Summary of Meeting on Modern Trends in Human Leukemia

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An international meeting concerned with various aspects of leukemia, including etiology, diagnosis, pathogenesis, and clinical treatment, represents a major challenge and a promise for interaction among scientists with various backgrounds and representing many disciplines. The organizers of the third meeting on human leukemia in Wilsede molded the framework for this interaction by assembling a distinguished group of scientists, thus providing both formal and informal opportunities to discuss problems pertaining to leukemia. All sessions included highlights of new and exciting findings that were well presented by the investigators. Regrettably, many found it difficult (and in some instances impossible) to communicate information to a mixed group of scientists in such a way that those not directly involved in a particular type of research were able to digest, interpret, and comment on the work. Despite this shortcoming, it became obvious during the meeting that major progress is being made in better diagnosis of different forms of leukemia and that the clinician is better able to respond to the challenge of curing the patient because of it.

The magnitude of the problem in the human population can best be summarized by noting that there will be an estimated 88300 cases of leukemias and lymphomas in the United States resulting in approximately 57900 deaths. Translated on a worldwide level, these estimates would suggest that1 766000 new cases will develop during 1978 and that approximately 1 160000 deaths will occur because of these diseases. Leukemia alone will claim 21500 new victims in the United States and 430000 victims globally, causing an estimated 15100 deaths in the United States and approximately 300000 deaths on an international basis. Thus, these diseases represent a significant impact on society and the number of cases is likely to increase as the population continues to rise unless measures are found to prevent new cases or to abort the disease early after its onset.

It is obvious that the etiology of leukemias and lymphomas in the human population still remains elusive despite large-scale efforts to demonstrate causation. While some epidemiologists continue to claim that the absence of clusters of childhood leukemia indicates that an infectious entity plays no role in the disease, it has become increasingly evident that no single environmental factor or group of factors can yet be singled out as the offending agent. This, coupled with the well-known ability of viruses to cause leukemia and lymphoma in a wide variety of animal species, continues to focus atten-

tion on this area. Recent information concerning feline leukemia suggests that clusters are absent in the natural population (except when cats are concentrated in large numbers in households) despite the fact that this disease clearly appears to be caused by a leukemia virus which generally spreads by horizontal transmission. In fact, cat registries did not reveal that the disease was infectious until households were examined and seroepidemiology was employed. Of great importance is the recent finding concerning the absence of additional copies of virus sequences in some leukemic cats, a situation that may be analogous to human leukemia and may explain the difficulty in finding specific sequences relatable to viruses in human leukemic cells.

It has not yet been possible to incriminate recent human oncornavirus isolates in the etiology of leukemia. Clouding these isolations of putative human viruses is the fact that after careful examination, most of the isolates consist of a mixture of viruses of simian and rodent origin. The explanation for such mixtures remains obscure. It is noteworthy, perhaps, that sequences that can be related to those found in the genome of Gibbon ape sarcoma virus have been detected in human cells. These results require confirmation and their significance is unclear at this time. Thus, the continued failure to come to grips with the etiology of leukemia focuses more attention on early diagnosis and better classification of the various neoplasias.

Improved methods of chromosome analysis continue to reveal specific changes in the karyotype of leukemic cells. For example, in 97% of chronic myelogenous leukemia, chromosomes 9 and 22 are involved in translocations. In 50–75% of acute promyelocytic leukemia, there is a translocation of chromosome 17 to chromosome 15 and in Burkitt lymphoma cells, a translocation of chromosome 8 to chromosome 14 is regularly observed. The origin of these translocations is not known, but they clearly serve as useful markers for diagnosis and it is beginning to appear that they will help clarify the regimen of therapy to be used in individual patients. The use of enzyme markers, such as glucose-6-phosphate dehydrogenase, is also proving useful in the continued study of pathogenesis. Certainly, these and other studies are valuable in understanding differentiation, but the hope that differentiation studies will further knowledge of the neoplastic process has not yet been definitively realized.

