Benefits of Cardiac Rehabilitation and Exercise Training

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ANNOUNCEMENT

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It's Time To Pick the Low-Hanging Fruit

The epidemic of lung cancer continues unabated. Success in preventing teenagers from becoming addicted to tobacco has been effectively thwarted by the continued and unrelenting efforts of the tobacco industry. Today, approximately 49-million people continue to smoke in the United States. Although there are more quitters today than ever before, many persons have been exposed to enough carcinogens from tobacco to remain at excess risk, probably for their lifetimes. In fact, more lung cancer is diagnosed in former smokers today than in active smokers.[1] Even if we had unexpected and miraculous success in reducing smoking in the next few years, lung cancer would not substantially decline for > 20 years.[1]

The dogma against lung cancer screening that has been promoted for > 2 decades has led to indifference in case finding, and essentially no efforts in screening. This policy comes from studies conducted in the 1970s that have been questioned.[2,3] Many cancers were missed due to limitations of the screening techniques that were employed.[3] We know exactly who gets lung cancer, and where the yield of new diagnostic techniques would be high. The highest risk is in smokers with any degree of airflow obstruction. Approximately 2% of these individuals have lung cancer at the time of diagnosis by sputum cytology.[4] Approximately 25% of these patients have moderate to severe dysplasia, which are probably precancerous lesions.[4] Cancers that are found by sputum cytology are mostly central squamous carcinomas. CT scans help to identify peripheral nodules that are most often adenocarcinoma. Today, new helical CT scans are becoming more widely available. They should be employed today in patients at highest risk. Even a standard chest radiograph can improve detection and survival.[5]

Earlier, we showed in a community-based case finding study that both squamous and adenocarcinomas can be found when they are roentgenographically occult. When treated by surgery or radiotherapy, the 5-year survival is $> 50\%$.[6] Most of these patients had coexisting airflow obstruction. The Lung Health Study, which focused on mild to moderate COPD, revealed a 1% death rate in 5 years from unexpected cancer.[7] Late follow-up now reveals 2% lung cancer in this group of middle-aged smokers with only mild degrees of airflow obstruction (D. Miller, MD; personal communication; February 1999). The presence of airflow obstruction yields four to six times more lung cancer than in matched patients with normal airflow.[8,9]

When lung cancer is diagnosed in early stages, the survival is excellent. This is the case for other common cancers, such as breast, colon, uterine, and prostate cancer, all of which are aggressively pursued by appropriate screening techniques where reimbursement is no longer a question. We need the same for lung cancer. A very recent study offers a pragmatic approach to lung cancer screening via high-resolution CT scanning.[10] The yield rate of diagnosis of small noncalcified malignant lesions was increased fourfold over standard chest radiology. When early small lesions are resected, the survival can be $\geq 80\%$.[10] This study was done in smokers of > 10 pack-years who were > 60 years old.

I believe the evidence strongly indicates that smokers > 40 years old who have smoked ≥ 30 pack-years along with airflow obstruction, as measured by simple spirometry, should have a combination of sputum cytology (done in a qualified laboratory) and a low-radiation helical CT scan to identify otherwise occult lung cancer. Fiberoptic bronchos-

copy can locate many lesions, but fluorescent endoscopy is a more sensitive technique for identifying and treating early-stage lung cancers.[11] If we follow this simple approach, we will find that we can identify and cure lung cancer in its early stages. It is likely that together, the techniques now available to us will yield approximately 90% of early-stage carcinoma. We can learn the cost of early lung cancer treatment and compare it with the costs of treating lung cancer as it is usually diagnosed based on symptoms or from chest radiographs taken for measures other than to diagnose lung cancer. These costs are approximately $50,000 per patient, with a survival rate of only 22% after 2 years.[12] The costs of treating early-stage lung cancer remain to be determined. A reasonable estimate would be no more than $10,000 per patient, including diagnostic costs and resectional surgery. Here the survival rate would be at least 80% at 5 years.[13]

It could be argued that this approach will miss some lung cancers. Certainly this is likely to be the case, but we are missing most lung cancers now through a policy of nonscreening that has blocked progress.[14] Case findings in high-risk patients will give a high yield of lung cancer, as has been suggested before.[15] This is the low-hanging fruit that can be readily harvested by using new lung cancer diagnostic techniques at virtually all major hospitals in the United States today. Once we succeed in this harvest, we can climb higher into the tree!

