Review of Clinical Reports and Discussions

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The Conference on Obstacles to the Control of Acute Leukemia has succeeded far beyond the hopes of the program committee, not only in the clarity of the formal presentations but, more importantly, in the innumerable discussions in the hallways and on the terraces. During these informal associations, the kaleidoscopic regrouping of clinicians, biochemists, radiation biologists, immunologists, pathologists, and many others has given rise to a completely unexpected windfall—that of letting one's imagination roam freely around the overcoming of these obstacles. On behalf of the National Cancer Institute, I want to thank all of you for your generous contribution of time and talent during this weekend.

It is not possible to summarize in any meaningful way all the important points that have come to my attention in the formal and informal exchanges. The best I can do is to mention by title a few of the obstacles in the clinical control of acute leukemia, and I will group these under 3 headings: obstacles to the study of viral etiology of leukemia, obstacles to the destruction of all leukemic cells, and obstacles to the repair of deficits caused by leukemia.

As to viral etiology of acute leukemia, it seems quite clear that tailed, virus-like particles, similar to those that cause murine leukemia, are commonly found in the blood of patients with acute lymphoblastic leukemia. The next objective is to discover the relation of the particles to disease, and there are several problems to be solved The 1st of these is to establish an assay system for the presence of the particles, in order that their relations to the natural history of leukemia can be examined. When do they appear? In what tissues are they found? Do they circulate in the blood of asymptomatic carriers? Are they picked up from the environment? Do they disappear during remission? The answers to these and a thousand other queries await an easy method for detecting the presence of the particles. At the moment, the particles can be demonstrated in patients only by the electron microscopist. Although morphology can never with certainty describe function, at this time it provides the only available assay. It would seem wise for physicians dealing with the natural history of acute leukemia to have close working relations with an electron microscopist.

Another and major obstacle to the understanding of the significance of the virus-like particles is the mystery of what might be their biologic effects on cells and organisms. If these particles could systematically induce acute leukemia in an experimental animal, we would be a ong way along the road to solution. So far this has not been possible, but you can appreciate that there is intensive activity in many laboratories to discover how this might be done. Similarly, a specific cytopathogenic change in tissue culture would provide some means of understanding the importance of these particles.

A 3rd obstacle is the lack of large amounts of pure virus from the animals with leukemias. Many of the studies mentioned above, as well as considerations of chemical structure, role in the DNA-RNA-protein sequence, relation to helper viruses, and the chemotherapy of virus leukemia await the ability to produce large quantities of purified viruses. The National Cancer Institute has undertaken attempts at large-scale production of the murine and fowl viruses, and what is learned from this effort may prepare us for overcoming the obstacles to production in quantity of the virus-like particles from acute lymphoblastic leukemia.

The 2nd series of obstacles is related to the inability of present drugs to kill all the leukemic cells. I will not dwell upon this problem, since Dr. Holland has reviewed the ways in which one might improve the therapeutic index of present drugs and Dr. Skipper has just summarized the theoretic and experimental problems of leukemic eradication. In the attempt in the clinic to obtain more extensive destruction of leukemic cells, we have had a number of discussions on the use of combinations and cycles of available drugs. Studies of these are under way in many clinics, but it is too early to make an unequivocal recommendation of optimal therapy. It has, however, been clear in several presentations that, in children with acute lymphoblastic leukemia, the early use of adequate doses of prednisone, in combination with 6-mercaptopurine or vincristine, results in survivals of unusual length. Dr. Burchenal's report of a number of 5-year survivals gives rise to the hope that in a few patients almost complete destruction of leukemic cells by means of 6-mercaptopurine, prednisone, and methotrexate is possible. Since there are 2 new agents, cyclophosphamide and vincristine, the record of 5-year survivals in all likelihood will improve. In the midst of this optimism, however, I join with Dr. Farber in cautioning about the use of the term "cure" with respect to leukemia. Many years must elapse before a case of leukemia can be said to be cured. On the other hand, in choosing the most effective combinations and cycles of drugs, judgment must be made quickly. In this context lies the importance of points made by Drs. Zuelzer and Frei: that there is a relation between the length of the 1st remission and the ultimate survival time. The duration of the 1st drug-induced remission might, then, be a good index of the thoroughness of the chemical destruction of leukemic cells.

In a number of discussions emphasis has been placed upon the need to increase permeability of leukemic cells to drugs, in order to increase the completeness of kill. Many suggestions have been made as to how this might be ac-

complished. One of the most intriguing of these is that of Dr. Mathé, who has obtained a few prolonged remissions by the use of immunotherapy in conjunction with chemotherapy. One wonders if the immune response induces increased passage of the drugs into the leukemic cells and thus, speculatively, might provide a few extra measures of leukemic cell destruction.

Finally, I should like to mention that there has been considerable discussion of choriocarcinoma at this conference on leukemia, presumably because this is an example of another malignant disease that, like leukemia, is exquisitely sensitive to drug control. I do not believe that we have made full use of this observation on the trophoblastic tumors, homografts though they may be. Is it not conceivable that, if physicians, biochemists, and immunologists could understand the reason for this success and the reasons for the success in leukemic patients with long-term drug-induced survivals, we might be able to design truly curative therapy for leukemia? My point is that in chemotherapy it is not only by the study of obstacles, but also by the analysis of the mechanisms of success, that we progress. Such indeed has been the history of chemotherapy of the bacterial diseases, and such, we hope, will soon be the history of the control of acute leukemia. May I extend my appreciation to all of you for advancing our understanding of acute leukemia during these 3 days.