Current Concepts in the Management of Lymphoma and Leukemia

Edited by

J. E. Ultmann · M. L. Griem · W. H. Kirsten · R. W. Wissler

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With 46 Figures

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Preface

This volume summarizes the Proceedings of the fourth biennial Cancer Teaching Symposium held on March 7 and 8, 1970, at the University of Chicago Pritzker School of Medicine. The program was prepared by Drs. LAWRENCE ALLEN, MELVIN GRIEM, WERNER KIRSTEN, LEON JACOBSON, JOHN ULTMANN, ROBERT WISSLER, and STANLEY YACHNIN. The purpose of the Symposium was to present current advances in the area of lymphoma and leukemia to the staff and students of this medical center and to students and interested physicians from other institutions in the Chicago area. Like the other teaching symposia held in 1964, 1966, and 1968, this Symposium attracted over 450 physicians and scientists. In the course of one and a half days the audience had the opportunity to listen to the twenty-four invited speakers and to lively discussions. The formal presentations as well as discussions are recorded in these pages.

This Teaching Symposium could not have been undertaken without the faithful assistance of the Program Committee, the Cancer Training Grant Advisory Committee, the staff who recorded and transcribed the Proceedings, and the editorial assistants. We wish to thank the following for their efforts: DOROTHY A. WILLIS, Administrative Secretary for Institutional Cancer Training Grant, Dr. ROBERT L. HUNTER, Dr. ROBERT H. KIRSCHNER, Dr. ROBERT A. ORLANDO, Dr. STEPHEN STRUM, RANDOLPH HUGHES, JULIA KANT, GEORGIA MOHR, TERRY PEARSON, FRIEDA RANNEY, and CAROL REESE.

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JOHN E. ULTMANN, M.D.
ROBERT W. WISSLER, Ph.D., M.D.

Introduction

During the past decade, great strides have been made in the diagnosis and management of patients with lymphoma and leukemia. Stimulated by advances in radiotherapeutic techniques, clinicians have looked for new ways to classify and stage the disease in patients with lymphoma to determine curability. In so doing, they have re-examined previous staging procedures and have expanded the approach to staging by the introduction of new techniques, including lung tomography, inferior venacavography, lower extremity lymphography, and isotope scanning of liver, spleen, and bone. These approaches have led to revisions of clinical staging criteria. More recently, laparotomy and splenectomy have been introduced as part of the work-up of patients with lymphoma in an attempt to delineate further the criteria for curability.

Pathologists re-examining histologic features useful for the diagnosis and classification of lymphoma have developed precise diagnostic criteria permitting more meaningful differentiation of these tumors than heretofore possible. The advances in the clinical and pathologic diagnosis of lymphoma were summarized in the present symposium by Drs. HENRY RAPPAPORT, chairman, and ROBERT LUKES, WILLIAM SHEEHAN, SAUL ROSENBERG, and LAWRENCE ALLEN.

Review of treatment failures and modern considerations of radiobiology have resulted in new approaches to the cure of lymphoma by means of radiotherapy. Wide field, intensive radiotherapy appears to offer an opportunity for cure to a significant number of patients with lymphoma. Current concepts in radiotherapy of lymphoma were reviewed by Drs. VERA PETERS, chairman, ROBERT BRUCE, HENRY KAPLAN, RALPH JOHNSON, MELVIN GRIEM, and EUGENE CRONKITE.

During the past few years, laboratory data in animals with acute leukemia demonstrated the possibility of achieving cure by application of intensive chemotherapy. The prerequisites for understanding current therapy of patients with acute leukemia are an understanding of the biochemical and pharmacologic properties of agents used in the managment of acute leukemia and considerations of the cell cycle applicable in the chemotherapy of this disease. These subjects, together with the current status of clinical therapy, were reviewed by Drs. GORDON ZUBROD, chairman, ALAN SARTORELLI, EMIL FREIREICH, BAYARD CLARKSON, and PAUL CARBONE.

