Future Directions in Clinical Research for Lung Cancer*

Paul A. Bunn, Jr., MD

Even since the Surgeon General's 1964 report, the mortality rate from lung cancer has continued to rise. Although there is evidence that this continued increase in mortality will slow or level in the next decade, lung cancer mortality is a major health problem destined to remain with us for at least the next generation. There have been no established advances in the early detection or prevention of lung cancer in the last 30 years and our therapies have increased the cure rate only from 5 to 13% in this 30-year interval. Biologic advances have outpaced clinical advances in recent times and many of the advances are now ripe for clinical exploitation. There are currently more exciting clinical trials for all phases of lung cancer than at any time and it will be stimulating to witness the results of the clinical trials discussed herein. Hopefully, the results of these studies will lead to a decrease in lung cancer mortality in the next century, much as it increased in the past century.

Lung cancer is the second most common cancer in the United States and by far the leading cancer killer in the United States. The cure rate is only 13%, which explains why it is the leading cause of cancer death even though it is not the most common cancer. Most patients present when the cancer has already spread from its site of origin in the bronchus, which accounts for the low surgical cure rate. Thus, we need major advances in prevention, early detection, and systemic therapy to improve the outlook for this dread cancer. Fortunately, recent increases in our understanding of the biology and pathogenesis of lung cancer and a variety of new active drugs with novel mechanisms of action have opened the door for new approaches in each of these areas.

CLINICAL TRIALS IN LUNG CANCER PREVENTION

The primary prevention of lung cancer can be achieved by a reduction in the use of tobacco by (1) preventing people from starting smoking and (2) by getting current smokers to stop. While this seems very straightforward, quit rates remain disappointingly low and smoking prevalence is no longer declining in the United States. Clearly, new strategies need to be developed and such strategies are being evaluated for their effectiveness. These primary prevention strategies will not be discussed further in this article. There is also no question that political changes can be as important as the scientific primary prevention strategies in reducing tobacco use and all scientists interested in cancer should support the political and scientific efforts to reduce tobacco use.

The secondary prevention of lung cancer is a rapidly evolving field. Patients who have had a primary lung cancer cured by conventional therapy (surgery, radiotherapy, and chemotherapy alone or in combination) are at high risk for the development of second primary aerodigestive cancers. For small cell lung cancer, this risk may be as high as 50% or more at 10 years. For non-small cell lung cancers (NSCLC), the risk probably exceeds 1% per year. Smoking cessation at the time of the first cancer or before clearly decreases the risk, but a markedly increased risk remains even after smoking cessation. Many studies showed that vitamin A analogues (retinoids) could induce keratinocyes and malignant cell lines to differentiate in vitro. In addition, vitamin A deficiency induces squamous metaplasia in trachea organ cultures and squamous changes in cultured lung cancer cells. Abnormalities in the retinoid acid receptor beta protein have been reported in lung cancer and the normal protein has tumor-suppressive effects in epidermoid lung cancer cells. These observations led to clinical investigation of retinoids in patients with aerodigestive cancers potentially cured by standard therapy. In a trial from Italy, retinol reduced the risk of a second cancer in patients with completely resected lung cancer from 10 to 5% after 4 years. This difference was of borderline statistical significance. A similar trial was conducted in the United States in patients who had undergone complete resections with cancers of the head and neck. This study, conducted at the M.D. Anderson Cancer Center, randomized patients to receive 13-cis retinoic acid or placebo. Patients in the 13-cis retinoic acid group had a significantly reduced rate of second malignancy. This risk of relapse of the primary cancer was not affected.

Vitamin A is not considered standard therapy for patients with lung cancer at present, because one of the trials above was confined to patients with head and neck cancer and because the one study in patients with lung cancer had a marginal statistical result. This means that further clinical trials are sorely needed. Several such trials have been instituted or are being planned in the United States and Europe. The results of these studies will not be certain for many years and it is obvious that better chemoprevention strategies can be devised.

It is just as obvious that we need better intermediate markers that can identify cancer risk so that trials of new agents can be done more rapidly and with fewer patients. There are many candidate intermediate markers that are under investigation. These include suppressor oncogenes such as p53, Rb, and genes on chromosome 3p; dominant oncogenes such as ras, and the myc family; several growth factors such as EGF and its receptor and neuropeptides and their receptors; and several antigens such as NCAM and aberrant mucins. Clinical trials are necessary to evaluate these markers in an expeditious manner.

