

IS CHILDHOOD CANCER A CHRONIC DISEASE? - A DISCOURSE\*

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The topic assigned for this Endowed Lecture is, on the face of it, a question with a clear and easy answer: 'Is childhood cancer a chronic disease?' The obvious short answer is 'No'. However, that answer may be too hasty and dismissive, and it would be far better first to parse the sentence carefully. The definitions of 'chronic', among the listed synonyms in the *Oxford Universal English Dictionary (OUED)*, include 'inveterate' and 'persisting over a long period of time'. So, do childhood malignant diseases persist over a long period of time? No, they do not - they either kill or are cured. But what about consideration of the word 'disease'? The first definition of that word in the *OUED* is 'absence of ease', i.e. disquiet, worry. Thus, if the following question is asked: 'Is childhood cancer associated with disquiet and worry that may persist over a long period?', then the answer is an emphatic 'Yes.' How, and in what ways?

The cartoon in Figure 1 depicts the consequences that follow a child who falls ill. It is as though he or she were thrown into previously calm waters. These, as a direct consequence, become agitated and turbulent with the resultant waves extending out to engulf not only the child but the family, Society, and members of the medical team. Ripples can persist even after the child is cured of cancer, and rob the cured patient of the fruits of a normal life. Arguably, no slogan is nearly as apt as the one often used for paediatric oncology, namely: 'Cure is not enough.'<sup>1</sup> It applies despite - or even better, because of - the notable progress made in raising the survival probabilities of children with cancer. Five-year cure rates have risen from the 25-30% of three decades ago to 70% today (Figure 2). Although these numbers are striking, it is the 'area under the curve' that matters no less because it represents the number of person-years gained for these children. Indeed, if looked at three-dimensionally, this volume would include the family members and Society, all of whom must share in the vicissitudes as well as the joys that are entailed.

One of the important factors is that the years gained for the child are life's most productive decades. This is unlike the case for adults who develop cancer and are cured during their sixth, seventh, or eighth decades, i.e. during the declining years of their productive life. In concrete terms, there are currently more than 75,000 survivors of childhood cancer alive in the United States. If one assumes

a remaining life-span of 60 years for each of these patients, this represents 4,500,000 person-years of useful life. The task of all those who manage children with cancer is to ensure that those forthcoming 60 years can indeed be as productive and as normal as possible.



FIGURE 1  
The consequences when a child falls ill.

TRENDS IN CANCER SURVIVAL FOR CHILDREN UNDER AGE 15, ALL SITES OF CANCER 1960-1992

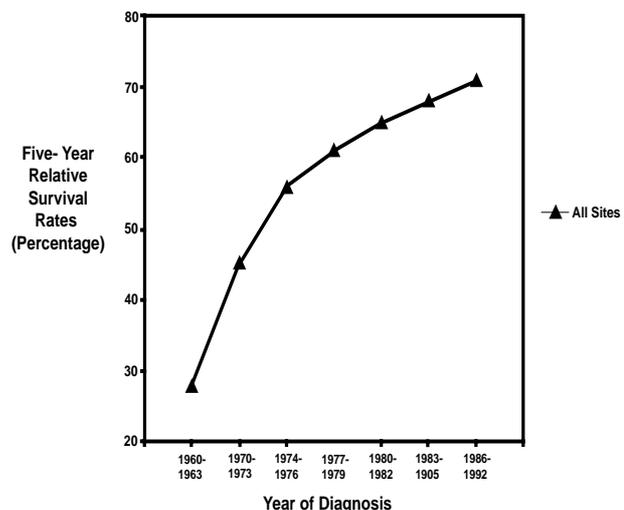


FIGURE 2  
Trends in cancer survival for children under age 15, all sites of cancer 1960-1992.

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## LATE EFFECTS OF TREATMENT

Concern about the 'late effects' of multi-modal anti-cancer management go back to the early years of this century. In 1903 Perthes, the great German surgeon, ran what may be the first 'clinical' radiobiologic experiment on a group of chicks.<sup>2</sup> He irradiated one wing of each chick, and noted that growth of the irradiated limb was stunted when the animals were fully-grown. Perhaps the next serious inquiry was that of M.H. Wittenborg, who 50 years ago was struck by the roto-scoliosis that developed after irradiation of the flank in young children.<sup>3</sup> As only one half of the vertebral bodies received the full dose of radiation, he deduced correctly that it would be better to irradiate the entire vertebral body. Although becoming flatter than normal as a result, it would at least be stunted symmetrically. Thus, although the trunk might be shortened, the treatment would not be accompanied by the invariable pathological curvature that had been recorded previously.