Profiting from the lessons apparent from the management of patients with acute leukemia, new strides have been made in the chemotherapy of the chronic leukemias and in the management of patients with lymphoma who cannot be cured by radiotherapy. A review of this area was presented under the chairmanship of Dr. STANLEY YACHNIN, by Drs. GLYNN WHEELER, DAVID GALTON, and VINCENT DEVITA.

The final portion of the Symposium was devoted to the presentation of new approaches to the management of lymphoma and leukemia. Particular emphasis was

placed on understanding of the immunological reactivity against tumor specific antigens and on experimental approaches to the immunotherapy of lymphoma. These areas were discussed by Drs. THOMAS HALL, chairman, KARL ERIC HELLSTRÖM, and ALEXANDER FEFER.

The editors are grateful to all the participants in this conference who permitted publication of their manuscripts.

J. E. ULTMANN, M. L. GRIEM,
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Chairman: STANLEY YACHNIN

New Approaches to Management of Leukemia and Lymphoma

Chairman: THOMAS HALL

Welcoming Remarks

Leon O. Jacobson

As I look around, it's easy to recognize a large number of distinguished guest speakers from around the world and many of my former colleagues throughout the country. I also recognize faculty and students in the room.

It is a great pleasure to welcome you here to the University, especially for a conference such as this. There are a few who are as old as I am and have been involved in the lymphoma-leukemia field for many years. Some of you were working in the endeavor in the early 40's. Many of us shared in the introduction of nitrogen mustard with a great deal of fear and trepidation as we applied it to those first few patients.

I know that this conference is going to be most interesting and rewarding and, as is true with most conferences that are led by the kinds of people that are speaking here, surely new ideas will come through. I do hope you enjoy these two days with us and will profit from these deliberations.

Keynote Address

CARL G. BAKER

First, I want to thank Dean JACOBSON for his kind hospitality and for the invitation of the Program Committee to participate in this symposium. I anticipate learning new things along with those of you in the audience. I thought perhaps you might be interested in some comments regarding the fiscal stresses we face these days, about problems of priorities, and how these priorities look from the point of view of scientists and of laymen, including members of Congress. Perhaps we can gain a little insight on how the Congress and the public may now be looking at these priorities, which seems to me to be very germane to the present situation on funding. I will try to use examples from the lymphoma and leukemia areas to illustrate some of the aspects of priority decision making.

This meeting itself represents an important link in a complex chain of forces and events that deal with the question of priorities. Meetings such as this symposium are important for bringing together the latest information, summarizing the state of the art, and indicating where the research leads are. At times, we develop important syntheses from such meetings. We are here to learn and to teach, and to stimulate each other, particularly in obtaining new perspectives and new concepts. I hope we succeed in those aims.

If one looks at the relative amounts of fundings in different areas of cancer research, it is notable that the area of leukemias and lymphomas has been for some time one of the areas of high priority, receiving relatively higher funding than most other cancer research areas. For example, of the total budget of the National Cancer Institute of $ 184 million last year, leukemia and lymphoma research accounted for somewhere in the neighborhood of $ 40 to $ 50 million. Why should this kind of research consume, so to speak, that high a proportion of the dollar resources? What are the events that led to this situation? Certainly in terms of the number of cases of leukemias and lymphomas, even taken together, this amount is out of proportion to the other problems of the cancer field as a whole. Why is the public willing to support this area? Why does science put that much stress on it? What are the elements that lead to priority decisions?

It seems to me that there are three main elements in making priority decisions. One element is the *importance of the problem.* Although leukemia is not as important as colon cancer or lung cancer in terms of the number of cases, the fact that many leukemias occur in children has given an impetus to this area of research in public interest that goes beyond the mere numbers. Or, to say it in another way, in our cultural system, the value of children is placed at a high level. I might remind

you that not all cultural systems look at children in this way. This value judgment has led the public to provide relatively generous support to leukemia efforts, and this is reflected not only in the Congressional appropriations, but also in the leukemia societies and activities of the American Cancer Society. Importance is also ascribed to the problem because prevention or cure of fatal disease in *young* people means longer lives than similar successes with older diseased subjects. Perhaps also, more significance is afforded leukemia because surgery and radiation are not effective therapeutic means.