There are an increasing number of potential chemoprevention agents that need study. Beta carotene and e-tocopherol are currently being studied, usually in combination with a retinoid. The role of calcium and flavonoids will undoubtedly be the subject of clinical trials in the near future. Growth factors such as epidermal growth factor (EGF) and neuropeptides clearly play a role in the pathogenesis of many lung cancers. Growth factor antagonists

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*From the Division of Medical Oncology, University of Colorado Cancer Center, Denver
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Reprint requests: Dr. Bunn, 4200 E. 9th, Box B188, Denver, CO 80262

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will need study as chemoprevention agents as well as therapeutic agents. Genetic therapies including gene therapy will also need to be evaluated. For example, p53 is mutated in many bronchial dysplasias.22 Aerosolized gene therapy with the wild type p53 gene in adenovirus vectors is an appealing approach.27,28 Antisense ras gene therapy and neutral endopeptidase (NEP) gene therapy are also potential approaches.27,29 NEP is a secreted and cell surface protein that degrades neuropeptides and that is decreased by tobacco smoke.30,31

**Early Detection/Screening**

The National Cancer Institute (NCI) supported three large screening trials in the 1960s and 1970s that were designed to determine the value of yearly chest radiographs and three times yearly sputum cytology examinations in the early detection of lung cancer.32-34 The trial design of these studies is summarized in Table 1. The trials from Johns Hopkins and Memorial Sloan-Kettering Cancer Center were primarily designed to determine the value of sputum cytologic study because all patients received annual chest radiographs. The ability to determine the true value of annual chest radiographs in the Mayo study was limited by their standard policy of recommending annual chest radiographs for all heavy smokers. All three of these studies performed both studies (chest radiographs and sputum cytology) in all patients at the time of enrollment. Only a small minority of the cancers detected in this initial screen were detected by the sputum cytology examination alone. Thus, it is not too surprising that a reduction in lung cancer mortality was not detected in any of these studies despite the fact that there was more than the expected number of early cancers and the 5-year survival rate for the patients who had undergone resection was high.

Because of the deficiencies of these trials in evaluating the true value of annual chest radiographs as a screening test in high-risk individuals, the NCI is sponsoring a new trial that randomizes high-risk smokers to an annual chest radiograph or to no screening. This is part of a large national trial also looking at the role of other tests in the early detection of prostate, colorectal, and ovarian cancers. The study is referred to as the PLCO (prostate, lung, colorectal, ovarian) early detection trial.

The group from Johns Hopkins saved the sputum samples and follow-up cancer information on the patients from their study. When it became apparent that nearly all lung cancers have aberrant expression of several antigens and that monoclonal antibodies could be developed that recognize these antigens, the Hopkins group showed that ar-chived sputum specimens could be stained and evaluated with these monoclonal antibodies.35 They evaluated stored sputum specimens that had dysplastic cells but no cancer cells and they knew which of these patients subsequently developed lung cancer. They reported that 20 of 25 patients whose sputum specimen stained positively with one or both of two monoclonal antibodies developed lung cancer in contrast to only 2 of 37 patients whose specimens were not positive for either antibody. The Lung Cancer Study Group (LCSG) planned a prospective study to confirm these results. Those selected were patients with completely resected stage I disease. This study was initiated after the unfortunate termination of the LCSG and should become an intergroup study in the near future. In other studies, genetic analyses of sputum, bronchial lavage fluid, and bronchial biopsy specimens are under investigation for the ability to detect cancers at an early stage.

Standard white light bronchoscopy is a very poor technique for visualizing bronchial dysplasias and early carcinomas such as carcinoma in situ. Recent studies have shown that noninvasive treatment of such lesions with photodynamic laser therapy can eliminate the lesion without recurrence for many years.36 Thus, the ability to detect such early lesions could reduce both mortality and the morbidity of therapy. A group from Vancouver has performed preliminary analyses of a fluorescent laser bronchoscope (produced by Xillix Corp.).37 Their preliminary studies showed that this technique could detect dysplastic lesions not detectable by standard bronchoscopy. Further evaluation of this technique with randomized clinical trials are in progress.