Even though progress in pathogenesis of human leukemias and lymphomas is agonizingly slow, major advances are being made in model systems designed to demonstrate how the addition of virus genetic information can cause transformation. Thus, one of the more exciting reports at the meeting involved the possible structure and function of the gene product coded by the sarcoma (src) gene of the avian sarcoma viruses. Identification of a protein with a molecular weight of 60000 daltons by immunoprecipitation using rabbit serum revealed that the purified product has protein kinase activity which may affect regulation of various cell characteristics. What remains unknown is how this kinase specifically affects regulation and leads to a malignant phenotype. Additional information concerning the gene products of other sarcoma and leukemia viruses and their roles in oncogenesis should be forthcoming soon.

The isolation of putative human leukemia viruses and the possible existence of some simian sarcoma virus sequences in human leukemic cells has also prompted examination of human sera for reactivity against a variety of known animal oncornaviruses. Regrettably, observations concerning antibody in the sera of some patients against the simian sarcoma virus p70 antigens are not matched by findings of those antigens in human tissues. Rather, human tissues contain a protein that appears to be similar to the p30 of these viruses and this discrepancy clearly needs to be resolved. Overall, evidence that human neoplastic tissues contain virus-specific antigens and that the sera contain antibodies against those antigens remains relatively weak and requires further clarification.

Luckily, progress in leukemia treatment has been substantial and represents a major achievement. Remission rates remain better than those observed in other common neoplastic diseases such as breast and lung carcinomas, although improvement is still required to reduce both morbidity and mortality. Treatment results still vary considerably from one center to another and more communication between clinicians and basic scientists would go far to facilitate new approaches. Unfortunately, the language of the research scientist and clinician often differ, and their views of the problems involved often diverge considerably. It is meetings of the kind that took place in Wilsede that hopefully will bring those divergent views to a common level. Among the major problems besetting continued progress is the variety of systems being developed by individual investigators despite their similarities to many existing systems. Perhaps it is time to remind those working in oncology that great progress was made in understanding the properties of bacterial viruses because most investigators agreed to work on only certain viruses in an effort to facilitate progress. In an era of diminished funding, this may well serve as a model for current studies in oncology.

The relative rarity of leukemia in the human population remains instrumental in its confusing etiology. However, there are numerous infectious diseases known to be caused by viruses that are equally uncommon (such as encephalitis due to herpes simplex virus or subacute sclerosing panencephalitis due to measles virus) and which fail to cluster in the population. Clinicians, with the help of virologists, immunologists, and pathologists, have been able to demonstrate etiology using sensitive virus isolation techniques and sensitive (and specific) methods involving serology. However, this requires the preparation of specific probes which, unfortunately, are not yet available for studies of human leukemias and most lymphomas. The failure to generate such specific molecular and immunologic probes has perpetuated confusion when looking for genetic sequences and antigens in human tissues, and the corresponding antibody in sera or other fluids in the human body. Hence, as brought out by the meeting, further refinement of technology and extremely conservative and careful interpretation of observations continue to be the leading requirements in this field.

In summary, it would appear that leukemia may be the first important human neoplastic disease to be controllable. Theoretical model systems are highly encouraging, and are leading to a better understanding of cell conver-

sion from a normal to a malignant phenotype. If etiologic studies concerning viruses are to be pursued, it would seem logical to look for agents early in life (in healthy children and during pregnancy), because if such viruses are to persist in the population, they clearly must replicate in most members of the population early in life, only to cause disease at some subsequent time. Although viruses may play a prominent role in cancer etiology it is plausible that other factors are involved in initiating disease. Techniques that have been developed in the infectious disease laboratory clearly should be applied more effectively to study the etiology of human leukemia and other neoplastic diseases with the long-range hope that isolation of such agents and identification of the disease may lead to prevention, rather than to the more expensive and more traumatic treatments that are now available. The field seems ripe for a breakthrough. No one will benefit more than future generations who will thank the dedicated efforts of investigators such as those attending the Wilsede meeting.