of tumors of the lung. Lastly, immunotherapy may be of benefit in tumors of the lung, both in the induction of remission when the burden of tumor is small and also in the prolongation of remission following conventional therapy. Each of these methods is being explored in an attempt to provide an increased number of remissions and significant prolongation in the quality of life for patients with cancer of the lung.

REFERENCES

Immunologic Aspects of Lung Cancer*

Donald L. Morton, M.D.; E. Carmack Holmes, M.D.; and Sidney H. Golub, Ph.D.

Surgeons are often puzzled by variations in the natural history of lung cancer. Some patients with large neoplasms of borderl ine resectability may survive for many years after surgical treatment, whereas others with smaller, easily resectable carcinomas die from disseminated metastatic disease within a few months. The occasional success encourages the surgeon to treat lung cancer, but it is obvious that any improved survival in patients with lung cancer cannot come from further progress in surgical therapy.

The purpose of this presentation is to review some of the reasons why the use of surgical therapy alone often results in failure of treatment; these reasons are reviewed in the light of newer concepts of the basic immunobiology of lung cancer.

Surgery for cancer is based upon the concept that cancer begins as local disease that spreads in an orderly fashion from the primary site to adjacent tissues by direct extension to regional lymph nodes via the lymphatic and the blood vessels. The surgical procedure is designed to remove the primary neoplasm and the usual contiguous routes of spread. Theoretically, the aim of surgery is to remove every last cancer cell from the body. Advances in surgical techniques, anesthesia, and supportive care have permitted the development of progressively radical, extensive surgical procedures. Unfortunately, these more complex procedures have failed to increase the rates of cure for lung cancer. In fact, for the past several decades, there have been few significant improvements in the management of lung cancer by surgery alone, and it is doubtful that surgical techniques, as practiced today, can contribute to increased survival.

Because lung cancer is the leading cause of death from cancer in the United States today, it is perhaps worthwhile to explore some of the reasons behind these failures. First, it would appear that many of the assumptions upon which the principles of surgery for cancer were based are, in fact, inaccurate. We are particularly concerned with the concept that the surgeon cures the patient by removing, with his surgical resection, every last tumor cell. We know, for a fact, that this is not the case, because many patients in whom one finds tumor cells in the washings of surgical wounds, in the lymphatic vessels draining a primary tumor, or even in the circulating blood, have been "cured" by surgical resection. If these findings are correct, then we must assume that the operation has influenced the host-tumor relationship in some way.

Recent reports describing the relationships between the host's immune defenses and the growing neoplasm suggest that the growing tumor can invade the host's immune responses in order to facilitate its own growth. We suggest that the surgeon's major role in many cases is to remove the bulk of the tumor, which lowers this level of immunosuppression, both specific and nonspecific, induced by the neoplasm and allows the host's immune defenses to recover sufficiently to destroy the microscopic foci of

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640 SYMPOSIUM ON LUNG CANCER

CHEST, 71: 5, MAY, 1977
tumor cells scattered throughout the body. Unfortunately, in most cases the quantity of tumor cells in these metastatic foci is too great a burden for the host’s immune defenses, and the metastases progress.

In order to better understand these concepts, we will briefly review some characteristics of the immune response to cancer. Tumor cells are known to contain antigens not found in normal adult cells that are capable of eliciting humoral antibody and cell-mediated immune responses in the patient with cancer. These tumor-associated antigens on the membranes of cancer cells are constantly shed into the microcirculation of the tumor and find their way into the lymphatic vessels and blood stream. The antigens may combine with antibody and form complexes that are removed from the blood by cells of the reticuloendothelial system. Since each antibody has at least two combining sites, one site can combine with antigen, while the other combining site is free to react with tumor-associated antigens, either in the blood or on the surface of the tumor cell. If this second combining site complexes with antigen on the surface of the tumor cell, it could prevent destruction of the tumor cell by lymphocytes that are only exposed to the antigen occupying the other combining site. Thus, the neutralizing complexes tend to protect the tumor cell from immune destruction by cytotoxic lymphocytes.

As the tumor grows, the concentration of tumor-associated antigens in the blood increases to the point where all antibody has been neutralized and there is a state of excess free tumor antigen. This free tumor antigen can react directly with the antigen receptor sites on lymphocytes, which again protects the tumor cells from destruction by the immune lymphocytes. Again, the free-floating antigens or the antigen-antibody complexes can very effectively immobilize the immune system to create a condition that we call specific immunodepression.