It took rather a long time for our colleagues in chemotherapy to perceive that the long-term effects of anti-mitotic agents on growing cells would mimic in many ways those resulting after irradiation. Searching the world literature for the key words 'late effects' - a rough and ready measure, to be sure - this discrepancy in awareness becomes obvious. During the period 1966 through 1975, only two articles were found dealing with the 'late effects' of chemotherapy, which is in contrast with more than 2,000 papers on radiation therapy during that same period. The number of publications has climbed steadily over the ensuing three decades although most of the papers currently - and quite properly - deal with the effects of **combined** therapy. Thus, in the period 1990 through 1994, more than 3,000 such articles were published.

It may be easily forgotten that even a drug such as methotrexate, which today seems so innocuous (insofar as late effects are concerned), did produce severe lung, liver and orthopaedic problems in the early days.<sup>4</sup> A goal, therefore, for the specialists who treat children with cancer has been to understand the contribution that each treatment modality and each drug administered makes to the deleterious consequences of therapy. Ideally, a joint multidisciplinary approach is necessary. Surgeons should interact with radiation oncologists, who in turn discuss patients with their colleagues in chemotherapy, who consult their surgeons, each understanding the role that he or she should play, and the synergistic and additive influence that one modality of care can have on the other. It is now possible, for example, to salvage limbs or organs that previously were amputated or extirpated for rhabdomyosarcoma. This is because chemotherapy can be expected to help in controlling microscopic residual disease that may have been left behind after excision of the primary lesion.<sup>5</sup> Radiation therapy is required in much lower doses to complement the conjoined attack.

## CHRONIC DISEASE

Chronic problems may be due to intrinsic or extrinsic causes in the individual child; they can be episodic or progressive. Among the intrinsic factors are such precursor lesions as nephrogenic rests. These may or may not be part of predisposing syndromes: the aniridia and the Beckwith-Wiedemann complexes, for example.<sup>6</sup> Neuroblastoma, an extraordinary childhood tumour, can disappear spontaneously, but sometimes shows a late exacerbation and

the development of a frankly malignant lesion, as has long been known.<sup>7</sup> Patients may have the constitutional predisposing *RBI* mutation that too often presages the development of osteosarcoma, let alone retinoblastoma.<sup>8</sup> Still others may carry the mutated *p53* gene that is associated with the Li-Fraumeni syndrome.<sup>9</sup> In short, some patients may not have frank cancer, but are predisposed to the development of a malignant lesion in any of several tissues. They therefore can be said to be 'chronically' at risk.

Extrinsic factors are largely iatrogenic. These can lead to dysfunction of any organ after higher doses of radiation therapy, or specific organ damage caused by certain chemotherapeutic agents. An example is the cardiomyopathy produced by doxorubicin.<sup>10</sup> Disruption of growth and development can again be secondary to chemo- and/or radio-therapy. The possible eventual appearance of a second malignant neoplasm<sup>11</sup> can be associated specifically with the chemotherapy used when, for example, the alkylators and topoisomerase II inhibitors are associated with the appearance of acute non-lymphoblastic leukemias.<sup>12</sup>

These many, and complex, interactions are beyond the scope of this discussion, but one review can be cited to exemplify how multi-faceted the problem can be. Oberfeld *et al.* studied thyroid and gonadal function, and development and growth in 36 long-term survivors of medulloblastoma.<sup>13</sup> The patients had received radiation therapy (RT) to the craniospinal axis, with or without the addition of chemotherapy. The authors state, '...17 of the 28 children who had not achieved final height at the time of diagnosis and who underwent growth hormone (GH) stimulation testing were GH-deficient.' The response to treatment with exogenous GH was gratifying in the first year, but disappointing thereafter in the children who were so treated. Twenty-five of the 36 had deficient thyroid hormone levels, 19 due to primary hypothyroidism, and two from hypothalamic dysfunction; the onset of these thyroid abnormalities ranged from six months to six years following treatment. The interplay of RT and its direct effects on growing bone, taken together with the secondary results caused by disruptions of both the thyroid and growth hormone levels, are good examples of the complexities of the problems facing those who study the late effects of therapy.