A second element in priority decision making is the assessment of *the state* of *the art,* or the *maturity of the field,* and the extent of richness of research leads. Some of the most important recent progress in cancer research lies in the area of leukemias and lymphomas. Not only are we beginning to see concrete statistical evidence of therapeutic improvement, but developments that we see today are providing new insights into the treatment of these diseases which in turn will have important ramifications, not only to leukemias and lymphomas themselves, but for other kinds of cancers as well. Moreover, studies on etiology are moving very rapidly and many leads are ready for development which can occur quickly with the present program capability. Thus, from the standpoint of the scientist, one reason we have high emphasis on leukemias and lymphomas is that most cancer investigators see the possibilities for further development because of maturity of concepts and knowledge of the field. Most of these scientists see this as an area with more opportunity than, say, the lung cancer or colon cancer areas. In other words, we know more, at least we think we know more, about what to do.

The third element is the *probability that successses will be attained if additional investments are put into the field.* While this element is related to the previous one, it differs in the same sense that the *closeness* to one's destination differs from the *rate* at which one is moving along.

A layman, I believe, looks at these same three elements with a somewhat different perspective than the scientist does. The layman is primarily concerned with practical solutions to real life problems of cancer patients, either with successful treatment of those diseases already in being, or with an area which has not received as much emphasis: cancer prevention. If you solve the problem, will it lead to practical results in terms of patients? The scientist often considers, I think, the importance of the problem in terms of whether the area is ready for a new conceptual development. The problem area is important if we can obtain new conceptual advances in science.

How these two viewpoints are welded together is a complex subject. Part of the problem is to communicate with the layman as to why scientists think certain areas are of high priority. We as members of the scientific community need to devote more effort to understanding what the layman expects to obtain for providing funds through appropriations and voluntary organizations. Regarding the question of state of the art, the laymen in Congress have to depend on testimony from experts. Occasionally, a problem results from experts with perfectly equal high-quality credentials before the committee giving opposite views in answer to important questions posed at the Hearings. And if you were the Congressman listening to that in an area you did not understand in detail, I think you would conclude — "Well, I guess they don't know what the answer is on this point." We may need

to admit we don't know more than we have on occasion in the past. I think the Congressmen also are quite interested nevertheless in having expert opinion: "All right, suppose we give you funds, what are the chances of having success?" They mean success, I think, again in terms of will there be a better cure rate. For example, will there be fewer patients?

This blending of these two broad points of view plus many others becomes crystallized in the development of budget put together each year and in the actions taken on each budget. The number of forces that are brought to bear in this process are many and complex. Forces afoot today in society, such as new interest in urban development, transportation, race problems, and so on, have brought forth a whole array of new elements in competition with funds for health research. These forces were not present with the same degree of insistence three or four years ago. Congressman have to face up to the difficult question of allocating money. The first kind of decision many Congressman, I think, try to make is: Of the total resources available from appropriations, how much should be devoted to *health?* Then once that decision is roughly settled, there are a series of forces competing for dollars within the total area to determine the proportion for health *research.* In earlier times, medical *research* was certainly one of the more popular parts of competition within the total health dollar category. Nowadays, health *care* is getting much more attention. Medical research is faring somewhat less well in this competition now than has been the case over the last several years.

There are many other forces involved, some of which are political, and I don't mean this in a derogatory sense. The job of politics really, it seems to me, is to decide among various points of view as to where priorities ought to lie. The Congress is a main force in settling this kind of question. How much should go into cancer research is primarily a political question, not a scientific one. What proportions of that money should go into different areas of cancer research, however, is primarily a scientific question. I think most of us would hope that the Congress would not place too many earmarkings on these categories of cancer investigation. Nevertheless, there are occasions when Congressional committees will put very stringent constraints or strong earmarkings in a particular appropriation.

