Summary of the First Emil J Freireich Symposium

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The first Emil J Freireich Symposium was an awesome tribute to an extraordinary human being. The Freireich Symposium was M. D. Anderson Cancer Center (Houston, TX) at its best, with the faculty, fellows, staff, alumni, friends and the new President fully involved in the intellectual life of the institution. The Symposium reminded us who we are, why we are here, where we have been, and what must still be done. Quite simply, our goal is to cure cancer in our lifetimes, or, more precisely, to eliminate this disease through prevention, earlier detection, and more effective treatment.

The Symposium was a marvelous tribute to J Freireich and an important opportunity for our entire faculty. During my years in North Carolina I encountered another extraordinary individual: Jim Valvano. Jim Valvano was the head coach of the North Carolina State basketball team that won the national championship in 1983 with a buzzer-beating shot against the University of Houston. A memorable video clip pictured Coach Valvano in the mayhem after the game running around a crowded floor looking for someone to hug. Over the years Jim became a color announcer for ESPN; he also developed metastatic cancer from an unknown primary site. He received his care at the Memorial Sloan-Kettering Cancer Center and at Duke University. In a remarkable talk during the Espy awards just before he died, Jim recalled one of his favorite quotations from Rudyard Kipling, that at times, life’s embers burn low and need to be rekindled. Jim Valvano’s enthusiasm and courage rekindled all of those whose lives he touched. In a similar spirit, the Freireich Symposium rekindled the spirit of the M. D. Anderson Cancer Center that was established in Developmental Therapeutics.

The Symposium brought together an assembly of giants from whom we all have learned. Tens of thousands of patients worldwide owe their lives to the efforts of the people involved in this Symposium through their passion, creative insight, and achievements. The Symposium was a marvelous tribute for J’s seventieth birthday, and there are many reasons to celebrate. In 1996, for the first time in history, cancer mortality in the United States declined. Although this relates in part to changes in smoking habits, it also reflects the impact of effective chemotherapy.

In his eloquent tribute to J, Emil Frei (1) described the wheel of progress that resulted in the cure of a majority of children with acute lymphoblastic leukemia. You have read how J, Tom Frei, and Jim Holland established the principles of combination chemotherapy (1). These principles were then extended to acute myelogenous leukemia, Hodgkin’s disease, and breast cancer by Paul Carbone (2) and many others. Using these principles, Larry Einhorn and his colleagues over two decades changed testicular cancer from a disease that was 90% lethal to a disease that is 90% curable (3). Fernando Cabanillas (4), George Blumenschein et al. (5), and Bob Benjamin (6) updated the contemporary impact of combination regimens on non-Hodgkin’s lymphoma, breast cancer, and sarcoma, respectively. Bob Livingston (7) described the complexities of multimodality, multidrug regimens in obtaining local and systemic control of lung cancer.

More effective antibiotic therapy developed by Gerry Bodey (8) and blood product support provided by Jeane Hester (9) and her colleagues permitted dose intensification and the use of high dose chemotherapy described by Bart Barlogie (10) and Axel Zander et al. (11). Although the role of high-dose chemotherapy is still debated, this approach is clearly of value in hematological malignancies and, in all probability, cures a subset of breast cancer patients.

Despite the impressive advances provided by combination chemotherapy, multimodality adjuvant therapy, and high-dose treatment, there is a growing perception that these approaches have plateaued in their ability to cure patients with commonly occurring epithelial cancers. As our population ages, the incidence of these cancers is rising. What provides so much genuine hope is the explosive growth of the new biology and new technology. The impact of the new biology was seen throughout this Symposium: J’s own studies of cytogenetics in acute myelogenous leukemia (12); Grady Saunders’ (13) description of the role of Wilms’ tumor in multiple cancers and in normal genitourinary differentiation; Razelle Kurzrock’s (14) and Moshe Talpaz’ impressive investigation of interleukin 1 dysregulation in chronic myelogenous leukemia and lymphoma; and the molecular targets that have been described by Jo Oppenheim (15), Sandy Stass et al. (16), Bernie Weinstein et al. (17), and John Mendelsohn (18).