## SECOND MALIGNANT NEOPLASMS (SMNS)

Many publications are concerned with the appearance of second malignant neoplasms after treatment for childhood cancer. A recent report from the National Wilms Tumor Study is representative, and can be cited. It is based on a huge number of patients who were followed up for a long period of time.<sup>14</sup> 5,514 children were registered in the period 1969 through 1991, with 39,461 person-years of observation through to the year 1993. There was an increased frequency of SMNs, though a low incidence was recorded. Myelogenous leukemia, if it appeared, did so relatively early (two to five years after diagnosis), while solid tumours developed later. The cumulative index of all SMNs at the time of the report was 1.6% - and the curve was still rising. Of note was the fact that three malignant liver tumors were represented among the solid neoplasms: this is an extraordinary association, and a lead for epidemiologic research and studies of the pathways of oncogenesis. Another noteworthy observation was that the risk of an SMN was higher in irradiated patients, and was even higher by a factor

of about 2 in those given doxorubicin as well as abdominal RT. The RT dose was a factor, with the frequency of SMNs rising steadily with increasing doses through 35 Gy and above. The risk was also heightened in patients with recurrent disease given salvage regimens that included RT and drugs that *per se* are oncogenic.

This report has been specifically selected for more detailed comment, not only because it is based on a large number of patients treated in a standardised manner, but also because it shows the important interplay among the various treatment modalities. It also emphasises the need to cure the patient when first treated; re-treatment for relapse adds to the 'late effects'.

## PSYCHO-SOCIAL-ECONOMIC CONSEQUENCES

Although somatic changes have been discussed so far, important psycho-social-economic consequences also follow after a child is found to have cancer. Among these are the future insurability and employability of survivors. One study in the United States found that survivors pay higher premiums and are denied insurance 15 times more frequently than their siblings.<sup>15</sup> Often, if and when the insurance policies are granted, they include exclusionary language that declares 'pre-existing conditions are not included'. As one long-term survivor has made clear, it is not the pre-existing condition - cancer - that recurs. These patients are cured; the cancer is gone. It is the consequences of achieving that cure that may cause problems.

The 'Damocles' and the 'holocaust' syndromes figure prominently in both the patients who survive and their families.<sup>16,17</sup> The threat of a recurrence lingers on, if not of the primary tumour then of a second malignant neoplasm, in those known to have precursor lesions or syndromes. Survivors are often troubled by memories of other children on the ward who did not survive, often asking: 'Why did I?' The impact on the family can also be great and varied. The economic consequences are sometimes staggering. Even though there may be adequate coverage by either governmental sources or insurance, the out-of-pocket expenses can be crippling.<sup>18</sup> This refers to the losses that cannot be recovered such as days off work, the cost of providing babysitters for siblings who remain home while the parent attends the patient in clinic or hospital, expenses entailed in transportation and/or hotels while the patient is under treatment, etc.

Not to be ignored is the 'forgotten child' effect. Several (but not all) studies have shown that it is the sibling who very often suffers the most because of parental deprivation.<sup>19,20</sup> This happens even though the parents may make every effort to include all the family in projects, travel, and similar pursuits. The siblings may understand completely the reason that the mother or the father is not available at a particular moment; they nonetheless remember and resent (despite themselves) that their mother or father was not at home because attention was being devoted to the sick sibling.

There is greater marital tension, even though the divorce rate may not be increased.<sup>20</sup> The stress felt by the mother and father is often reflected in the children. These secondary psychological effects may persist well beyond the period that the child dies or is cured and becomes an adult. Smouldering sibling rancour and jealousy very often cannot be completely dispelled.

## HEALTH CARE TEAM

All those who care for children with cancer are confronted daily with the anguish of parents, and with the fear and distress of their young patients. Especially trying are the children - they must undergo rigorous, and at times painful, diagnostic and therapeutic measures that are not always successful. Team members are thus under constant stress with wide swings from elation when remission is obtained, to gloom, and even despair, if a relapse occurs. There is no need to expand further on these themes; suffice it to say that the turbulent waters of Figure 1 can engulf even the hardest, despite in-service counselling and support. Such persons are well advised to change to another field; not everyone is suited to the demands of the specialty, any more than all can or wish to meet the stresses of intensive care medicine or surgery.

