Translational Research Is Hurting

There are two “Sounding Board” articles published in the September 3, 1998, issue of the New England Journal of Medicine that at first glance, do not seem to have much relationship to one another.1,2 The first article describes ethical guidelines for practicing physicians to prevent financial considerations from interfering with decisions about medical care. The second article reviews the process of taking basic science research and translating it for clinical purposes. The terms “translational research” and clinical “evaluative research” are introduced to describe the important process that takes discoveries from bench to bedside.

American medicine has excelled and led the world through the 1970s and 1980s. This leadership has emanated from academic medical centers where basic and clinical research was done side by side. The introduction of managed care into the practice of medicine is clearly intended to produce efficient, cost-effective practitioners. The discussion of capitation, incentives, and bonuses in the first article is exclusively aimed at the private practice of medicine.1 However, these same capitations, incentives, and bonuses are being applied to academic practitioners so that they can generate their own salary. Two-track systems are almost mandatory in academic health centers. Researchers must generate their salaries from grant support. The clinician must generate a salary from billing patients. There is little or no room for the “triple threat” academician who can teach, research, and provide excellent clinical care. In fact, the second article2 points out that “only 27% of all research funds awarded in fiscal year 1996 were partly or completely earmarked for clinical research, a category that includes but is not limited to clinical evaluative research.”

This type of research is exactly the type that was previously done in academic health centers and translates the findings generated in the laboratory to the bedside. There are a limited number of academic clinicians who have the luxury of doing clinical research; they must earn their salaries. Private industry has taken up some slack, but paying private practitioners to test a drug hardly qualifies as translating basic findings to the bedside.

Is American medicine falling behind? I submit that it is falling behind in the areas mentioned above. I believe that the two “Sounding Board” articles are very much related to one another and to the problem in academic American medicine. It has never been clear to me why academic practitioners must be held to the same standards as those in private practice.3 They perform additional services and deserve additional consideration. It is likely that the academic physician, capable of recognizing the unintended application of a research discovery, will be too busy earning his salary by seeing patients. Thus, blinders will have been placed on the aspect of academic medicine that has made the United States a leader in the scientific world.

A. Jay Block, MD, FCCP

Gainesville, FL

Dr. Block is Editor-in-Chief, CHEST, and Emeritus Professor of Medicine, University of Florida.

Correspondence to: A. Jay Block, MD, FCCP, Seagle Building, Suite 408, 408 W University Ave, Gainesville, FL 32601

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Pulmonary Rehabilitation
Sisyphus or Odysseus?

Sisyphus,1 the legendary king of Corinth, committed such crimes in his life that on his death he was sent to Hades for judgment and sentenced to the unattainable task of rolling a heavy stone up a hill. Each time he would near the apex of the hill, the
stone was condemned to repeat this cycle for eternity. As a practicing pulmonologist in a rural community in upper east Tennessee, establishing a pulmonary rehabilitation program was a Sisyphean task. Armed with vision, passion, and determination to succeed, 6 years were spent planning, marketing, and selling the idea of pulmonary rehabilitation to the community. The formidable hurdles of apathy, ignorance, and indifference were finally overcome. Within months of opening the doors of our newly established program, we had an extensive waiting list and were already outgrowing the existing facility. Obviously, there had been a strong need for pulmonary rehabilitation in this community. A need that was not being met by conventional therapies alone.

I wondered how many other communities were facing a similar dilemma. How many other communities did not realize that such a service even existed for patients with chronic lung disease? An excess of 20 million people in the United States have chronic lung disease. COPD has been identified as the only major disease that is experiencing an increase in prevalence and mortality and is now considered to be the fourth leading cause of death in the US. Why was it that only a limited number of these people had access to quality pulmonary rehabilitation? If I had not been exposed to pulmonary rehabilitation during my pulmonary fellowship training, it is very unlikely that the life-changing benefits of pulmonary rehabilitation would now be available to the individuals in my community with chronic lung disease. The question then presented itself, was the lack of pulmonary rehabilitation exposure during pulmonary fellowship training the reason?

There are 185 pulmonary fellowship programs in the United States, with an excess of 1,200 fellows enrolled. From a list of existing pulmonary fellowship programs in the United States provided by the ACCP, a telephone survey was conducted to assess the extent of pulmonary rehabilitation education received during pulmonary fellowship training. I contacted program directors and informed them that I was a practicing pulmonologist, on faculty at my regional medical school, conducting a brief survey regarding the availability of pulmonary rehabilitation training at their institution. Of the 85 programs contacted, I was only able to speak directly with 53 of the program directors. Responses ranged from elusive, suspicious, and resistant to honest, open, and supportive. Of this random sampling, in only approximately 1 out of 4 programs (26%) was pulmonary rehabilitation training a required component of their pulmonary fellowship education. Many of the program directors stated that pulmonary rehabilitation was offered as an elective, though most described that elective as “loosely structured,” “not well defined,” and “broad based.” When program directors, the most visible role models for pulmonary physicians in training, use such statements as “no scientific basis,” “no increased survival,” and “not rocket science” in reference to pulmonary rehabilitation, it is not surprising that few, if any, pulmonary fellows elect to take the rotation.