**Therapeutic Trials**

**Operable NSCLC (Stages I to IIIA)**

Surgery produces the highest cure rates for patients with NSCLC who have potentially resectable disease. Nevertheless, surgery cures less than half of the patients who have a complete surgical resection. Table 2 summarizes the sites of relapse in these patients who have undergone complete resection.38 The vast majority of relapses (~80%) occur in distant sites. Recurrences that occur in the chest alone occur in only about 20% of patients. Randomized trials evaluating postoperative radiotherapy showed that chest irradiation could virtually eliminate these local recurrences but had no effect on other recurrences or on survival.39 Clearly some effective systemic therapy is necessary to improve survival in these patients.

There were four randomized trials evaluating CAP (cyclophosphamide, doxorubicin [Adriamycin], cisplatin)

**Table 2—First Recurrence After Curative Resection for Lung Cancer by Cell Type in the M.D. Anderson Series, 1965-1976**

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>No. of Patients</th>
<th>Regional</th>
<th>Distant</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous</td>
<td>72</td>
<td>24</td>
<td>71</td>
<td>5</td>
</tr>
<tr>
<td>Adenocarcinoma and</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>large cell carcinoma</td>
<td>71</td>
<td>17</td>
<td>79</td>
<td>4</td>
</tr>
</tbody>
</table>

*Mountain et al.38*

Clinical Research: Future Directions (Paul Bunn)
chemotherapy as a postoperative adjuvant therapy in the 1970s and 1980s.\textsuperscript{40-42} The LCSG compared CAP chemotherapy with immunotherapy with bacillus Calmette-Guérin (BCG)+levamisole in patients with stage II and IIIA NSCLC who had undergone complete resection and found that the patients on the CAP arm had a better survival which was 8 months longer at the median and 10% higher at 4 and 5 years.\textsuperscript{46} However, the differences in survival were not significant given the relatively small number of patients in each arm. The LCSG conducted another randomized postoperative CAP chemotherapy study in patients with stage I disease in which the control patients received no therapy.\textsuperscript{41} There were no differences in survival. In contrast, a group from Norway conducted a randomized trial comparing CAP chemotherapy with no therapy in patients with T1-T3N0 NSCLC disease who had undergone complete resection.\textsuperscript{42} They found a significant improvement in the survival of the CAP-treated patients that was reflected in a 10% improvement in the 5-year survival. The fourth and last study, conducted by the LCSG and reported on for the first time at this meeting showed no survival benefit.

Randomized chemotherapy studies conducted after the studies listed above were instituted showed that several chemotherapy programs were superior to CAP chemotherapy. Adjuvant studies in other cancers and theoretical studies showed that preoperative chemotherapy might prove to be more useful than postoperative chemotherapy. These two observations led investigators from the M.D. Anderson Cancer Center and from the Spanish Lung Cancer Group to evaluate preoperative and postoperative chemotherapy compared with surgery alone in patients with stage IIIA NSCLC.\textsuperscript{43,44} The M.D. Anderson group used CEP (cyclophosphamide, etoposide, cisplatin) chemotherapy,\textsuperscript{44} while the Spanish Lung Group used MIC (mitomycin, ifosfamide, cisplatin) chemotherapy.\textsuperscript{43} Both studies were closed at an early stopping rule (about 60 patients in each study) because of a highly statistically significant improvement in the survival of the chemotherapy-treated patients. Table 3 summarizes the survival results from these two studies. Because the studies were closed early, there were very few patients in each of the many subsets of stage IIIA disease. Therefore, it cannot be determined whether some subsets had more benefit than others. These studies did not include any patients with the following stages: T2N0; T1N1; or T2N1. These patients with stage IB and II disease have a recurrence rate in excess of 50%, which is not much different from the survival experience of patients with stage T3N0 who were included in all the studies discussed above.

In summary, I believe that prospective randomized trials of preoperative and postoperative chemotherapy vs surgery alone are needed in stages IB through IIIA operable NSCLC. The chemotherapy should optimally include one of the two regimens used in the recent M.D. Anderson or Spanish trials or a regimen shown to improve survival in patients with more advanced stage disease (eg, vinorelbine+cisplatin). Any future regimen shown to be superior to these regimens in patients with more advanced stages should be moved rapidly to the neoadjuvant setting. The sites of failure in these studies must be examined closely. If local relapses are common, some studies should be conducted combining radiotherapy with the chemotherapy.

