Human leukemias are many diseases. Even if discussion is restricted to human acute leukemias, the topic ordinarily discussed in the context of animal model systems, these still are many diseases. They are subclassified by characteristics of cytological type. In some animal model systems one can modify the host by such maneuvers as aging or by splenectomy or thymectomy and thereby alter the cytological type of leukemia that appears. Thus different acute leukemias in man may be interrelated. The different morphologies or different antigens do not necessarily imply different etiological agents. The classic disease called acute leukemia of childhood peaks at about 3 to 4 years of age. The frequency of acute leukemia drops to a constant plateau of low incidence until about age 40, after which it continuously increases until the end of life. The cytological type is predominantly acute lymphocytic in childhood and changes to acute myelocytic and myelomonocytic in adult life (8).

Acute leukemia is a group of diseases with rapid growth kinetics. With what we know about the kinetics of leukemic cell multiplication, the time from presumptive onset to symptoms or to death is very short. The likelihood of making a diagnosis of acute leukemia by using immunodiagnostic techniques before recognizable clinical features appear is, in my view, remote. One need only look at current practice in pediatrics and how often pediatricians use antibiotics for diseases known to have bacterial origin without making bacterial cultures. Although acute leukemia is the commonest cancer of childhood, it still constitutes only 4 to 8 cases among 100,000 children per year, superimposed upon thousands and thousands of viral and bacterial diseases for which diagnostic tests are not now taken. It is improbable that immunological tests for diagnosis would make any significant impact on leukemia discovery and treatment, even if a test were available. The same phenomenon is true in adults.

There is, in my view, no accepted known virus responsible for human leukemia. The observation of virus recovery from acute myelocytic leukemia is a few months old but is not yet accepted as demonstration of a causal agent, albeit an associated one (6). This detracts, for the present, from the concept of a vaccine prepared from a leukemic virus.

Acute lymphocytic leukemia occurs primarily in the 1st decade of life. This should be the easiest of all leukemias to prevent. Furthermore, one could gain an end point while the investigator was still alive. Despite its early occurrence, acute leukemia is not a heredofamilial disease. Data supporting this view stem from epidemiology and molecular biology. Baxt et al. (1) have shown that DNA synthesized by the reverse transcriptases of 2 men with acute myelocytic leukemia hybridized with their own leukocyte DNA. This indicates some homology of DNA nucleotide sequences in their leukemic leukocytes with sequences in the RNA from which the transcript was made. Each man had a normal identical twin sibling, but no homology was found within the siblings' leukocyte DNA. These data are best explained by postzygotic insertion of the leukemia-related sequences (1). Doll (5) has accepted as suggestive evidence of horizontal transmission of acute lymphocytic leukemia 15 pairs of children 6 years of age or less, culled from 3 separate reports, who have had space-time clustering within 1 mile and within 90 days of one another. In 27 of these 30 children the age was 4 years or less. If other kinds of human neoplasms are found to be related to similar or identical C-type particles, the epidemiological study could be broadened considerably.

Even if we were to agree on what kind of a vaccine might be active and what might be tested in acute lymphocytic leukemia of childhood, this vaccine would need evaluation in the context that the disease is not an isolated phenomenon of virology. There has also been therapeutic advance. As of now, in university centers, one-third or more of children with acute lymphocytic leukemia can be cured of their disease, cure being defined as survival after 5 years, off all treatment, without evidence of disease (8). Therefore, the burden for prevention has been reduced to 2 to 4/100,000 children. Certainly, at that level the benefit-to-risk ratio of vaccination becomes an enormously complex problem, what with the alterations that one might make in the patient with respect to other diseases, let alone other neoplasms. If the vaccine were of value in terms of preventing acute myelocytic leukemia, then the end point to evaluate the effect is some 4 to 70 years ahead.

I believe that there are 3 requirements before one could ethically embark upon any kind of prophylactic immunization programs against acute leukemia of man: (a) the isolation of a virus from several kinds of leukemia which is accepted as the putative agent(s); (b) an experimental animal other than man in which one can reproducibly induce a disease with this virus; and (c) demonstration that the disease can be prevented in this experimental system. None of these conditions has yet been fulfilled. If indeed, such a virus(es) exists and if the model system were discovered, the experiments to test prevention are easy. It would probably take only a few years to develop an optimal vaccine and then one could justify an entry into the human population.
Clinical trials, including immunization trials, are difficult, particularly for rare diseases. The problem is compounded when the rare disease is subject to remarkable change in the course of time because of therapy, which might vitiate a long-term proposal.