The question of communicating then between the scientific community and the Congress and public may become more insistent now with these tighter priorities. One of the points I would like to leave with you is some considerations of how all of us can do a better job in communicating to the public and to Congress why we think certain areas in medical research are important, or even, why medical research should compete successfully in the complex arena of determining priorities. This can be done in part by many of us devoting a little more attention to the problem than we have in the past. The question of letting your Congressman know about the kinds of problems that you face in your own institution is certainly legitimate and the proper thing to do. Congressmen are looking for information on the effects produced by what they do in the Congress. Perhaps we need to devote a little more attention to our relationship with the press, i. e., the magazines and the printed and TV news media that are trying to communicate with the public. How we convey some of these complex ideas to laymen is not the simplest thing in the world, but I think perhaps we haven't devoted enough attention to that. In view of the present situation, we may need to do more of that.

Once priorities get settled, the question, of course, arises on the means of implementation. The various sections of this symposium illustrate major components in the fields of leukemia and lymphomas. I would like to make just a few remarks on some of those features. In reference to the first section on diagnosis of lymphoma, I want to put in a plug for things that some people consider mundane. I'm talking about things like *definitions, terminology, classification* and *standardization.* Counting seems to be a very simple matter, but unless we have our standards set fairly clearly in such complex things as the different kinds of lymphomas, counting cannot be done appropriately. We often fail to pay enough attention to these more mundane things of struggling with clear definitions and clear terminology and settling on classifications we can agree on and live with. Careful attention to these more mundane things, coupled with the idea of sound experimental design of the studies, are really the foundation stones for the good use of computers. Too often people are trying to jump in and use computers without having gone through the more laborious clarifying definitional problems. Many people are bored to tears in developing clear definition, but it's essential that we pay considerable attention to these areas, and I'm glad to see that the symposium starts out with this subject. I know Dr. RAPPAPORT has been a leader in defining some of the problems in lymphoma.

I do not have time to comment on the other areas of the symposium very much. I do want to put in one more plug for the value of empiricism in the area of chemotherapy. We now have a number of drugs that are active and we are beginning to see cures. We are moving out to a new phase of gaining a deeper insight into how these drugs are acting. But before we had the drugs we were not able to do that. And how do we get the drugs or how do we find new drugs? I believe that basically we're still in a phase of having to do it with a heavy element of empiricism. I think we will keep on finding drugs that way. It seems to me that the history of drug development by and large has shown that most new drugs come from empiricism; it is only after the drugs are available that we begin to get insight into the mechanisms of action. However, once a critical mass of compounds is reached, we are quite hopeful that new drugs can be developed based on the understanding of the activities of those first few drugs that we picked up by empiricism. An area of shortage in this regard is manpower in pharmacology and chronic toxicology, both in cancer chemotherapy and in carcinogenesis investigations. I will make a plea for attention in medical schools in this area along with perhaps trying to make preventive medicine a little more respectable. In medical schools, we have not given due attention to the areas of prevention and causation. Too often the whole area of preventive medicine in medical schools is looked down upon, and it doesn't seem to get attention commensurate with its importance. So I will ask those of you in the medical schools to give considerations to perhaps helping out in that area.

These are the main points I will leave with you. I hope that we will have the successful symposium which I anticipate from looking at the program. Thank you very much for the opportunity of being here with you.

Malignant Lymphoma: Histologic Considerations

Robert J. Lukes

With 9 Figures

Introduction

The morphologic identification and classification of malignant lymphomas have been the subjects of confusion and controversy for decades. The remarkable diversity of the histologic and cytologic manifestations of the malignant lymphomas and the difficulty of precise cytologic identification in tissue sections, particularly of poorly differentiated cells, have produced a unique terminologic maze that has precluded effective comparison of case series from different centers. The traditional classifications of malignant lymphoma have been employed in an unappreciated, extraordinarily variable fashion and have proved ineffective in prognostication and communication in my experience.