### Locally Inoperable NSCLC (Stages IIIA and IIIB)

Recent randomized trials and a meta-analysis of these trials showed that the combination of chemotherapy with chest radiotherapy prolongs survival in these patients compared with chest radiotherapy alone.\textsuperscript{34-46} The optimal means of combining the two modalities, the optimal features of the chemotherapy (drugs, schedule, dose), and the optimal features of the radiotherapy (dose, volume, fractionation) are all unknown. Clinical trials are needed to evaluate each of these parameters. These studies should be based on preclinical models designed to determine the optimal interactions between the chemotherapy and the radiotherapy. The clinical trials should be designed to determine the sites of failure as well as the response rates, response duration, and survival.

A number of new drugs have shown promising results in patients with far advanced NSCLC.\textsuperscript{47-58} These new drugs are summarized in Table 4\textsuperscript{45,49-50} and below and include the microtubule disrupting agents paclitaxel (Taxol)\textsuperscript{49,50} and docetaxel (Taxotere);\textsuperscript{51-53} the topoisomerase inhibitors, CPT-11 and topotecan;\textsuperscript{54,46} the antimetabolites, 10 EDAM (edatrexate)\textsuperscript{51-53} and gemcitabine;\textsuperscript{58,60} the vinca alkaloid vinorelbine;\textsuperscript{46,64-67} and the cytokines interleukin 2 (IL-2)\textsuperscript{70,71} and interleukin 4 (IL-4).\textsuperscript{72,73}

These agents should be tested in combination with radiotherapy in preclinical models. Where the results show synergistic results, clinical trials should follow. If there are no synergistic or additive effects, the agents should be considered for testing given before or after the radiotherapy.

The role of surgery in patients who are believed to have inoperable, but potentially operable conditions needs to be defined. Numerous phase 2 studies showed that the initial chemotherapy or chemoradiotherapy produces responses in about two thirds of treated patients.\textsuperscript{3} As with other

### Table 3—Randomized Trials of Surgery vs Preoperative and Postoperative Chemotherapy and Surgery in Stage IIIA NSCLC

<table>
<thead>
<tr>
<th>Source</th>
<th>Treatment</th>
<th>No. of Patients</th>
<th>No. Resected</th>
<th>Median Survival, mo</th>
<th>3-yr Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosell et al\textsuperscript{45}</td>
<td>Surgery</td>
<td>30</td>
<td>27</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>MIC+surgery*</td>
<td>30</td>
<td>23</td>
<td>26</td>
<td>30</td>
</tr>
<tr>
<td>Roth et al\textsuperscript{44}</td>
<td>Surgery</td>
<td>32</td>
<td>21</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>CEP+Surgery†</td>
<td>28</td>
<td>17</td>
<td>64</td>
<td>56</td>
</tr>
</tbody>
</table>

*MIC=mitomycin, ifosfamide, cisplatin.
†CEP=cyclophosphamide, etoposide, cisplatin.
cancers, these response rates were higher than the response rates reported in patients with more advanced stages (stage IV). These phase 2 studies also demonstrated that most patients could undergo complete resection after such induction treatments with acceptable operative morbidity and mortality. Some studies suggest that the complete resection rates and survival in patients with stable disease after induction chemoradiotherapy are similar to those in patients with objective antitumor responses. These studies also suggested that the results were similar in patients with stage IIIB compared with stage IIIA disease. This latter result suggested that the induction chemoradiotherapy was sufficient to control nonbulky regional disease. Very few of the phase 2 studies have reported 5-year survival rates. The few that have reported results to this point report 15 to 20% 5-year survival rates. There are also few studies of combined chemoradiotherapy alone that report 5-year survival rates. Those studies that have reported late survival show rates in the 10 to 15% range. Since the 2-yr survival of the patients with locally advanced disease approximates 6%, randomized trials are clearly necessary to determine whether postinduction surgery is indicated in these patients. At least one such randomized trial has been instituted by the Southwest Oncology Group. This will become an intergroup study in the near future. The role of radiotherapy in these combined approaches is also in question and a randomized trial evaluating the role of radiotherapy has been instituted by the Canadian NCI.