So, what are we up against? Along with lack of training of future pulmonologists in rehabilitation medicine, we also face the fact that despite the recently published Joint ACCP/AACVPR Evidence-Based Guidelines, which unequivocally supports pulmonary rehabilitation, many pulmonologists as a group are not convinced that pulmonary rehabilitation has substantial value. They are either not informed or not interested in preventative medicine and wellness. If pulmonologists, leaders in the field of pulmonary medicine, do not support pulmonary rehabilitation, how can we expect the general medical community to support pulmonary rehabilitation programs? The prevailing attitude among physicians in my community is that obstructive lung disease is self-inflicted, brought on by the addictive behavior of smoking. These same physicians view smokers as weak, dependent, and lacking character rather than recognizing that nicotine addiction is a complex physiologic and psychological disease. Again, it is no surprise that physicians appear to have developed a nihilistic, almost punitive attitude toward patients with COPD.

The National Heart, Lung, and Blood Institute (NHLBI) held a workshop in 1995 entitled “Building a National Strategy for the Prevention and Management of and Research in Chronic Obstructive Lung Disease.” The purpose of this workshop was not only to formulate a national strategy for dealing with the public health dilemma of COPD, but also to focus efforts at prevention and delay of premature morbidity and mortality associated with this disease. With the rapid expansion of managed care and the growing emphasis on wellness, pulmonary rehabilitation is in a unique position to play a pivotal role in working towards the goal of the NHLBI. As a result of this workshop, a new healthcare initiative was developed and incorporated into the National Lung Health Education Program (NLHEP). Pulmonary rehabilitation was subsequently identified as both a secondary and tertiary strategy in the preventive management of COPD. The NLHEP, in conjunction with the ACCP, will serve as the major education vehicle to target primary care physicians and the public in the hope of increasing awareness of COPD and detecting the disease at its earliest stages. If the focus of the NLHEP and its “major educational arm,” the ACCP, is on early detection and preven-
tion, pulmonary rehabilitation should be an integral part of patient management. For this to happen, I believe we have to clean house and set an example. We have to show we believe education, prevention, and quality of life are important. Unlike the existing guideline, I believe that the ACCP should mandate that pulmonary rehabilitation education be a required component of pulmonary fellowship training for program accreditation. Only then are we going to have pulmonary fellows teaming with their communities, establishing pulmonary rehabilitation programs, and making these services available to the over 20 million people with chronic lung disease.

With the growing body of supportive scientific evidence and a commitment to education and prevention, we, the members of the ACCP, unlike Sisyphus, have the strength to push that heavy stone over the steep and unyielding hill. Have we, however, adequately prepared for the battles to come? As did Odysseus on his return from Troy to his home kingdom of Ithaca, we will encounter Lotus-eaters, Cyclopes, and Lestrygonians at every turn. We have to unite and remain focused in our vision, passion, and determination so that we can meet the rehabilitation needs of the growing number of individuals in our communities who struggle daily with chronic lung disease.

Frederic D. Seifer, MD, FCCP
Jennifer L. Hefner, BS, RD
Deborah Cestaro-Seifer, MS, RN
Jay B. Mehta, MD, FCCP
Johnson City, TN

The Emerging Role of Leukotriene Antagonists in Asthma Therapy

The drug therapy of asthma has remained essentially unchanged over the past 3 decades, comprising use of glucocorticoids, β2-agonists, and theophyllines. The antileukotrienes and particularly the leukotriene antagonists represent an important new class of drug therapy for asthma. At present, the use of the 5-lipoxygenase inhibitor zileuton is somewhat limited due to its four-times-daily dosing regimen and the need to monitor biochemical liver function tests. The advantages of the available leukotriene antagonists are the use of once-daily (montelukast) or twice-daily (zafirlukast) dosing in terms of improved compliance, as well as there being no need to routinely monitor liver function. The leukotriene antagonists seem to be effective over a wide range of asthma disease severity, although their precise role in asthma management guidelines has yet to be established due to the relatively small published database on long-term clinical efficacy.

One of the fundamental questions regarding the leukotriene antagonists is whether they should be positioned in the guidelines for use as first-line preventive monotherapy as an alternative to inhaled glucocorticoids, or whether their use should be restricted to second-line controller therapy in addition to inhaled glucocorticoids. Interestingly, in the United States, both zafirlukast and montelukast have been approved for use as monotherapy, whereas in Europe, montelukast has been approved for use as add-on therapy in patients with persistent asthma whose disease is inadequately controlled with inhaled glucocorticoids.

The cysteinyl leukotrienes (leukotrienes C4, D4, and E4) are potent inflammatory mediators in the pathophysiology of asthma as well as producing bronchial smooth muscle constriction. It is therefore not surprising perhaps that the leukotriene antagonists exhibit effects that are attributable to both bronchodilator and anti-inflammatory activity. The glucocorticoids, by contrast, have more widespread effects on a variety of inflammatory and structural cells in the airway as well as their inhibitory effects on cytokines and transcription factors. There are
also good data from biopsy studies to show that inhaled glucocorticoids have marked effects on asthmatic airway inflammation. This is backed up by long-term clinical studies showing sustained effects of inhaled glucocorticoids on markers of asthmatic disease control as well as established benefits of early intervention therapy. Until comparable data are available for the leukotriene antagonists, there seems to be little justification for their use as first-line preventive therapy instead of inhaled glucocorticoids, particularly as the leukotriene antagonists interfere only with one part of the inflammatory pathway.