## SOCIETY

Finally, there is the impact on Society, of which Medicine is a component.<sup>21</sup> Medicine is responsible for medical costs and their containment. The co-operative clinical trial mechanism is an ideal way of determining which elements in complex treatment protocols are truly necessary in order to achieve success. This strategy formed the background for the design of the fourth National Wilms Tumour Study. There, the results of a standard regimen of five daily doses of dactinomycin and three daily doses of doxorubicin were contrasted with single daily doses of the two agents.<sup>22</sup> The total period of treatment of approximately 15 months was also compared with about six months of treatment (or even less) for early stage, 'favorable histology' disease. The total annual savings using such modifications of treatment are almost \$2,000,000 even for this rare tumor, there being only 400-500 children found to have Wilms tumor in the United States each year. Added to these considerations are the sometimes extremely complex forms of treatment - for example, the bone marrow transplant avenue - that are very expensive and may not be warranted by the results.<sup>21</sup>

Society must confront these issues. The expenses entailed in each case may seem minuscule when compared to the summed costs accruing from the total delivery of health care, but added together, they may well be more compelling.

Two other major problems have to be confronted by Medicine and by Society. The *first* is the need to establish effective means of following up cured children as they become adolescents and adults. Many different systems are in use.<sup>23</sup> Some young adults are seen in children's hospitals by the paediatric oncologists who had treated them originally. Not all adults find this arrangement satisfactory. Also, the patient may well outlive his paediatric oncologist. What then? Some survivors are referred to oncologists who treat adults. These specialists are busy with their own patients and with other cancers, and can devote little time for an apparently cancer-free patient treated as a child ten or more years before. Moreover, the treatments used in children and their potential late consequences are unfamiliar. To abbreviate an otherwise-lengthy discussion, two important points can be made:

- A. The best conduit for the requisite data is the patient him- or herself.<sup>24</sup> A dossier outlining the treatments used and their possible late effects can be given to the parents, and eventually to the patient when he/she attains

a suitable age. An example would be to document the surgery, the chemotherapy and the radiation therapy (RT) administered to a child cured of medulloblastoma. The potential late adversities of these treatments would be listed, and attention would be called to the thyroid. That organ, being in the exit RT field, is subject to dysfunction, and/or cancer. These are risks that are often forgotten by any but trained personnel.

- B. The best long-term follow-up is probably found in a clinic devoted to these problems and staffed by specifically taught nurses and physicians. Such a clinic is best attached to a cancer centre where health professionals keep abreast of current oncologic information; both of treatments and their consequences.

The *second* major problem is the cured child who becomes a severely handicapped adult. An example is again provided by the child cured of medulloblastoma who never develops his or her full mental capacities. Though not completely incompetent, such children often become reclusive 'stay-at-homes', unable to work, and incapable of mixing in ordinary society, with parents who worry about future care. Who is to look after this mature but severely-handicapped person when the parents are gone? Questions of this nature remain unanswered.

So it can be seen that childhood cancer certainly does produce chronic dis-ease of many forms. It affects the child and the family, and has vast implications for Society as a whole and in its parts. These problems will increase as the cure rates rise, and more and more children cured of cancer become adults. The responsibility is ours in Medicine to devise ever-better methods of achieving long-term survival while lessening the associated complications, some of which may take years to develop.

A photograph, recently received, encapsulates much of the foregoing discussion. It shows a lovely young woman I shall call Estelle (because she is a star) who is a survivor of metachronous bilateral Wilms tumours. She has part of one kidney left after several operations and multiple courses of chemotherapy. She has held and fulfilled responsible governmental positions with an excellent attendance record. Her sister, long estranged because she felt like a 'forgotten child', is now on friendly terms. By Estelle's side in the photograph is her devoted husband, a happy couple if ever there was one. And to demonstrate that not every enlarging pelvic mass in a long-term survivor is bad news, Estelle's came to term, and she holds the result - a beautiful, normal baby - in her lap.

Indeed, cure is **not** enough. There is more - much, much more.

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