In addition to the specific immunodepression, cancer cells are known to produce humoral factors that cause a general suppression of the response of the immune system to any antigen. We call this nonspecific immunosuppression. We can evaluate the immunocompetence of the patient with cancer in two ways: (1) by administering dinitrochlorobenzene as a cutaneous test; and (2) by an assay of the function of the patient’s lymphocytes (or lymphoblastogenesis) in tissue culture.

Since 97 percent of the normal population can be sensitized to dinitrochlorobenzene, a contact allergen, it has been used to measure the ability of the patient with cancer to respond to a new antigen. Dinitrochlorobenzene is topically applied to the skin of the arm at a dosage of 2,000μg. Fourteen days later, a smaller dose is applied to another site on the same arm. A delayed response of cutaneous hypersensitivity to the second dose represents an actively functioning immune system. Responses vary from patient to patient, and a scoring system has been developed to define the various degrees of sensitivity. Figure 1 shows a normal response to challenge doses of 100μg, 50μg, and 25μg of dinitrochlorobenzene. The response to antigens encountered sometime in the past, such as tuberculin and mumps, can be measured by the patient’s delayed response of cutaneous hypersensitivity to a battery of recall antigens, such as purified protein derivative of tuberculin, streptokinase-streptodornase, Candida, and mumps.

Table 1 summarizes these data from a series of patients with lung cancer who were tested both before and after surgery. In this group, it can be seen that patients who had a positive reaction to testing with dinitrochlorobenzene before surgery were more likely to have resectable disease, whereas those that were anergic to dinitrochlorobenzene were less likely to have resectable neoplasms. Similarly, patients who had positive reactions to dinitrochlorobenzene after surgery were able to remain positive to tuberculin, while those who were negative developed a positive delayed skin reaction to dinitrochlorobenzene.
Table 2—In Vitro Lymphocytic Blastogenesis in Patients with Lung Cancer

<table>
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<tr>
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<th>Age-Matched Controls</th>
<th>Patients with Lung Cancer</th>
<th>P</th>
<th>Value*</th>
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</thead>
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<tr>
<td>No. of subjects</td>
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<td>28</td>
<td></td>
<td>...</td>
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<tr>
<td>Average age, yr</td>
<td>55</td>
<td>60</td>
<td></td>
<td>...</td>
</tr>
</tbody>
</table>

Unstimulated lymphocytes
Average log$_{10}$ counts per minute ± SE
2.360 ± 0.0651 2.2600 ± 0.0813 NS
Numerical average
counts per minute
230 185 NS

Pokeweed stimulated
Average log$_{10}$ counts per minute ± SE
4.5010 ± 0.0893 4.1310 ± 0.1533 <0.05
Numerical average
counts per minute
31,696 13,521 <0.05

Concanavalin A stimulated
Average log$_{10}$ counts per minute ± SE
4.5750 ± 0.0651 3.9790 ± 0.1433 <0.01
Numerical average
counts per minute
37,636 9,532 <0.01

Mixed lymphocytic culture
Average log$_{10}$ counts per minute ± SE
4.1069 ± 0.0877 3.8750 ± 0.1408 <0.02
Numerical average
counts per minute
12,791 4,732 <0.05

*NS, Not significant.

free of disease, whereas those who were anergic to dinitrochlorobenzene had more recurrence of tumor. In contrast, the response to recall antigens did not appear to correlate with the preoperative or postoperative status of the disease. These results imply clearly that the degree of immunosuppression as measured by cutaneous testing with dinitrochlorobenzene is directly related to the preoperative or postoperative burden of tumor.

Another reflection of immunosuppression characteristic of patients with lung cancer can be found in the assay of lymphocytic blastogenesis (Table 2). After exposure to the mitogens, pokeweed and concanavalin A, it can be noted that the lymphocytes of the patient with lung cancer were significantly less likely to respond to the mitogens or to a mixed lymphocytic culture than age-matched control lymphocytes. The degree of lymphocytic responsiveness correlated with the status of disease in these patients with lung cancer.

Recent reports indicate that the serum of the patient with lung cancer contains a factor that has the ability to inhibit the proliferation of normal lymphocytes in response to these same mitogens. In this assay the degree of inhibition in the serum was directly related to the amount of the burden of tumor cells in the patient. The sera from patients with lung cancer are among the most suppressive of all sera we have tested from patients with many different types of neoplasia.

In Figure 2, we offer a schematic representation of the influence that a malignant tumor may have upon the host's immune response. The immunologic defect in lung cancer is probably a secondary manifestation of the malignant state. If we assume that the cancer cell acts as a factory that is constantly producing both the immunosuppressive factors and tumor-associated antigen, we can see how both the specific and nonspecific immunodepression affects the host's immune defenses against the growth of the tumor. This resulting immunodepression facilitates the growth of the cancer.