There are perhaps compliance arguments in favor of using a once- or twice-daily tablet with montelukast as an alternative option to low-dose inhaled glucocorticoid for patients with mild persistent asthma, in keeping with the current US guidelines. The compliance factor with leukotriene antagonists may be reinforced by their peak onset of action within the first 24 h of treatment in contrast to the more gradual effects of inhaled glucocorticoids over several weeks. The potential problems with delivering inhaled glucocorticoids by metered-dose inhalers can easily be overcome by using a breath-actuated pressurized aerosol, a spacer attachment, or a dry powder inhaler device. Furthermore, the use of a once-daily dosing regimen with inhaled glucocorticoids is as effective as twice daily, at doses of up to 800 μg/d in patients with mild-to-moderate asthma. The choice between leukotriene antagonist and low-dose inhaled glucocorticoid will therefore depend on other factors such as patient preference, degree of long-term disease control, and cost. With respect to the latter, low-dose inhaled glucocorticoid (400 μg/d of beclomethasone dipropionate, triamcinolone acetonide, or budesonide) is less expensive compared with a leukotriene antagonist.

Multicenter studies in adults and children have shown superiority of montelukast or zafirlukast over placebo when given to patients with mild-to-moderate asthma for a period of up to 13 weeks. In this issue of CHEST (see page 336), Kemp and coworkers report on a pooled subgroup analysis of data from four clinical trials in which zafirlukast 20 mg twice daily or placebo were given as monotherapy over a 13-week period to 261 patients identified as having severe persistent asthma. Their results showed significant improvements in all efficacy outcome measures as compared with placebo. The main problem with this study is that zafirlukast was evaluated in severe persistent asthmatics who prior to randomization were being treated inappropriately with β2-agonists alone. Such patients would normally be taking an optimized dose of inhaled glucocorticoid before adding in a leukotriene antagonist. Indeed it is evident that despite their taking zafirlukast, the patients’ asthma remained inadequately controlled and that the differences from placebo, although statistically significant, were of relatively small magnitude, as compared with what one would normally expect with optimized inhaled glucocorticoid as monotherapy in these types of asthmatics. This points to the importance of following the recommended management guidelines in terms of using inhaled glucocorticoid as first-line anti-inflammatory therapy in step 3 or step 4 in patients with moderate or severe persistent asthma.

Another important issue is whether leukotriene antagonists confer additional benefits to low-dose inhaled glucocorticoid when used as adjunctive controller therapy. This hypothesis was tested in a multicenter study of 642 adult patients with mild-to-moderate chronic asthma who were randomized to receive treatment for 16 weeks with placebo, beclomethasone dipropionate 400 μg daily via a spacer, montelukast 10 mg once daily, or montelukast 10 mg once daily plus beclomethasone dipropionate 400 μg daily. There was also an initial 4-week run-in period when all of the patients received beclomethasone 400 μg daily, followed by tapered withdrawal of morning and evening doses of beclomethasone after 2 and 4 weeks of active treatment, in the groups receiving montelukast alone or placebo. Follow-up over the subsequent 12 weeks of the study showed that compared with placebo, there was significantly better control with montelukast alone, which in turn was less effective than beclomethasone alone, with the combination of montelukast plus beclomethasone being superior to beclomethasone alone. Similar findings have been reported with zafirlukast 40 mg twice daily in addition to 336 μg daily of beclomethasone dipropionate in comparison to monotherapy with 672 μg daily of beclomethasone dipropionate, in terms of an equivalent degree of improvement in asthma control over a 13-week follow-up period. The use of montelukast 10 mg once daily compared with placebo has also been shown to permit a significantly lower effective maintenance dose of inhaled glucocorticoid during tapered step-down over a 12-week period, as assessed in 236 adult patients with chronic asthma requiring moderate to high doses of inhaled glucocorticoid. In this respect, it is interesting to note that oral or inhaled glucocorticoid therapy is not effective in inhibiting increased synthesis of cysteinyl leukotrienes in response to allergen challenge. Moreover in vitro studies have demonstrated glucocorticoids to increase expression of 5-lipoxygenase activity. The additive effects of leukotriene antagonists on asthma control may at least in part be due to their anti-inflammatory activity, as shown by their effects on
airway inflammatory cells, in terms of sputum eosinophil levels or BAL segmental antigen challenge.\textsuperscript{16,17}

Long-acting inhaled $\beta_2$-agonists such as salmeterol and formoterol also have additive effects on asthma control on top of inhaled glucocorticoid therapy,\textsuperscript{18} although regular therapy is associated with $\beta_2$-adrenoceptor down-regulation and a tolerance of clinical efficacy.\textsuperscript{19} The development of tolerance with long-acting $\beta_2$-agonists is greater for bronchoprotector than bronchodilator activity, as has been demonstrated with their functional antagonism against methacholine or exercise-induced bronchoconstriction.\textsuperscript{20,21} A randomized double-blind comparison of salmeterol 50 $\mu$g twice daily and montelukast 10 mg once daily was made in 191 adult asthmatics, with exercise challenge performed at trough (24 h for montelukast and 12 h for salmeterol) after the first dose and after 4 and 8 weeks of treatment.\textsuperscript{22} The results showed that montelukast produced a higher level of maintained protection when comparing the first and last dose effects (60\% vs 57\% inhibition of area under curve), whereas salmeterol showed a marked degree of tolerance at the same time points (41\% vs 17\%). As salmeterol is devoid of anti-inflammatory activity,\textsuperscript{23} and may actually mask uncontrolled inflammation,\textsuperscript{24} it might seem more prudent to use a leukotriene antagonist instead as additive second-line controller therapy in view of its anti-inflammatory properties as well as its lack of tolerance. Another potential spinoff of leukotriene antagonists is that they are also effective in treating coexistent allergic rhinitis.\textsuperscript{25} Further longer-term follow-up studies are indicated to compare the effects of leukotriene antagonists and long-acting $\beta_2$-agonists as second-line therapy to look at long-term disease control and exacerbation rates, particularly in patients with moderate-to-severe persistent asthma.

