemotherapeutic drugs still carries significant weight. Future advancements in the treatment of Hodgkin's lymphoma and other similar diseases lie in a better understanding of the cellular pathways that first lead to aberrant proliferation. With this knowledge, researchers will potentially be able to limit toxicity while providing effective treatment.

For Tommy, the next 14 years of his life after diagnosis kept him and his family on an emotional and physical roller coaster. Tommy was on various novel combinations of chemotherapeutic drugs that were often considered investigational, and underwent three bone-marrow transplants. Often at the expense of their own personal aspirations, his family tirelessly fought to ensure not only that Tommy received the best available medical care, but that he always be surrounded by a positive and enriching environment. When Tommy was ten, his doctors told the family he only had six months left to live, and that there was nothing else they could do. Refusing to accept this answer, the family inquired if other facilities could do any better, only to be told, "Alas, we all follow the same protocols." After calls to hundreds of institutions across the country, Tommy's mother stumbled upon a renowned facility where the doctors not only had access to new investigational drugs they believed would benefit Tommy, but to the family's excitement also declared, "We can help him." They were right, and in combination with the latest treatments available, Tommy lived another ten full and loving years.

One limitation in treatment options, the dearth of safe and effective chemotherapeutic drugs, is possibly the result of an average $800 million cost of bringing one drug to market (DiMasi et al. 2003), which simply makes pediatric cancers not lucrative for the pharmaceutical industry. This is evident in that, on average, only one in five thousand novel compounds receives FDA approval (PhRMA 2004). This nonexistent financial incentive, and the commensurate lack of funding, add to the difficulties that normally face drug development such as sparse preclinical models (DHHS 2003a), the lag time between adult and pediatric clinical trials for the same drug (DHHS 2003a), and the often inadequate sample size (Assent Task Force 2010). Unfortunately, not every family is as fortunate as Tommy's. And not every family refuses to accept the status quo and realizes that there are more options out there.

However, despite this bleak reality, there are some nonprofits that are working tirelessly to close the disparity in pediatric malignancy research funding. Organizations such as the Sean Hanna Foundation, Alex's Lemonade Stand, and the Pediatric Cancer Foundation have taken up the challenge to provide for research leading to novel therapies, early detection, and personalized patient care. Ultimately, though, change must come from Capitol Hill.

In what had initially seemed a breakthrough moment in the funding war, on December 16, 2009, President Obama signed H.R. 3288, effectively increasing the NCI's 2010 budget by 2.7%, to $5,103,388,000. Regrettably, pediatric malignancies continued to remain underfunded (NIH 2009b). According to Dr. Reaman, there will be consequences. "It's very frustrating. It's very disappointing. I think it will cost lives. And I think that is what people on Capitol Hill who make decisions about the federal budget need to understand. This will cost lives" (Budget cuts may hurt children with cancer 2007).

In 2007, at the age of 20, Tommy succumbed to graft-versus-host disease soon after his third bone marrow transplant, but he died disease-free. His passing was an indescribable loss

to those close to him, but his life—like the example of sacrificial love embodied by his family—is a stark reminder of our duty to enact necessary reform and unrelentingly advocate for all our patients, especially those who are most dependent on us.

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