In the past decade evidence of disenchantment has appeared in the literature, but much of it has past unnoticed. The meaningless status of the term *reticulum cell sarcoma* has been demonstrated by Gall [1]. The existence of follicular lymphoma has been challenged by Rappaport, Winter and Hicks [2], and I have recently demonstrated the extreme variability in the use of the term *lymphosarcoma* [3]. The superiority of clinical staging over traditional cytologic classifications in prognosis has been demonstrated by Peters [4]. Finally we have challenged the position of Hodgkin's disease in the scheme of malignant lymphoma [5—7].

This presentation will be limited to a brief consideration of (1) the terminologic and conceptual problems; (2) the definition of 4 cytologic groups of malignant lymphomas; (3) the interrelationship of leukemias and lymphomas and the significance of the distribution of involvement; and (4) the position of Hodgkin's disease, mycosis fungoides and macroglobulinemia in the scheme of malignant lymphoma.

Terminologic Problems

Communication in the field of malignant lymphoma has become increasingly difficult during the past few decades because of terminologic confusion resulting from the problem of precise cytologic identification, particularly of poorly differentiated

cells in tissue sections and the lack of correlative histologic and cytologic studies on lymphomas and leukemias.

The majority of pathologists in the United States generally agree that malignant lymphoma be defined as a malignant neoplasm of lymphoid tissue derivatives; but beyond this there is little accord. The lack of agreement on cytologic types, the related character of distribution, the relationship to leukemia, the site of origin, all have permitted wide divergence in basic concept, led to marked differences in terminology, and in essence, accommodated any pathologist's personal viewpoint.

The following is a definition which I have employed for a number of years and includes these basic features of lymphomas. *Malignant lymphoma* is a neoplastic proliferative process of lymphoreticular tissue involving stem cells (undifferentiated cells) and lymphocytes or histiocytes in varying degrees of differentiation. It occurs essentially in a homogeneous population of a single cell type; when mixtures are found, they appear to represent variations in the size or configuration of a single cell type. The character of histologic involvement is either diffuse (uniform) or nodular, and the distribution of involvement may be irregular or systemtic (generalized). Leukemias and lymhomas of stem cells, lymphocytes and histiocytes are fundamentally identical processes for each cell type. The occurrence of lymphoma cells in the peripheral blood seems to be related to the character of the distribution of the cellular proliferation.

From this definition of malignant lymphoma terminologic problems are inherent in the nature of the process. Upon comparative evaluation of a few of the most commonly used classifications of malignant lymphoma recorded in Table 1, there seems to be little difference between the classifications. Upon closer examination we see that many terms are used for poorly differentiated cells; at times identical terms are employed in a different fashion in the various classifications. Furthermore, the term *lymphosarcoma* has been used with extreme variability from a specific cell type to a synonym for malignant lymphoma. It is commonly employed to refer to all lymphoma cells with scanty cytoplasm in histologic sections including well differentiated lymphocytes, poorly differentiated lymphocytes, stem cells, leukemias of poorly differentiated types, and erroneously at times, tumor cells of nonreticuloendothelial origin where the cytoplasm is scanty or the cytologic details are obscured by technical factors. From this comparative evaluation of the classification of lymphomas of lymphocytes and poorly differentiated reticulum cells or stem cells listed in Table 1, it is obviously necessary to specify the classification employed and require the definition of the term. The lymphosarcoma of JACKSON and PARKER [8] is not equivalent to the lymphosarcoma of CUSTER and BERNHARD [9], since the latter includes lymphocytoma and lymphoblastoma of JACKSON and PARKER [8], and possibly the stem cell of GALL and MALLORY [10]. The lymphoblastic lymphoma of GALL and MALLORY [10] is not equivalent to that of BERMAN [11], since GALL and MALLORY [10] have separated and identified the stem cell as a distinctive type of lymphoma.

From an evaluation of Table 1, *reticulum cell sarcoma* does not seem to present a terminologic problem, but its usage is more variable than the term *lymphosarcoma*. The marked variation in the use of the term *reticulum cell sarcoma* in the literature was pointed out by GALL [1] who demonstrated the meaningless status and undesirability of this term in his comparative evaluation of the major reports of the