The use of regular treatment with once- or twice-daily sustained-release theophylline may also confer improvements in asthma control in addition to inhaled glucocorticoid therapy,\textsuperscript{26} and like leukotriene antagonists, theophylline has been shown to possess anti-inflammatory properties.\textsuperscript{27} Theophyllines have a less predictable pharmacokinetic profile than leukotriene antagonists and are less well tolerated with potential drug interactions, as well as requiring therapeutic drug monitoring. However, as theophyllines are less expensive than leukotriene antagonists, they may be considered as a reasonable option for second-line controller therapy, particularly when there are more rigorous pharmacoeconomic constraints, as for example with managed health-care provision or in the National Health Service. It is also worth pointing out that there is a degree of variability in the clinical efficacy response to leukotriene antagonists that may be related to regulation of cysteinyl leukotriene synthesis by genetic polymorphism of 5-lipoxygenase enzyme activity.\textsuperscript{28}

The next 5 years of basic science and clinical research into leukotriene antagonists will hopefully help to define a clearer role for these agents in asthma management guidelines, in terms of use for first-line preventive monotherapy or second-line additive controller therapy. Clinicians and the pharmaceutical industry need to collaborate closely together so that appropriate research studies are performed to answer these important clinical questions.

Brian J. Lipworth, MD
Dundee, Scotland, UK

Professor of Allergy and Respiratory Medicine, Department of Clinical Pharmacology and Therapeutics and Department of Respiratory Medicine, Ninewells Hospital and Medical School, University of Dundee, Dundee, Scotland, UK.

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Extra-Fine Corticosteroid Aerosols From Hydrofluoroalkane-134a Metered-Dose Inhalers

Potential Advantages and Disadvantages

To comply with the mandatory phase-out of chlorofluorocarbons (CFCs) that destroy ozone in the stratosphere and allow excessive ultraviolet radiation to reach the earth’s atmosphere, CFC-based metered-dose therapeutic aerosols are in the process of being reformulated with more environmentally friendly alternative propellants, such as hydrofluoroalkanes (HFAs). This process has created formidable technical challenges as well as new opportunities for potentially improved aerosol delivery. Beclomethasone dipropionate (BDP), the oldest inhaled corticosteroid molecule with high topical-to-systemic activity, has been used in asthma therapy for over two decades. Reformulation of BDP with HFA-134a results in a solution preparation that delivers an aerosol with a much smaller mean particle size (mass median aerodynamic diameter [MMAD] 1.1 μm) than that of aerosols generated by conventional CFC-based metered-dose inhalers of BDP (MMAD, 3.5 to 4 μm). Mathematical models that relate particle size to the site of deposition in the respiratory tract predict that extra-fine particles with an MMAD of approximately 1 μm would deposit to a greater extent in the lung periphery than less fine particles with an MMAD of 4 to 5 μm, which would tend to deposit more centrally, as well as in the oropharynx. Since this theoretical model does not take into account a number of other factors that influence aerosol particle deposition in vivo, such as variations in inhalation technique (inspiratory flow, breath-holding time) and airway morphology (narrowing or occlusion caused by disease), in vivo studies are required to ascertain actual sites of aerosol deposition in both healthy subjects and patients with asthma disease. Using an optimized method of metered-dose inhaler use and lung imaging techniques incorporating procedures validated to ensure consistency of drug radiolabeling in the different ranges of particle size, Leach demonstrated that a large proportion of HFA-BDP (51 to 56%) was delivered uniformly throughout the lungs (ie, presumably to peripheral, as well as large- and medium-sized airways) of both normal volunteers and patients with mild asthma with relatively little oropharyngeal deposition (28 to 30%), in contrast to CFC-BDP that deposited mainly in the oropharynx (94%) and large central airways with little peripheral penetration.
The above data predict that patients with moderate asthma who are still symptomatic with low doses of CFC-BDP (up to 400 μg) might have their asthma well controlled with an equally low actuated dose of HFA-BDP, owing to a more efficient delivery of the latter to the lower respiratory tract. Essentially, this prediction has been borne out by the results of a randomized, placebo-controlled study published in this issue of CHEST (see page 343), in which a 400-μg dose of HFA-134a BDP was shown to produce significant benefits (compared with placebo) that were equivalent to those produced by double the dose of CFC-BDP in oral-steroid-responsive patients with moderate asthma whose asthma had not been adequately controlled with 0 to 400 μg/d of inhaled corticosteroids in conventional formulations.

Moreover, the HFA preparation was tolerated at least as well as the CFC formulation of BDP with comparably negligible effects on morning serum cortisol level.

