Editor:  
Thirty or forty years ago a diagnosis of cancer inevitably spelled doom for a child. Today, the outlook appears brighter. What is the revised prognosis for children with cancer?

Dr. D’Angio:  
The relentless, aggressive attack against childhood cancer has led to remarkable progress in a relatively short time. For example, osteogenic sarcoma and rhabdomyosarcoma, the despair of physicians only a few years ago, are slowly responding to treatment with surgery, radiotherapy and chemotherapy. And where once leukemia routinely caused death within a year from diagnosis, today the median survival time exceeds five years. Also, according to the National Wilms’ Tumor Study, the two-year cure rate for Wilms’ tumor has soared to well over 85 percent, and in certain patients with localized disease is approaching 100 percent. Yet, despite a constantly growing list of successes for which medicine can take justifiable pride, many of us are still not satisfied with the results.

Editor:  
But, why not?

Dr. D’Angio:  
Many problems remain. As children with cancer live longer, the long-term harmful consequences of radiation and chemotherapy are becoming apparent. Of course, every treatment has undesirable side effects, some minor, some major. Unfortunately, those associated with pediatric oncology are too often the latter.
Apart from minor temporary reactions to radiotherapy such as alopecia and blanching of the skin, what long-term damage can occur?

Impairment of growth, loss of genetic function, organ insufficiency and the development of secondary neoplasms have all been linked to irradiation, generally in direct relationship to the total dose and in inverse proportion to the age of the child. Rapidly growing long bones are especially vulnerable to irradiation, producing bone growth disturbances; usually, the younger the child, the greater is the impairment. Also, severe damage to development of the gonads may either destroy the child's reproductive capacity or result in genetically defective progeny. Dysfunction of organs including the lungs, heart, liver, renal tissue and bowel can be crippling or lethal, even many years after treatment. And while radiotherapy can successfully eradicate pulmonary metastases, 10 or 15 years later it may lead to pulmonary insufficiency and even death. Injury to the parenchyma may set the stage for the development of future cancers.

Now that chemotherapy is being used more extensively, will the threat of potentially harmful side effects be reduced or increased?

Since there are relatively few survivors of long-term chemotherapy, detailed and protracted studies have not yet been done. However, chemotherapy probably causes many, if not all, of the same adverse effects as radiotherapy.

In addition, unusual sensitivity to a chemotherapeutic agent, such as actinomycin D, or inadvertent over-dosage can lead to profound, sometimes lethal, bone marrow depression. All chemotherapeutic agents are toxins, affecting the most rapidly dividing cells; however, some cause specific organ damage to the lungs, liver or kidneys, which over the years can be crippling or even fatal. Furthermore, justifiable concern about late mutational effects has recently been aroused by the example of actinomycin D, which binds DNA and inhibits transcription of RNA. Some drugs are carcinogenic in animals and must be evaluated to determine their effects in man.

Does the combination of radiotherapy and chemotherapy potentiate deleterious reactions?

Radiotherapy and chemotherapy sometimes enhance the local effects of one another, thereby increasing the potential for long-term harm. Irradiation, which alone may produce reparable damage, may cause death when combined with chemotherapy. Conversely, the toxic potential of a drug is often increased when radiotherapy is given concomitantly. After surgery, such as a partial liver resection, the combination of irradiation and chemotherapy may be particularly damaging.
There are many unknowns, and further research is essential to evaluate accurately the risks of treatment. Results of one investigation designed to detect the late consequences of chemotherapy in children can be cited as an example. It was found that patients who were given actinomycin D, a proven carcinogen in animals and a known enhancer of radiation, showed a decrease in the risk of developing a second neoplasm by a factor of five. These findings, although preliminary, and obviously requiring substantiation, are a complete surprise and indicate the amount and kind of work that must be done.

Editor: What can be done now to minimize deleterious effects of therapy?

Dr. D'Angio: The child cured of cancer must be followed for life, not so much to detect late recurrence of disease, but to permit early diagnosis of any side effects of treatment. Additionally, treatment must be refined to the absolute minimum necessary to achieve the best results.

Editor: How can this be done?

Dr. D'Angio: First, systems of therapy must be based on an assessment of several important variables including age of the child, stage of disease, site of origin, histologic grade and type. The concept of tailoring treatment to prognosis is obvious, yet only recently accepted.

We must also assess whether more therapy will better suppress both primary and metastatic disease or if less treatment will give equally good results. More therapy is not necessarily better treatment, particularly in view of its potentially deleterious side effects. For this reason, the indiscriminate concatenation of therapies, however laudable the intent, should be discouraged, and the introduction of new or even standard methods into existing programs must always be based on a sound rationale. Recent results from the National Wilms' Tumor Study support this philosophy.

Editor: In what way?

Dr. D'Angio: Initial findings suggest, for instance, that a baby with early Wilms' tumor does not need to be irradiated to have a very good life expectancy. The same may well be true for chemotherapy. Rather, the simple surgical removal of the tumor may be sufficient in a high proportion of patients. We are going through the material again to nail down the results, but the preliminary indications are that it is better not to irradiate, and then attempt to retrieve the children who fail rather than damage 99 of 100 patients with unnecessary therapy.
Editor: *Are any other significant investigations being conducted in this area?*

Dr. D'Angio: Yes. Not dissimilar in ultimate aim are the attempts to diagnosis the disease in an early stage or, ideally, to prevent its occurrence. Advances are being made in defining familial patterns and clinical syndromes associated with a high risk of cancer. Today we know, for example, that the child with neurofibromatosis or retinoblastoma has a high risk of developing a second neoplasm and must be kept under careful scrutiny. Perhaps, in the future, these cancers might be prevented by so-called "genetic engineering."

Another promising area of research centers on efforts to restore immunocompetence to children with immunodeficiency diseases in the hope of reducing the associated high incidence of cancer. Finally, attempts to identify environmental oncogenes and onco- genic viruses in humans continue. Tantalizing leads such as the isolation of EB viruses in Burkitt's lymphoma and nasopharyngeal carcinoma spur on investigators in their search for a preventive or therapeutic vaccine.

Editor: *Putting pediatric oncology in perspective, where have we come from and where are we going?*

Dr. D'Angio: We are near the end of a long tunnel, looking back to the blackness of no hope and no cure. Ahead lies a wide open road with well-spaced way-stops en route to our final destination . . . insuring that the successfully treated children of today do not become the chronically ill adults of tomorrow. The ultimate aim through preventive measures is to insure that childhood cancer as a threat to life and limb is eliminated forever. Indeed, cure is not enough.

Editor: *Thank you, Dr. D'Angio.*