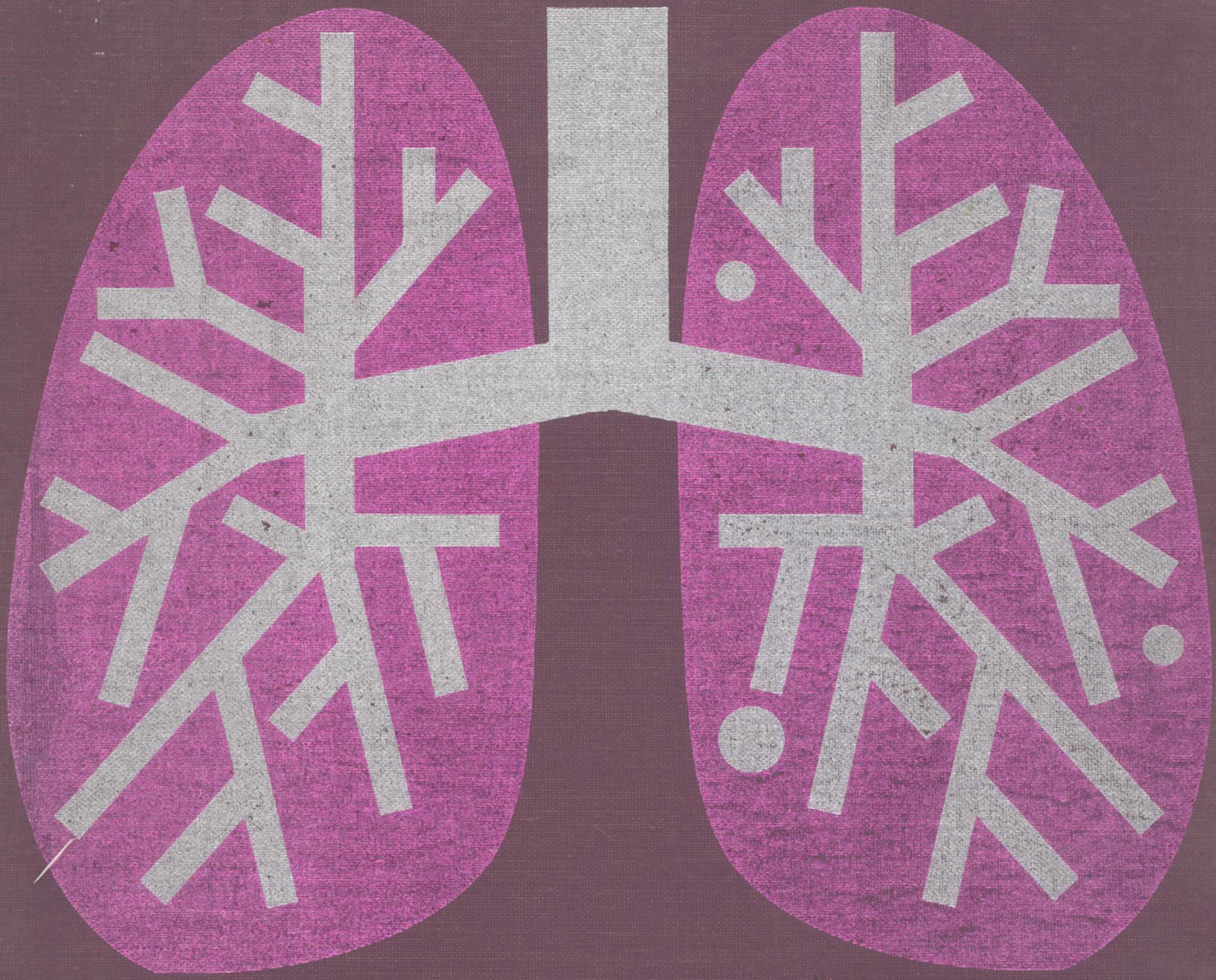

Pulmonary Metastasis

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Preface

On September 16 and 17, 1977, a small workshop on pulmonary metastasis was held at Roswell Park Memorial Institute, in Buffalo, New York. This is the first of what we hope will be a number of reports of workshops on site-oriented viewpoints on metastasis, in which we can bring a multidisciplinary approach to bear on some specific problems and assess the state of present knowledge in the field. For more general accounts of the metastatic process, the reader is referred to the texts by Willis (1973), Weiss (1967, 1976) and Gilbert and Kagan (1977).

In the comparatively few meetings held exclusively on metastasis in the past, we have been impressed by the large amount of relevant information available on different basic and clinical aspects of the metastatic process as well as by the gaps in our knowledge. These strengths and weaknesses become obvious when it comes to integrating a total understanding of the pathogenesis of metastasis in Man, and in using the available information to treat patients with metastases or to prevent patients with cancer from developing them, or both.