The results of this study imply some advantages of the extra-fine aerosol generated by HFA-134a BDP over the coarser aerosol produced by CFC-BDP. The most obvious advantage is a savings in cost (at least to the manufacturer), since only half the amount of HFA-based medication compared with CFC-based medication would be required to produce the same therapeutic benefit. However, a clinically more meaningful advantage would occur only if the lower dose of HFA-BDP yielded a higher ratio of therapeutic efficacy to side effects. Relatively lower effective doses and substantially reduced oropharyngeal deposition of the HFA preparation should translate into less frequent local side effects (dysphonia, candidiasis) than would occur with CFC-BDP, particularly if high doses of the latter were required, although an add-on spacer device could serve a similar purpose. Of greater importance is the potential for reduced systemic side effects of the extra-fine corticosteroid aerosol (hypothalamic-pituitary-adrenal axis suppression, purpura, osteopenia, ocular effects) as a result of both (1) reduced throat deposition and thus less GI absorption from swallowed BDP (which undergoes incomplete first-pass metabolism by the liver) and (2) the lower total ex-actuator doses needed to achieve comparable efficacy. However, while the total ex-actuator HFA dose may be reduced, the relative amount delivered to the lower respiratory tract appears increased compared with equivalently effective CFC doses. This enhanced lower respiratory deposition could result in an actual increase in systemic bioavailability of the BDP from the HFA preparation owing to greater absorption from the lung, as suggested by data from pharmacokinetic studies that imply the potential for equivalent or even increased systemic side effects from half doses of HFA-BDP compared with CFC-BDP. In contrast, results of a 12-week clinical trial in patients with moderately severe asthma point to a tendency to relatively greater effects on adrenal function from 1,500 μg CFC-BDP than 800 μg HFA-134a BDP in the face of comparable overall efficacy, suggesting a slightly more favorable therapeutic ratio for the HFA preparation. The apparent discrepancy between the latter clinical findings and results of deposition and pharmacokinetic studies might be due to differences in metabolism of BDP absorbed from different sites in the lung and from the gut, possibly leading to differences in the ratio of adrenally active metabolites to unchanged BDP and its nonactive metabolites. Further investigation of the latter possibility is warranted.

Another potential advantage of extra-fine corticosteroid aerosols is their apparently greater accessibility to peripheral airways (≤2 mm in diameter), which appear to be poorly penetrated by conventional CFC-based aerosols. On the basis of indirect physiologic studies, small airways were initially believed to be less affected in asthma than larger airways. However, more recent data indicate that airway inflammation is present in both large and small airways, as well as alveolar tissue, and that airway wall remodeling occurs in small airways, probably accounting for the marked increases in peripheral airways resistance that have been detected by direct measurements in even asymptomatic asthmatics with normal results of spirometry and plethysmographic airway resistance. The clinical significance of small airways involvement in asthma, its contribution to fatal asthma or to the accelerated rate of decline in lung function with age that occurs in asthma, and the consequences of treating (or not treating) the small airways component are as yet unclear. Now that it appears possible to deliver topical anti-inflammatory medication directly to the small peripheral, as well as to the larger more central, airways using extra-fine corticosteroid aerosols, we have an opportunity to assess the potential benefits of this new form of aerosol therapy, in comparison to more conventional coarser aerosols. Ideally, several different methods of assessment might be employed. These include the following: (1) conventional measures of asthma control (symptom scores, rescue medication use, morning peak flow and peak flow variability, airways responsiveness, exacerbation rate); (2) prospectively assessed longitudinal changes in FEV1 (as a reflection of the natural history of asthma); (3) indirect measures of small airways function (extent of regional air trapping as assessed by novel CT imaging techniques, including helical thin-section CT or single photon emission CT following inhalation of a bolus of...
technetium-labeled ultra-fine carbon particles\textsuperscript{15}; (4) bronchial and alveolar inflammation (assessed by BAL); and (5) possibly small airways histopathology (evaluated via transbronchial biopsy specimen\textsuperscript{5}). Results of such studies should provide valuable additional information concerning the clinical significance of small airways involvement in asthma and the impact of anti-inflammatory treatment partially targeted to these airways on the long-term course of the disease.

*Donald P. Tashkin, MD, FCCP
Los Angeles, CA*

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**Surgical Lung Volume Reduction in Emphysema**

**How Much for How Long?**

Lung volume reduction surgery (LVRS) originally proposed by Brantigan and colleagues\textsuperscript{1} and revived by Cooper and colleagues,\textsuperscript{2} has become a new therapeutic option for patients with end-stage emphysema, a disease that is frustratingly difficult to treat. Although LVRS has been greeted with enthusiasm by many physicians, skepticism on the safety and efficacy of this surgical intervention in comparison to conventional medical therapy has arisen.\textsuperscript{3,4}

Recently, a multicenter randomized trial, the National Emphysema Treatment Trial (NETT), has been started in the United States. NETT compares maximal medical therapy with maximal medical therapy and LVRS in patients with advanced emphysema. Four thousand seven hundred patients without other relevant comorbid conditions are randomized into one of the two treatment groups. All patients receive pulmonary rehabilitation regardless of their treatment arm. The objectives of this trial are to determine whether the addition of LVRS to best medical care improves health-related quality of life, reduces shortness of breath, and improves pulmonary function, and exercise capacity. Another question addressed by this project is the impact of LVRS on survival. Admittedly, many questions concerning LVRS remain unanswered and cannot be easily studied because of the inherent methodological problems that are typical for the scientific investigation of the efficacy of surgical interventions.

Even before the results of the NETT will be available, some preliminary conclusions based on published work of experienced groups on both sides of the Atlantic are possible:

- LVRS not only ameliorates health-related quality of life and reduces shortness of breath, but also improves lung function and exercise capacity in many of the carefully selected emphysema patients at a degree that clearly exceeds a placebo effect or even the efficacy of comprehensive pulmonary rehabilitation alone.
- Comparable functional results can be achieved by median sternotomy and by video-assisted thoracoscopic surgery.
Consideration of morphology and distribution of emphysema, as assessed by chest CT scan, seems to improve prediction of postoperative functional outcome as compared with assessment of baseline pulmonary function alone.

In experienced centers perioperative mortality has remained <5% as long as patients with vanishing lungs or far advanced functional impairment and those who are physically deconditioned or suffer from relevant comorbidity are excluded.

