

already tenuous existence of small hospitals, contributing to a worsening of the distribution of care, especially in rural areas. These complex problems must be addressed if we are to address the factors that underlie both the dissatisfaction of physicians and the

overall crisis in health care delivery.

Dr. Nowak is the director of the Institute and Outpatient Clinic for Occupational and Environmental Medicine at the Ludwig Maximilians University and a deputy for Occupational and Environmental Medicine at Technical University — both in Munich, Germany.

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FOCUS ON RESEARCH

The Two-Edged Sword of Curing Childhood Cancer

Philip M. Rosoff, M.D.

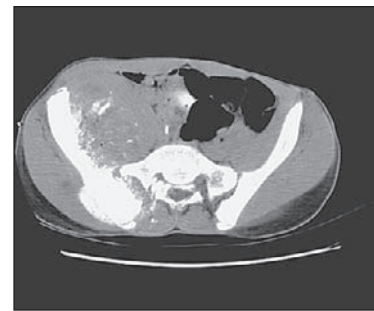
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In the June 3, 1948, issue of the *Journal*, Sydney Farber and his colleagues reported that they had successfully used aminopterin to induce temporary remission in children with lymphoid leukemia. This exciting article suggested that what had been a uniformly fatal disease might be amenable to treatment and, some dared to hope, cure. Then, in 1970, DeVita and his colleagues at the National Cancer Institute showed that a combination of non-cross-reactive chemotherapeutic agents, the MOPP regimen (mechlorethamine, vincristine, procarbazine, and prednisone), could induce sustained remission in advanced Hodgkin's disease. From such beginnings, an extraordinary success story unfolded, and today, more than 75% of children with cancer can be cured of their disease.¹ Nearly 20,000 children under the age of 21 receive a diagnosis of cancer each year in the United States, and more than 15,000 per year enter the ranks of the cured and are able to live into adulthood.

In the "war on cancer," this would appear to be a battle won. But what happens to these survivors? In this issue of the *Journal*, Oeffinger and colleagues (pages 1572–1582) report that the cure may be accompanied by a host of

adverse events, some of which may not appear for many years after treatment has ended (see image). These findings imply that vigorous and long-term monitoring of young cancer survivors, accompanied by early intervention when problems arise, is mandatory. There is a dark side to being cured of cancer as a young person.

Oeffinger et al. report the latest follow-up data from a remarkable long-term study, which does for the survival of childhood cancer what the Framingham Heart Study did for the natural history of cardiovascular disease. The Childhood Cancer Survivor Study (CCSS), established in 1994, is conducted by a consortium of 25 pediatric oncology treatment centers that have pooled data on their survivors who were treated between 1970 and 1986, when significant strides were first made in the treatment of many of the most common types of cancer in children. Although there have been a number of previous reports (from this group and others) that document the substantial incidence of specific long-term side effects of treatment that are faced by survivors, no study has approached the sheer number of patients in the cohort followed by



Computed Tomographic Scan of an Osteosarcoma in the Right Ileocecal Fossa of a Teenager Who Underwent Pelvic Irradiation for Neuroblastoma in Infancy.

the CCSS. This group is clearly the standard by which all future studies should be measured.

Oeffinger et al. confirm the extraordinarily high incidence of late, and often permanent, complications arising from intensive treatment with combination chemotherapy and ionizing radiation. They also demonstrate that the risks are cumulative, with no evidence of a plateau so far. For physicians and nurses who are dedicated to taking care of these patients, this is worrisome news indeed.

Looking at the outcomes in more than 10,000 adult survivors, the CCSS investigators found that almost two thirds of the patients reported at least one chronic health problem, one quarter had a severe

condition, and (perhaps most disturbing) almost one quarter reported having three or more chronic health problems. By any criteria, these results are alarming, and they bespeak a significant level of complications in a population in which only a minority of patients receive follow-up from specialists, as the CCSS and others have previously reported. Furthermore, the types of late sequelae run the gamut of affected organ systems, hinting that even more problems may cloud the future as this population ages.

Chronic illnesses that affect the elderly more generally will also emerge in survivors of childhood cancer, who already carry a heavy physiological burden, as well as a risk of psychological problems stemming from their experience with cancer.^{2,3} One can only speculate about how the combination of preexisting myocardial damage from anthracycline exposure or heart irradiation for Hodgkin's disease would affect cardiac risk factors, when combined with the high incidence of hyperlipidemia, hypertension, diabetes, and kidney disease in the U.S. population at large. Indeed, it is probable that survivors of childhood cancer will be especially vulnerable to many age-related chronic health conditions, their risk magnified by their previous medical treatment.

There is an unavoidable and noteworthy deficiency in the data from the CCSS cohort. All the patients were treated before 1986, and there have been considerable changes in therapy for most childhood cancers during the succeeding 20 years, often with an escalating intensity of treatment paralleling an improvement in survival rates.¹ At the same time, we have become increasingly aware of the potential for late effects

and have attempted to incorporate this knowledge into treatment protocols whenever it is possible to do so without sacrificing efficacy. It would be expected that patients who were treated more recently might have an analogous but different array of long-term complications. This historical effect argues for establishing another cohort for future study.

It would seem to be incumbent on us to ensure that survivors of childhood cancer are followed closely by physicians who understand the effects and outcomes of cancer treatment — who know what these patients have been through and what kinds of complications to look for in the future. Sadly, such follow-up is the exception rather than the rule.

To whom should we look for this expertise? Historically, most of these patients, especially the adolescents and younger adults, have been cared for by pediatric oncologists. But over time most of these patients drift away from the specialty clinic. It is clear that the complications, known and unknown, that will develop in survivors can demand a level of knowledge that is beyond the range of the general internist or family doctor, or even of medical oncologists. Oeffinger, himself a family practitioner, has argued for the wide dissemination of information about late effects,⁴ but this approach relies on self-education by interested physicians in the community. Perhaps we need to incorporate specific training in this area into our residency programs in internal medicine, pediatrics, and family medicine. As an alternative, we could develop a postgraduate training fellowship in an adult subspecialty, analogous to the fellowships in adult congenital heart disease that are

common in most major academic medical centers.

Patients themselves could be empowered by being furnished with a portable document describing their treatment, its potential late complications, and any types of behavior that could diminish their risk of late effects; certainly, cancer survivors and their parents would be very receptive to such recommendations.⁵ These suggestions do not supplant the need for physicians and nurses who are trained to provide seamless continuity of care from diagnosis to treatment to long-term follow-up.

Whatever the eventual approach, it is clear that the effects of childhood cancer — like those of sickle cell anemia, cystic fibrosis, and many other diseases that begin in childhood — do not end when the patient reaches the magic age of 18 or 21 years. Although the child with cancer may be cured, the effects of treatment are lifelong, and we need to study and treat these late effects.

Dr. Rosoff is an associate professor of pediatric hematology–oncology at Duke University School of Medicine and director of the Duke University Hospital Program in Clinical Ethics, Durham, NC.

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