Metastatic (Stage IV) NSCLC

For many years, the value of chemotherapy in stage IV NSCLC was in question because no randomized trials had shown a survival benefit for treatment with chemotherapy. In the past 15 years, multiple randomized trials have evaluated the role of chemotherapy compared with best supportive care (BSC). Best supportive care included palliative radiotherapy, antibiotics, pain medications, etc, but did not allow for any chemotherapy. Some of these trials have shown a survival benefit for treatment with chemotherapy.
trials showed a significant survival advantage for the chemotherapy but others did not. In all of the trials, the patients treated with chemotherapy survived longer than those receiving only BSC, but often the differences were nonsignificant. All of these trials had less than 100 patients per arm and lacked the power to detect small increases in survival. Therefore, both literature-based and individual patient-based meta-analyses of the data from these trials have been performed.76 All of these meta-analyses showed significant survival advantages for the chemotherapy arms. Thus, it can be concluded that chemotherapy adds a small but significant survival advantage for these patients. It must be stressed that these trials were limited to patients with a good performance status (≤2 Eastern Cooperative Oncology Group [ECOG]) and that there is still no evidence that chemotherapy prolongs survival in patients with impaired performance status.

Unfortunately, there are no randomized trials that evaluated the quality of life in the respective groups. In fact, there are no standard validated tools for measuring the quality of life in these patients, although several have been proposed.77 A major limitation in these quality-of-life tools is the high rate of dropout due to tumor progression. These censored observations limit the power of the tools. Additional clinical trials in this area are needed and are in progress.

One of the randomized chemotherapy vs BSC trials, the Canadian NCI trial, assessed the costs associated with the treatments. The results of this analysis showed that treatment with CAP chemotherapy was associated with lower costs compared with BSC.78 The explanation for the unexpected finding was that the patients treated with CAP chemotherapy spent less days in hospital and had less radiotherapy than patients on the BSC arm. This study also had a vindesine+ cisplatin arm. The costs associated with this therapy were higher than the other two arms because patients required hospital admission for the cisplatin therapy. Patients receiving chemotherapy lived longer than those receiving BSC; when the costs per added year of life were calculated, they showed that the chemotherapy was more cost-effective than many standard medical procedures such as coronary surgery, transplants, or dialysis. With rising costs of medical care around the world, additional studies of this nature are clearly needed.

There has been considerable recent enthusiasm surrounding the discovery of new active agents in NSCLC, especially those with new mechanisms of action. Table 4 shows a list of the agents and the response rates reported and Figure 1 shows the survival results from one of these agents, paclitaxel (Taxol).49,50 Paclitaxel produced responses in 24% of the patients treated at the M.D. Anderson Cancer Center49 and 21% of the patients treated by the ECOG.50 While these response rates do not seem impressive-high, it must be recalled that the most active drug, cisplatin, has a response rate of only 21% and the recently approved vinorelbine has a response rate of 14 to 33%.64,65 The survival results of these two studies are more impressive than the response rates. As shown in Figure 1, the 1-year survival rate was about 40% in both studies and the 2-year survival rates were about 28% and 18% in the two studies, respectively. This is higher than in nearly all combination studies. The excellent survival could be attributed solely to patient selection, but the ECOG study was a randomized phase 2 study with two other arms (pivatantrone and merbarone). The survival in these two arms of the study was not as good as the paclitaxel arm and closer to the expected survival of patients with stage IV disease. Future clinical trials will clearly need to evaluate paclitaxel in combination with other chemotherapeutic agents and in combination with radiotherapy. Initial paclitaxel studies administered the drug as a 24-h infusion. More recent studies in other cancers suggest that 3-h infusions are less myelosuppressive, more convenient, and equally effective as the 24-h infusions. The optimal dose and schedule of paclitaxel for lung cancer are unknown and need to be studied.

Docetaxel also appears to be active in NSCLC51-53 and also requires further study alone and in combination with other agents to determine optimal dose, schedule, and combinations.