In the majority of patients, none or only minimal and presumably clinically not relevant improvement in gas exchange, i.e., oxygenation, is observed after LVRS. A fundamental and yet unresolved issue is the lack of accurate information on the amount of tissue removed by the surgeon. This precludes studies, compulsory in pharmacological trials, on the dose effect relationship of LVRS. Furthermore, the inclusion and exclusion criteria, which serve as the basis for patient selection, are rather arbitrary and based on pathophysiological reasoning and speculative assumptions. The utility of selection criteria, i.e., their potential to predict success or failure and hence to choose suitable candidates for LVRS is difficult to study by randomized controlled trials. Therefore, selection criteria are inferred from retrospective analyses of the correlations between various preoperative patient variables and functional outcome. It is obvious that this methodology is much less powerful than a randomized controlled trial.

LVRS is a palliative intervention, which may be offered as a therapeutic option to highly compliant patients not helped by the best medical therapy. The impact of LVRS on survival, also an exciting question, seems of secondary consideration in this population of desperate patients. Nevertheless, it is of importance to gather information on the long-term survival (arbitrarily >6 months) in this selected group with advanced pulmonary emphysema, because it is inappropriate to expose patients, particularly those without relevant benefit from LVRS, to the risk of premature death as a remote consequence of this procedure.

Therefore, any data, such as those of Brenner and colleagues (see page 390 in this issue) are highly welcome. This study represents the first report on the long-term survival of a large cohort of patients after bilateral staple LVRS. Survival information is presented in 256 patients for a median follow-up time of 623 days. Data were available in 95% of the patients treated by a single group of physicians over a 3½ year period. Assuming that all 12 patients with missing information have expired—“worst case scenario”—the 1-year survival was 83 ± 2.4% and the 2-year survival 76 ± 2.9%. The following variables were found to correlate with a higher probability of survival: age ≤ 70 years, baseline FEV₁ > 0.5 L, PaO₂ > 54 mm Hg and an improvement in FEV₁ > 0.56 L after LVRS. It is well known that patients with severe COPD have a markedly reduced life expectancy and that a low FEV₁ and a low PaO₂ are reliable predictors of a grim prognosis. However, it is not appropriate to compare the survival of patients after LVRS with the survival of historical, conservatively treated control groups. Because no matched control group of nonoperated patients was included in the present study, the crucial question, if LVRS has a positive or negative impact on survival of patients with advanced emphysema, cannot be answered. Presumably, such answers will not be available until the completion of the NETT.

Also important and hitherto not well studied, is the question of how long and to what degree the improvement of clinically relevant objective parameters will last after the surgical intervention. Published results of small patient numbers are notoriously difficult to interpret and may be considerably biased because of a substantial loss of patient follow-up. Analysis of our own results suggests that maximal improvements in lung functions are achieved at 3 months after surgery and will start to decline after 1 year.

How much for how long? This question needs also to be addressed under the perspectives of cost-effectiveness. Admittedly, LVRS is an expensive procedure. So far it is unknown if this surgical therapy will reduce the cost for hospitalizations and other expenses associated with emphysema.

Because many important aspects of LVRS remain without answers for the time being, this type of surgery should be restricted to groups who enroll their patients in sound, prospective, scientific studies and who are willing to obtain close and as much as possible complete follow-up of their patients’ function and survival.

Erich W. Russi, MD, FCCP
Zurich, Switzerland

Professor of Medicine, and Head, Pulmonary Division, University Hospital.
Correspondence to: E. W. Russi, MD, FCCP, Pulmonary Division, University Hospital, Rämistrasse 100, CH-8091 Zürich; e-mail: pneuruss@usz.unizh.ch

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Asbestos Exposure, Asbestosis, and Lung Cancer

The first systematic assessment of whether exposure to asbestos or the fibrotic response to asbestos fiber inhalation (asbestosis) is the cause of excess lung cancer was raised in a 1949 report.1 Lung cancer occurred in 35 of 235 (13.2%) autopsied deaths where asbestosis was identified. In 1955, the first mortality study of a cohort of asbestos-exposed workers2 showed that among 105 deaths, lung cancer was found in 18 instances, 15 times in association with asbestosis. In the 3 without asbestosis, the latencies (time from first exposure to death) were 2, 12, and 11 years, respectively.

Twelve years have passed since Browne3 reviewed the epidemiologic and biological evidence that justified the hypothesis that lung cancer in asbestos exposed workers was due to asbestosis and not to asbestos exposure per se. What has come to be known as the “Browne hypothesis” in some quarters continues to be debated. Browne hypothesized that effect occurred because asbestos fibers become trapped in areas of fibrosis, disrupt the normal clearance mechanism, and adsorb and concentrate cigarette smoke and/or fibrotic scar tissue, which becomes the focus for carcinogenesis as in other “scar cancers.” In this issue of CHEST (see page 536) Weiss has reviewed 39 English language reports of cohorts exposed to asbestos in an attempt to address this question.

Weiss has presented relatively detailed data on seven cohorts (or subcohorts within larger population studies) who were without an increase in asbestosis or an excess of lung cancer deaths (mean relative risk for lung cancer for these seven studies = 1.00) and contrasted this with data from the remaining cohort studies where workers were recognized to have both asbestosis and an increased rate of lung cancer mortality. These seven reports have their own weaknesses when used as members of a comparison group, and in some instances their inclusion appears forced.