Most cancers arise from single cells that have undergone 4 or 5 mutations. With the new biology, it is possible for the first time to identify the unique genetic changes that have occurred in a particular patient’s cancer. J has long known and frequently taught that “not all cancer patients are the same.” We now have the understanding and the molecular tools to deal with that heterogeneity. In the past, we planned studies with the expectation that the correct combination of drugs at maximally tolerated dosage and in an optimal schedule would ultimately cure all patients with a particular form of cancer. Now studies can be planned to test regimens that are designed to fit more precisely each patient’s needs.

As Jordan Guterman (19) described, the new technology will help us to take advantage of the new biology. One of our greatest opportunities is to link molecular diagnostics with mo-

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lecular therapeutics. Availability of cDNA arrays and chip technology will permit the detection of differences in gene expression between normal and transformed cells. Combinatorial libraries and robotics will aid in developing designer drugs that inhibit oncogenes, replace or induce suppressor function, alter drug resistance, and intervene in apoptosis. These approaches should not only detect novel targets for entirely new drugs but also identify those patients who would benefit from them. In addition, the same technology can identify patterns of sensitivity and resistance to conventional agents. Individualized therapy should become a reality, triaging different patients with a particular solid tumor histology to distinct regimens as we now do in managing acute myelogenous leukemia.

Better vectors and better delivery systems should permit more effective application of gene therapy, as outlined by Evan Hersh (20) and Gabe Lopez. In the long run, “proof of concept” through the expression of whole genes may encourage the development of low molecular weight drugs that would mimic the functions of the gene products.

As therapy improves, markers for prognosis and for minimal residual disease will become more and more important for commonly occurring solid tumors, as they have for testicular cancer, chronic myelogenous leukemia, and lymphoma, as described by Larry Einhorn (3), Moshe Talpaz, and Fernando Cabanillas (4). Biomarkers will also be important to identify individuals at high risk for developing cancer and to monitor response to chemopreventive agents, such as DFMO, in trials conducted by Paul Carbone (2). Protein and lipid markers in combination with imaging modalities may permit cost-effective early detection of a number of cancers at their earliest stage.

To evaluate the substantially larger number of drugs and markers that will emerge from the new biology and the new technology, the lessons in clinical trials learned from J. Ed Gehan (21), Ely Estey (22), Peter Thall, and their colleagues will be particularly helpful. Jim Holland (23), as ever, has clear vision. We must choose when to use randomized and nonrandomized trials depending upon the magnitude of the anticipated benefit and the purpose of the study. Rapid evaluation of new agents should be facilitated by identification of study groups with regression analysis and by subsequent Bayesian analysis of clinical outcomes. At some point, however, the validity of this approach must be tested in larger groups with more conventional methods.

Over the years, M. D. Anderson Cancer Center has made major contributions in exploring the clinical application of novel cytotoxic and biological agents exemplified by the studies of Michael Keating (24) with fludarabine and Jordan Gutterman (19) with interferon. Even in times of managed care, our ability to perform Phase I–II trials with new drugs must have the highest institutional priority. With new agents, as with more conventional drugs, understanding the mechanisms of drug sensitivity and drug resistance with bridging studies like those described by Bill Plunkett and Bun McCullough (25) will continue to be critical. Rational plans must be made for evaluation of drugs in combination to exploit the distinctive biology of different forms of cancer, such as those outlined by Hagop Kantarjian (26) for chronic myelogenous leukemia.

In concluding his assessment of J’s career, Emil Frei (1) quoted Sophocles: “One has to wait until evening to see how splendid the day has been.” Tom Frei’s reference reminded me of a story about Benjamin Franklin at the conclusion of the Constitutional Convention in 1787. As our Founding Fathers were finally signing the Constitution after months of contentious debate, Franklin looked toward George Washington’s chair at the front of the room and remarked that he had often gazed at the half sun that was painted on its back, wondering whether that sun was rising or setting. As the last signature was written Franklin, said: “But now at length I have the happiness to know that it is a rising and not a setting sun.” With new biology, new technology, new leadership, and a new commitment to bridging the gap between the laboratory and the clinic, the sun of our mission is rising—this is a new day. J has been a wonderful mentor for us all. As we move into this new day together, we will continue to learn from him, to value his many contributions and to work with him toward the goal we all share.

References
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