Another novel group of agents are the topoisomerase-1 inhibitors CPT-11, topotecan, and 9-aminocamptothecan.54-56 CPT-11 has been the most extensively studied. As a single agent, it produced response rates of 29% in patients with NSCLC and 47% in patients with small cell lung cancer (SCLC). Phase 1 combination studies with cisplatin,56 etoposide,57 and cisplatin plus vindesine57 have shown promising response rates. The drug has been studied almost exclusively in Japan. Studies outside Japan, phase 2 combination studies, and eventually phase 3 studies will be necessary to determine the ultimate role of this agent. Topotecan has been studied in fewer patients and to my knowledge, there are no published combination studies, but it also appears to have considerable activity in patients with SCLC and lesser activity in patients with NSCLC.58,59 It is likely that there is cross-resistance between these three topoisomerase-1 inhibitors but not with other active drugs or radiotherapy.

Initial studies with the antifol, 10-EDAM, suggested considerable activity.51 Unfortunately, more recent studies have shown lower response rates52,53 and a phase 3 multiagent study of MV (mitomycin+vinblastine) vs MVE (mitomycin+vinblastine+edatrexate) showed no major advantage for the three-drug combination that was more

![Figure 1. Paclitaxel (Taxol) in NSCLC: survival results.](http://journal.publications.chestnet.org/pdaccess.ashx?url=/data/journals/chest/21705/ on 06/26/2017)
toxic.\textsuperscript{79} Thus, it appears that 10-EDAM has a limited role in the therapy of NSCLC.

Vinorelbine was shown to improve the survival of patients with stage IV NSCLC compared with fluorouracil+leucovorin.\textsuperscript{80} In combination with cisplatin, it was also shown to improve survival of patients with advanced NSCLC compared with vinorelbine alone or to the combination of vindesine and cisplatin.\textsuperscript{45} It remains to be determined whether the combination of vinorelbine plus cisplatin is superior to cisplatin alone. Vinorelbine also needs to be evaluated in combination with other new agents and with radiotherapy.

Gemcitabine, a new antimetabolite, has consistently shown response rates in the 20\% range in both SCLC and NSCLC with very few side effects and minimal myelosuppression.\textsuperscript{58,59} Thus, it is an excellent agent for combining with active drugs with other mechanisms of action, especially those with dose-limiting myelosuppression. These trials are just in the planning or early institution stages. The combination of gemcitabine with radiotherapy also needs investigation.

The role of cytokines in the treatment of lung cancer is uncertain but preliminary results have not been especially encouraging. Interferons (IFN) were shown to be capable of increasing the expression of tumor antigens and HLA antigens on lung cancer cell lines \textit{in vitro}. However, phase 2 studies of interferon alone in both SCLC and NSCLC were discouraging with response rates <15\%. In SCLC, natural interferon, rIFNa, and rIFN\textalpha{} were evaluated as maintenance agents to prolong remission duration and survival.\textsuperscript{81-83} None of three randomized trials showed a statistically significant improvement in response duration or survival. Thus, it is difficult to remain enthusiastic about further studies with interferons.

Interleukin 2 with or without lymphokine-activated killer (LAK) cells has been the most widely studied cytokine other than interferon. Interleukin 2 alone or with LAK cells has not shown promising responses in NSCLC. In one study, the combination of IL-2 with cisplatin produced promising results in patients with bronchoalveolar NSCLC.\textsuperscript{70} There are also some promising early studies with IL-2 in patients with advanced SCLC.\textsuperscript{71} Further studies in this setting are warranted. Interleukin 4 was shown to inhibit the proliferation of some lung cancer cell lines \textit{in vitro} and to stimulate the immune system.\textsuperscript{72,73} Preliminary phase 1 studies in patients with lung cancer showed an occasional response and some long durations of stable disease.\textsuperscript{72} These studies should prompt further study of this agent in patients with NSCLC. The role of other cytokines is largely unexplored in the clinical setting, but preclinical studies are necessary before large clinical trials are undertaken.

There is growing evidence that growth factors are involved in the pathogenesis and progression of lung cancer. For most NSCLC tumors, EGF appears to be a crucial autocrine and paracrine growth factor while neuropeptides appear to be important in the pathogenesis and progression of SCLC tumors and a small fraction of NSCLC tumors.\textsuperscript{85} There are a number of strategies to block these autocrine and paracrine growth pathways. These are receiving increasing study in preclinical model systems and early clinical trials are now indicated.

A number of the genetic events in the development of lung cancer are becoming elucidated. The biologic abnormalities are potentially reversible by gene therapy. Some \textit{in vitro} studies have shown that gene therapy with wild-type p53 and antisense \textit{ras} can lead to antitumor effects. Phase 1 clinical trials of these gene therapy approaches are indicated. Table 5 summarizes some important clinical trials that will be conducted in the next few years.