Of the seven, the mortality experience of two cohorts is relatively small and inadequate to identify the presence or absence of a relationship between asbestosis and lung cancer.4,5 In the first of these,4 a female cohort with the least mean exposures within the entire population under study (less than one tenth of the heavily exposed group) showed no increase in lung cancer or asbestosis. However, men grouped in the same exposure category had a standard mortality rate (SMR) for pneumoconiosis of 2.98 (but no increase in lung cancer risk), implying that even though both gender cohorts were in the same exposure category, the presence of dust-induced fibrosis in the male population means that the asbestos exposure in the women’s cohort was likely to be, on average, much less. Two reports6,7 reflect populations with brisk turnovers, making it very difficult for investigators to identify a relationship that might be attributable to workplace exposures. In the first,6 over half of the population studied was employed for less than 2 years, and three quarters worked for less than 4 years. In the second,7 more than half of the workers had less than 1 year of tenure at the factory and the airborne dust levels were low due to the wet nature of the cement making process.

In work by Peto and colleagues8 and McDonald and colleagues,9 subcohorts with lesser durations of exposure within a much larger cohort were selected. In both reports, these two illnesses occur at a greater than expected rate as the duration of exposures and latencies are increased. McDonald and colleagues9 reported the mortality experience of 3,641 workers (1,267 died) employed at a chrysotile asbestos friction products plant and noted an increase in asbestosis deaths, but even after excluding workers with less than 1 year of employment (paradoxically, those with the highest SMR), there was an increase in respiratory neoplasms. The SMR for respiratory cancer after workers with less than 1 year of employment were excluded was 136.7. Six of the 12 dead coded as pneumoconiosis had worked less than 1 year in this workplace and only 3 of 12 had an accumulated exposure of 10 million particles/ft²/yr. None of the death certificates of these 12 reported asbestosis.

Importantly, two additional references complicate the hypothesis that excess lung cancer risk in worker cohorts exposed to asbestos occurs only among those with asbestosis. Work by Liddell and colleagues10 cited in Weiss’s Table 4 (see page 538) shows a substantially elevated risk for lung cancer when chest radiograph abnormalities other than small opacities

were reported. In 11 of the 37 with other abnormalities, a “large opacity” was described (an unusual feature of asbestos exposure and likely to be associated with advanced asbestosis in those with the most extensive exposures). In the remaining 26, there is no description of these other abnormalities. However, based on Table 6 in Liddell’s article, these workers were likely to have uncalcified or calcified pleural plaques or additional symbols.

None of these papers reviewed in detail above were designed to define the interaction between asbestos exposure, asbestosis, and lung cancer, nor were the great majority of the additional papers reviewed by Weiss and described in the text.

Hillerdal\textsuperscript{11} reported a large number of individuals with pleural plaques in a single cohort, and added a lesser number of workers (without malignancy, serious lung disease, or other serious illnesses) from different populations who had been accidentally recognized to have this finding in an attempt to define the risk for lung cancer. This was not a prevalence study regarding the number with pleural plaques in a population, but rather a chance to define the risk for lung cancer among those with pleural plaques. Among those with pleural plaques independent of asbestosis, the SMR for lung cancer was 1.4. The presence of plaques and asbestos-induced fibrosis made this relationship even more apparent. We recognize Weiss’s concern regarding potential bias, but in view of the fact that all the cases came from the same national population and all were compared with the same national rates, we cannot identify the bias. Furthermore, Weiss’s calculated Relative Risk for workers in the age group 40 to 69 years appears to be in error, as age was mistaken for years from first exposure.\textsuperscript{11} (Table 7)

There is no doubt that patients with clinical and radiographical evidence of asbestosis have a high risk of dying from lung cancer. Both asbestosis and lung cancer are dose-related (Figs 4 and 5 in Weiss’s report are clear examples of this). The great majority of studies that have serially evaluated sufficiently exposed populations over an adequate time have verified this relationship. It is only logical then, that when exposures are less (as in some in the series of comparisons chosen by Weiss) or for a relatively lesser duration, if follow-up is short, or if the number of deaths are small, neither asbestosis nor an excess rate of lung cancer mortality is likely to be recognized. The presence of both asbestosis and an excess of lung cancer in the majority of reports presented by Weiss are consistent with a dose-related effect. That the recognition that pleural abnormalities (another marker of clinically important asbestos exposure) may well be associated with an increased risk of lung cancer leads one to speculate that lung cancer can occur at an excessive rate in populations without clinically recognized asbestosis.

Thus, we can agree that both asbestosis and asbestos-related lung cancer occur at a rate commensurate with exposures, however, it appears unlikely that epidemiologic studies are adequate to convince all parties that asbestosis must be recognized in a population to place the members of that cohort at excessive risk for lung cancer.\textsuperscript{12} Perhaps the issue can be solved by molecular biology techniques. Asbestos fiber inhalation results in inflammation and the release of active oxygen species which may induce alterations in genotoxicity and cell replication, features which are likely to play critical roles in initiation, promotion, and progression of lung cancers. In this context, fibrosis is the end-product of inflammation, but the events are thought to be dependent on inflammation.\textsuperscript{13} On a molecular level, whether inflammation is sufficient to induce malignancy, and what mechanisms of fibrosis or fibrogenesis are essential for the initiation of transformation is not known.\textsuperscript{14}

Experts\textsuperscript{15} have estimated that the relative risk for lung cancer is roughly doubled for cohorts exposed to asbestos fibers at a cumulative exposure of 25 fiber-years or with an equivalent occupational history, at which level level asbestosis may or may not be present or detectable (in Weiss’s report, Figs 4 and 5 show an increased SMR for lung cancer in the face of cumulative asbestos exposure rates likely insufficient to induce asbestosis). Asbestosis is an indicator of high exposure and contributes additional risk to lung cancer beyond that conferred by sufficient asbestos exposure alone. In our opinion, the hypothesis that the excess lung cancer risk in worker cohorts exposed to asbestos occurs only among those with asbestosis is insufficient to explain this heightened risk of carcinogenicity.