One limitation of previous meetings on metastasis is that, because of limitations of time and space, too many generalizations are made in extrapolating from animal to clinical studies without reference to cancer type or metastatic site. The behavior of many cancers is not totally explicable in terms of the cancer itself but also depends on its interactions with its host, which may vary with anatomic site. In this Workshop, we will be focusing on metastases in one site, the lung. We hope that with this self-imposed restriction in breadth, we will be able to go into pulmonary metastasis in depth from the viewpoint of both pathogenesis and treatment.

Although the ultimate objective in cancer research is the prevention or cure of cancer in Man, for obvious reasons many of our studies cannot be pursued in Man, but must be made in model systems, including experimental animals. Thus, in common with most of the contributors, we would have preferred to further restrict the Workshop to human data, but such limitations would have resulted in the significant loss of data relevant to pulmonary metastasis in Man.

We chose pulmonary metastasis as the first topic for the Workshop series for a variety of reasons. First, it is a common site, and there are obvious advantages in studying common diseases. The clinical experience with lung metastasis provides a considerable clinicopathologic data base with which studies on animals and in vitro systems may be correlated. Second, over the last decade or so, the treatment of pulmonary metastasis has in several tumor types become more positive for the patient, as distinct from the earlier palliative approach.

In many respects, clinical measurement and investigation can be

more precise with pulmonary lesions than with any other metastatic site except the skin. Chest X rays and other lung evaluation studies permit accurate differential diagnosis of lung lesions, their early detection, and morphometric assessments of their response to therapy and growth kinetics.

Part I deals with some of the basic mechanisms and pathways involved in pulmonary metastasis, from the release of cells from primary cancers to their arrest in the lungs. Part II deals with patterns of pulmonary metastasis, and after a brief review of the literature, data is presented from the considerable autopsy experience of the Sidney Farber Cancer Institute in Boston and the Children's Hospital of Los Angeles. In Part III, after reports on the growth kinetics and radiographic diagnosis of pulmonary lesions, the experiences of a number of both surgical and radiotherapy units in treating lung metastases are described and compared.

We thank Mrs. M. C. Terhaar for her help in dealing with the secretarial tasks of the Workshop and Mr. Kevin Craig (RPMI) for arranging many of the details.

We gratefully acknowledge the support for the Workshop provided by funds from the International Cancer Research Data Bank Programme of the National Cancer Institute (National Institutes of Health), under Contract No. NO1–CO–65341 with the International Union Against Cancer (I.U.C.C.), and by Roswell Park Memorial Institute (New York State Department of Health).

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Contents

Part 1

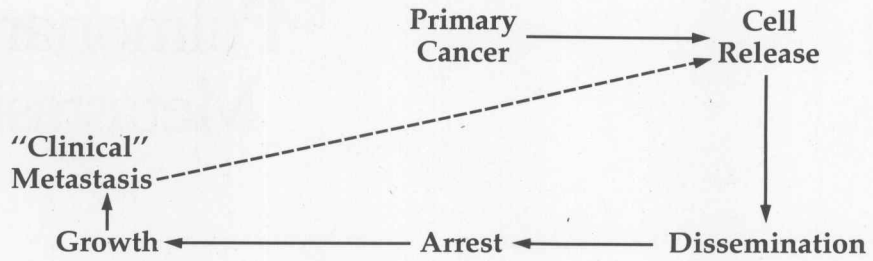
Mechanisms and Pathways of Pulmonary Metastasis

1

Introduction

Part I is concerned with some of the basic mechanisms involved in the development of pulmonary metastases from primary cancer. Although, for obvious reasons, most of the work discussed in this part is concerned with experimental animals and cell and tissue cultures, it would be surprising if the general principles involved were not relevant to the situation in Man.

The steps leading from a primary cancer to pulmonary metastasis can be summarized in a simplistic manner as follows:



Weiss (Chapter 2) notes that whatever mechanisms are subsequently involved, by definition, metastasis is dependent on the detachment of cancer cells from primary tumors. This process is complex and is not simply dependent on the inherent properties of the cancer cells themselves, although the ease with which they may be detached depends on their internal metabolic and mitotic status. Detachment is perhaps best considered in dynamic terms of the whole tumor, in which interactions among healthy or degenerate cancer cells, or both, and non-cancer cells and their products affect the ease and the rate with which malignant cells may gain access to the various ports of entry of the ongoing metastatic cascade.

In spite of repeated mechanically and biochemically mediated trauma to cancer cells, enough survive to form hematogenous metastases. Nonetheless, for an individual cell, entry into the circulation and its subsequent arrest must be fast events if the arrested cells are to be alive and capable of forming metastases. If arrested cells are detached from the vascular endothelium, they will be subjected to another cycle of trauma, during which many will perish.