It is clinically obvious that lung cancers of all histologic types develop acquired drug resistance that often has the clinical features of "multidrug resistance" with resistance

<table>
<thead>
<tr>
<th>Table 5—Proposed Future Clinical Trials</th>
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<tbody>
<tr>
<td><strong>I. Prevention</strong></td>
</tr>
<tr>
<td>A. Phase 3 chemoprevention trials in patients with completely resected stage I NSCLC</td>
</tr>
<tr>
<td>- retinoids+beta carotene or a tocopherol (ongoing and proposed to NCI)</td>
</tr>
<tr>
<td>B. Phase 3 chemoprevention trials in patients with SCLC in complete response after induction therapy,</td>
</tr>
<tr>
<td>- retinoids+beta carotene or ( \alpha ) tocopherol (proposed to NCI)</td>
</tr>
<tr>
<td>C. Phase 2 studies of new agents using intermediate end point markers.</td>
</tr>
<tr>
<td>D. Phase 1 studies of new agents, including antigrowth factors and gene therapy</td>
</tr>
<tr>
<td><strong>II. Early detection/screening studies</strong></td>
</tr>
<tr>
<td>A. Phase 2 studies evaluating monoclonal antibody staining of sputum samples in high-risk patients (ongoing)</td>
</tr>
<tr>
<td>B. Phase 2 studies of fluorescence (LIFE) bronchoscopy (ongoing)</td>
</tr>
<tr>
<td>C. Phase 3 studies of fluorescence (LIFE) bronchoscopy (just starting)</td>
</tr>
<tr>
<td>D. Phase 3 study of annual chest radiographs (PLCO study in progress)</td>
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<tr>
<td>E. Phase 1 studies of intermediate markers in sputum and bronchial specimens</td>
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<tr>
<td>F. Phase 1 studies of new serum markers</td>
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<tr>
<td><strong>III. Therapeutic trials</strong></td>
</tr>
<tr>
<td>A. Operable NSCLC (stages IB-III A)</td>
</tr>
<tr>
<td>- Phase 3 trials of preoperative and postoperative chemotherapy with analysis of sites of failure (two small studies complete; large confirmatory studies needed; one in progress (SWOG) to be closed by a NCI mandate (why))</td>
</tr>
<tr>
<td>B. Locally advanced NSCLC (stages IIIA and IIIB)</td>
</tr>
<tr>
<td>- Phase 3 studies of chemoradiotherapy+survivin</td>
</tr>
<tr>
<td>- Phase 3 studies of chemotherapy+surgery+radiotherapy</td>
</tr>
<tr>
<td>- Phase 2 studies of chemoradiotherapy evaluating schedule, dose, fractionation, \textit{etc}, and sites of failure.</td>
</tr>
<tr>
<td>- Phase 1 studies of new agents and combinations with radiotherapy</td>
</tr>
<tr>
<td>C. Advanced NSCLC (stage IV and IIIB with pleural effusions)</td>
</tr>
<tr>
<td>- Phase 3 studies evaluating new combinations vs &quot;standard therapy,&quot; \textit{eg}, navelbine+cisplatin vs cisplatin (SWOG in progress) or CPT-11+cisplatin vs cisplatin, \textit{etc}</td>
</tr>
<tr>
<td>- Phase 1 studies of new agents in combination with one another, in combination with existing chemotherapeutic agents, and in combination with radiotherapy</td>
</tr>
<tr>
<td>- Phase 2 studies of these new combinations as soon as the phase 1 studies are completed</td>
</tr>
<tr>
<td>- Preclinical studies of antigrowth factors, gene therapies, and agents to reverse or prevent multidrug resistance.</td>
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</table>
to anthracyclines, vinca alkaloids, and epipodophyllotoxins whether or not the patient was treated with these drugs.\textsuperscript{84-87}

In some instances, the drug resistance was shown to be due to overexpression of the classic MDR-1 gene. In other instances, however, it is clear that the resistance is due to other mechanisms such as overexpression of the MRP protein or other proteins. Whether any modulator is capable of reversing or preventing multidrug resistance needs considerable investigation in lung cancer preclinical models and patients.

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