\textbf{Daniel E. Banks, MD, FCCP}  
\textbf{Mei-lin Wang, MD}  
\textbf{John E. Parker, MD}  
\textbf{Morgantown, WV}

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Carbon Monoxide Poisoning

A Disease of a Thousand Faces

Carbon monoxide (CO) is an odorless, colorless, and tasteless product of incomplete fuel combustion, whose ubiquitous but silent presence accounts for it being the leading cause of poisoning death in the United States. CO poisoning may account for as many as 5,000 deaths each year in the United States, with an additional 10,000 patients seeking medical attention for toxic exposure.1 CO poisoning may be deliberate (as reported in this issue of CHEST [see page 580]) or accidental; in the latter case, it may be acute,2 subacute,3 or chronic.4 CO poisoning from idling automobiles has occurred even with open garage doors or windows, suggesting that passive ventilation may not be adequate to reduce the risk of CO toxicity in semi-enclosed spaces. Poisoning has also occurred in working or living quarters adjacent to garages.5 Snow-obstructed motor vehicle exhaust systems may result in outdoor CO poisoning.6

Accidental CO poisoning can also occur in some unexpected venues: in the tragic case of tennis star Vitas Gerulaitis, in a summer cottage with improper venting of a pool heater into the air conditioning duct7; in indoor ice-skating rinks8; outdoors on tractors9 and motor boats.10

The symptoms and signs of CO poisoning are varied. Nonspecific symptoms include headache, nausea, vomiting, fatigue, and malaise. Because of the fixed oxygen needs of the circulatory and nervous systems, cardiovascular and neurologic symptoms are common and include symptoms and signs of myocardial ischemia, hypotension, congestive heart failure, arrhythmias, mental confusion, clumsiness, emotional lability, impaired judgment, diminished visual acuity, stupor, and coma. Patients with loss of consciousness are at risk of developing delayed neuropsychiatric symptoms, which vary from mild intellectual impairment or personality changes to specific neurologic deficits such as deafness, blindness, and parkinsonism.12 However, every organ system may be affected either primarily or secondarily to coma (pulmonary aspiration, crush injury with renal insufficiency and peripheral neuropathy). Pathognomonic physical findings of flame-shaped retinal hemorrhages or cherry-red skin are specific but not sensitive signs of CO poisoning.3 Hence, because of the insidious, protean, and often nonspecific manifestations of CO toxicity, a high level of suspicion is needed, particularly when individuals or groups living or working together present with an afebrile influenza-like illness or are found with unconsciousness of uncertain etiology.13-15

CO diffuses rapidly across the alveolar membrane and binds reversibly to hemoglobin with a 200-fold greater affinity than oxygen. Hence, exposure to even low concentrations of CO can result in a clinically significant diminution in the oxygen-carrying capacity of the blood. Moreover, the presence of carboxyhemoglobin shifts the oxyhemoglobin dissociation curve to the left; tissue oxygen tension must fall to lower levels before oxygen can be released by oxyhemoglobin. This combined effect of reduced blood oxygen-carrying capacity and impaired release of oxygen at the tissue level results in oxygen starvation more severe than an equivalent reduction in Po2 or hemoglobin. Tissue hypoxia is exacerbated by CO binding to the cytochrome system, myoglobin, guanylate cyclase, nitric oxide synthetase, and endothelial and platelet dysfunction.4 The resultant severe tissue
hypoxia causes anaerobic metabolism and lactic acidosis. In addition, CNS manifestations may be exacerbated by the release of leukocyte proteases, free radicals, and alterations in excitatory amino acids.1

Clinical manifestations of CO poisoning are related to the blood carboxyhemoglobin level, time course of exposure, respiratory rate, age and health of the victim, and concomitant medications (affecting hepatic enzymes) or toxins (drugs, alcohol, etc).1 The carboxyhemoglobin level is dependent upon the ambient CO level, which is determined by the source of CO production, meteorologic and climatic factors, size of space, and adequacy of ventilation.4 Arterial blood gas measurement reveals metabolic acidosis, a normal PO2, variable PCO2, and decreased oxygen saturation when measured by co-oximetry. Calculated oxygen saturation or that measured via pulse oximetry may be in the normal range.

In this issue of CHEST, Vossberg and Skolnick report the changing face of intentional CO poisoning via automobile exhaust due to the presence of a catalytic converter. With the institution of the use of catalytic converters, smog, “freeway” angina due to CO poisoning,16 and successful suicides have decreased.17–19 Suicidologists have documented a dramatic decrease in suicide attempts using domestic gas in the United Kingdom between 1963 and 1971, concomitant with the conversion to natural gas with reduced CO content, and a decline in the rate of car exhaust suicides in the United States following the introduction of catalytic converters in the 1960s17; these unfortunate souls want to terminate, not exacerbate, their suffering. However, the syndrome of CO poisoning via automobile exhaust may change further in the future: catalytic converters have been implicated as a significant contributor to global warming.20 If the automobile catalytic converter is further modified, so again may be the face of CO poisoning.

Jeffrey Fisher, MD, FCCP
New York, NY

Clinical Associate Professor of Medicine, New York Presbyterian Hospital–Weill Medical College of Cornell University.
Correspondence to: Jeffrey Fisher, MD, FCCP, 311 East 72nd Street, New York, NY 10021

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