The key to recovery of the balance in the host-tumor relationship depends upon destruction or removal of the tumor cell "factory." This is the purpose of surgery for cancer per se. Once the mass of the tumor is gone, the patient with cancer is more likely to be able to mount an immune response that can destroy any subclinical foci of tumor cells; however, if his immune response is inadequate, or if the number of tumor cells in any distant metastatic focus is too large, he may fail to regain control of his disease. Nonetheless, the surgery for cancer becomes the first step in the immunotherapy for lung cancer.

If this thesis is correct, it would follow that the approach to the surgical treatment for solid neoplasms must change dramatically. The future lies not...
in treating every patient with a solid neoplasm as one with localized disease, but in assuming that the local disease is merely a manifestation of a systemic illness, whether or not the patient has overt metastatic disease. Not until we accept surgery as merely the first step in the treatment of lung cancer can we significantly improve our rates of cure. Therapeutic advances eventually must come from a multimethod combination of immunotherapy, chemotherapy, and surgical therapy. Unlike surgery and radiotherapy, both local treatments, the triple combination repre-
sents a systemic treatment effective against tumor cells already metastatic to distant sites; however, at present, systemic therapeutic techniques have greater potential for curing those patients with a minimal number of tumor cells, rather than those with clinically evident disease. Thus, although sur-
ery for cancer is not curative by itself, in most cases it can decrease the patient's burden of tumor cells and allow his immune responses to normalize so that further chemoimmunotherapy may become more effective.

Immunology of Lung Cancer*

E. Carmack Holmes, M.D.**

The importance of immunologic factors in the progression of cancer has become increasingly apparent over the past several years. The importance of the host’s immunocompetence has been emphasized, and immunodeficiency has been demonstrated to be associated with an extremely poor prognosis in patients with cancer of the lung and other forms of cancer.1 It is apparent from these studies that a large percentage of patients with lung cancer exhibit immunosuppression.

Many patients with lung cancer have impaired reactions of delayed cutaneous hypersensitivity, as measured by their ability to respond to the cutaneous testing antigen, 2,4-dinitrochlorobenzene. Patients with lung cancer who are unable to become sensitized to and react to dinitrochlorobenzene were found to have unresectable cancer or to have a very poor prognosis.2 In addition, lymphocytes from patients with lung cancer have been shown to have an impaired ability to undergo transformation in vitro upon stimulation with various antigens and mitogens. In view of the very poor survival in patients with both resected and unresected lung cancer and in view of this association of immunologic de-
fects in patients with lung cancer, it seems reasonable to explore the possible usefulness of immuno-
stimulation in patients following pulmonary resec-
tion for lung cancer.

The three most widely used nonspecific immuno-
potentiator drugs are BCG, Corynebacterium parvum, and L-tetramisole (levamisole). All three of these agents have been used extensively in trials in humans, and phase I studies have adequately identified the toxicity of these preparations. These three

agents are now being given to ambulatory patients and are quite well tolerated.

BCG is attenuated, viable bovine tubercle bacilli and is usually supplied in a lyophilized state. The lyophilized material can be reconstituted and administered to patients by intradermal injection. BCG has been extensively evaluated in tumors in animals.3 More recently, BCG has been evaluated in human neoplasms, and it has been shown by Morton and others4 that the intraslesional injection of BCG is capable of controlling cutaneous metastatic disease. BCG is also being evaluated as a postoperative ad-

junct to surgery, and the preliminary results in these clinical trials are quite encouraging. In addition, BCG is being employed as a surgical adjunct in patients after pulmonary resection. McKneally and Mauer5 are using the intrapleural route for the injection of BCG following pulmonary resection, and the one-year rate of recurrence is significantly improved with the use of intrapleural injection of BCG as a surgical adjunct.5

In contrast to BCG, C parvum is a formalinized killed bacterium. Corynebacterium parvum can be administered intravenously, and it appears to localize in the pulmonary parenchyma where a mild granulomatous process ensues, with stimulation of the regional mediastinal lymph nodes. There has been very little experience with the use of C parvum as a surgical adjuvant; however, C parvum has been shown to significantly augment the effects of chemotherapy when given in conjunction with chemotherapy. Israel6 has shown that the use of C parvum increases the rate of response to chemother-

yapy and the duration of the response and also diminishes the myelosuppressive effects of the chemotherapy. Corynebacterium parvum has also been effective in animal models. Intravenously administered C parvum has been well tolerated in the doses which are presently being used and is espe-

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CHEST, 71: 5, MAY, 1977