The process leading to contact of circulating cancer cells with the vascular endothelium and their subsequent arrest in the lungs may be partially defined but is by no means completely understood. It cannot

be overemphasized that, although arrest is an essential step in the development of metastases from circulating cancer cells, it is only a minority of the arrested cells which have the capability and opportunity to develop into metastases. It is not clear at present whether Paget's "seed-and-soil" hypothesis refers to the arrest process or to the subsequent growth of the arrested cancer cells. However, any hemodynamic hypothesis that attempts to explain metastasis solely in terms of arrest pattern is inadequate. At present, the arrest process cannot be manipulated in favor of the patient, although it would provide an advantageous point of attack.

The arrest process itself is dealt with from the ultrastructural viewpoint by Wallace (Chapter 3) for the special case of the Walker 256 carcinosarcoma of the rat. It is shown that arrest in these cells is immediately accompanied by platelet adhesion. Within a few minutes, fibrin is demonstrable around the tumor embolus, followed by platelet degeneration. By 12 hours after arrest, both fibrin and platelets have virtually disappeared, and the cancer has progressively compressed and destroyed the vascular endothelium and has invaded the basement membrane. Although the involvement of coagulative processes in tumor cell arrest has prompted the use of anticoagulant therapy to prevent or retard this phase of metastasis, the published results are contraindicative, and there is little solid support for this mode of therapy.

Fidler (Chapter 4) hypothesizes that metastases arise from comparatively small subpopulations of cancer cells from within the whole population of primary lesions. In support of this hypothesis, he describes in vitro studies in which clones of cells were developed from the B16 melanoma, which has stable, highly metastatic properties when injected into mice. These studies suggest that the efficacy of therapeutic agents should be gauged by their separate effects on primary tumors and their metastatic variants. These studies augment the view that resistance to therapy is due to anatomic features resulting in hypoxia, for example, or from the de novo development of drug-resistant populations. It is of interest in this connection that Slack (Chapter 24) revealed by his statistical studies on patients that, in Man, there is a differential response of primary and secondary cancers to the same chemotherapeutic agents.

Liotta et al. (Chapter 5) discuss an animal model in which they analyze the timing of the formation of pulmonary micrometastases and their therapy, when they are established. This paper relates to the earlier contributions by Weiss and Wallace, in that the observations indicate and formalize a relationship between the time taken for micrometastases to develop and the rate at which tumor cells leave the primary cancer and are arrested in the lungs. In contrast to traditional studies in which the efficacy of treatment is judged by the rather crude techniques of animal survival, and counts and in vitro plating efficiency of macroscopic metastases, Liotta et al. have developed a radiolabel technique in which systemic chemotherapeutic killing of micrometastases can be monitored directly by the loss of radioactivity from the lungs. An additional facet illustrating the complexity of the metastatic process is pro-

vided by Kim (Chapter 6), who describes his work on pulmonary metastasis in mice with respect to the effects of immunological factors in determining the relative importance of lymphatic or hematogenous spread. Two spontaneously metastasizing, antigen-shedding rat mammary adenocarcinomas, and two nonmetastasizing, growth-matched, immunogenic adenocarcinomas were each transplanted into athymic nude mice, which could be given immunological function. Kim concludes from his experiments that adequate T-cell function favors the development of metastases by the lymphatic route in the case of invasive, antigen-shedding tumor cells, whereas a T-cell-deficient environment favors dissemination by the bloodstream in the case of the ordinarily nonmetastasizing, immunogenic cells.

Part I concludes with a discussion by Sherwin (Chapter 7) of the use of the histoculture technique, developed by him and his associates to study cell interactions in vitro. By taking thin slices of operating-room specimens of lungs containing cancer, which can be maintained in a dynamic, viable state, Sherwin is able to make phase-contrast, time-lapse movie films of human material, which is usually studied in fixed sections. Although the technique is still in the documentary stage, it has considerable potential for the study of the interactions of normal and malignant cells in pulmonary metastases with each other and their environment, including therapeutic agents.

2

Factors Leading to the Arrest of Cancer Cells in the Lungs

Leonard Weiss

The steps leading from a primary cancer to pulmonary metastasis can be summarized in a simplistic manner (Figure 2.1). These include:

1. The release of cells from the primary cancer.
2. The dissemination of released cells.
3. The arrest of those cells withstanding the trauma of translocation.
4. The growth of arrested cells into clinically significant metastases.
5. Metastases from the metastases.

Some of these steps will be examined in detail in this chapter; others will be covered elsewhere in this volume.

CELL DETACHMENT

By definition, a metastasis is a tumor that is not contiguous with its parent primary. As will be discussed, the detachment of cells from a tumor is certainly not synonymous with metastasis formation. However, with the possible exception of metastases arising from liberated oncogenic viruses (Neiders et al., 1968; Yohn et al., 1968), which may occur in experimental animals but have not been demonstrated in Man, it follows from the definition that metastasis from a cancer cannot occur unless malignant cells are detached from it. It is, therefore, pertinent to

Some of my own work described here has been supported by a series of grants from the American Cancer Society, Inc.