It seems to me that immunology will make its major contributions in immunoquantification and in immunotherapy. Immunoquantification to assess the level of disease is of great importance. The patient who enters with a florid leukemia can relatively easily be induced to a status of remission. Reduction of his leukemic body burden by some 2 or more logs reduces the leukemic cell population in the marrow from near 100% to 1% or less at which time visual discrimination among cells becomes grossly inaccurate. Indeed, there is an urgent need to quantify leukemic cells when present in larger populations of normal cells. I am aware of investigations in this direction in which one can recognize with a degree of confidence 1 leukemic cell in 10,000. If translatable to marrow on a systematic basis this could be extremely useful. For example, when to change or intensify treatments would be apparent very early, below the threshold of ordinary clinical detection.

It would be possible to use a whole new strategy of clinical therapy if one could look at the subthreshold disease. The leukemic child does not always die from leukemia. He may die from toxic effects of therapy or from intercurrent disease related to immunosuppression. Immunoquantification would be of help in determining when to stop treatment. One major clinic in the United States has advocated stopping treatment of acute leukemic children at 2.5 to 3 years, thereby accepting a 20% relapse rate. In effect nearly all of the 20% of failed children will go on to die. In our own studies we have taken the proposition that, until we know who is cured, it is better to continue treatment for at least 5 years. At that point we are testing continuation versus discontinuation of the treatment among patients chosen at random. As yet there are no differences in the relapse rates between those who do and those who do not stop chemotherapy. Immunoquantification techniques that provided accurate assessment of the disease might allow one to treat with conviction until demonstrated cure was achieved.

Last, what is the role of antiviral or immunological procedures in therapy? I think here I would extend the thoughts that Bekesi et al. (2) reported for our own model systems with AKR leukemia. One can prevent the appearance of leukemia in the AKR mouse, known to be heavily infected with Gross virus by certain doses of interferon. By higher doses of interferon one elicits toxicity, and lower doses are ineffective. There will be no easy open and shut answer. Interferon used pharmacologically is a drug, and like other drugs there will be a proper dose and doses that are too great and too little.

We have been able to delay the appearance of leukemia in preleukemic AKR mice by using neuraminidase-treated synthetic or allogeneic leukemic cells carrying the Gross virus. More importantly, in established autochthonous leukemia as well as in established leukemia L1210, we have been able to augment chemotherapeutic cure rates by immuno-therapy with neuraminidase-treated cells. The phenomenon is true of many different animal tumors.

Neither treatment, interferon or immunotherapy with enzymatically altered cells, is effective against florid neoplasms. It is necessary to decrease the tumor burden, thereby improving the host's general condition as well as the ratio of immune active cells and molecules to residual neoplastic cells. With chemoimmunotherapy we have been able to transform the AKR disease from one that is uniformly fatal to one in which there is a high proportion of prolonged survivors. Very late relapse of the disease appears to be due to viral reinuduction. Reinuduction is also preventable in part by additional treatment: either endogenous interferon induction by statolon or the non-interferon-producing antiviral drug ribovirin. These data are shown in detail in Bekesi's paper.

I think that the principal immunological and virological impact in the near future will be therapeutic in association with other treatments that reduce the body burden of leukemic cells. With today's information this would allow us to make a concerted attack on the condition of some 85% of children who enter remission with currently known treatments. A similar attack could be made on the disease of 70% of adults who now can enter remission with good treatment.

The human biologists called clinical investigators have not been blind to these observations. Starting in the mid-1960's Mathé and coworkers began immunotherapy with BCG2 and irradiated leukemic cells. Their data have not been confirmed by others, who did not, however, follow the exact protocols nor use the same techniques. Clinical trials showing activity of BCG in prolonging remission of acute myelocytic leukemia have been reported by Crowther et al. (3) and by Gutterman et al. (7). Similarly, we have recently reported that the methanol extraction residue of BCG prolonged the remission duration of patients with acute myelocytic leukemia (4).

The time is propitious for the fruits of immunological and virological research to be translated to man while we await a wholly definitive exposition of the virus etiology of human leukemia. The purified virus or its components might be a valuable component of immunodiagnosis and immunotherapy. Immunoprophylaxis would appear, however, to be far off.

References

2 The abbreviation used is: BCG, Bacillus Calmette-Guerin.
Immunological Control of Human Leukemia: Discussion

James F. Holland


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