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Experience and Reason

> "In medicine one must pay attention not to plausible theorizing but to experience and reason together . . . I agree that theorizing is to be approved, provided that it is based on facts, and systematically makes its deductions from what is observed . . . But conclusions drawn from unaided reasons can hardly be serviceable; only those drawn from observed fact."
>
> Hippocrates

Epoprostenol (prostaglandin I2, prostacyclin) is a potent vasodilator and inhibitor of platelet aggregation produced by vascular endothelium. Epoprostenol decreases pulmonary vascular resistance and increases cardiac output and systemic oxygen delivery when administered acutely to patients with primary pulmonary hypertension. Furthermore, continuous IV epoprostenol has been demonstrated to significantly improve quality of life and hemodynamics as well as increased survival in patients with severe primary pulmonary hypertension who fail conventional medical therapy,[1] *ie*, warfarin anticoagulation and oral vasodilators. Pulmonary hypertension is also associated

with other conditions, including collagen vascular disease, congenital heart disease, liver disease, and thromboembolic disease. However, treatment of pulmonary hypertension associated with these other conditions has not been successful with conventional therapy. As opposed to patients with primary pulmonary hypertension in whom approximately 20% of patients respond with acute vasodilator drug testing and who can be effectively treated with conventional medical therapy,[2] the experience reported by Robbins et al in the current issue of *CHEST* (see page 14) as well as previous reports by Sanchez et al[3] demonstrate a significantly smaller proportion of patients acutely responding with vasodilator testing. Although Sanchez et al[3] reported that 15 of 57 patients with pulmonary hypertension associated with connective tissue disease had a significant fall in total pulmonary resistance with acute vasodilator testing, only 4 had a combined fall (> 20%) in both pulmonary arterial pressure and total pulmonary resistance (7% as opposed to the reported 20% acute response rate with primary pulmonary hypertension patients). Furthermore, despite anecdotal case reports[4,5] demonstrating acute pulmonary vasoreactivity in some patients with pulmonary hypertension associated with collagen vascular diseases, especially with CREST (*c*alcinosis, *R*eynaud's phenomenon, *e*sophageal motility disorders, *s*clerodactyly, and *t*elangiectasia) patients, long-term efficacy has not been demonstrated. These data confirm the lack of efficacy with conventional medical therapy in patients with pulmonary hypertension associated with connective tissue disease. Although pulmonary hypertension occurs in only 0.5 to 14% of cases with systemic lupus erythematosus,[6–9] and much more rarely in patients with rheumatoid arthritis, Sjögren's syndrome, and dermatomyositis, the prevalence varies from 2.3 to 35% in scleroderma[10–12] and may be as high as 50% in the CREST variant.[11] Furthermore, the reported 2-year survival rate of only 40% in patients with CREST syndrome and pulmonary hypertension, compared with 88% in patients with CREST syndrome without pulmonary hypertension, underscores our need for effective therapy with these patients.[10] In addition, patients with connective tissue diseases are often excluded from lung transplantation because of previous immunosuppressive therapy and possible involvement of other organs, such as the kidneys or liver with the underlying disease.

The experience with chronic IV epoprostenol in patients who have pulmonary hypertension associated with collagen vascular disease[13–17] remains limited despite the demonstrated efficacy with primary pulmonary hypertension,[1] and more recently with the "scleroderma spectrum of diseases" associated with pulmonary hypertension[18] (both demonstrating efficacy with 12-week randomized trials). Robbins et al report their experience with chronic IV epoprostenol in patients with pulmonary hypertension associated with systemic lupus erythematosus. Although their report is limited to a case series of six patients, epoprostenol was demonstrated to be effective for the treatment of pulmonary hypertension in the patients. Regardless, for the time being, we should be "cautiously optimistic" as we await longer follow-up with increased number of patients who have systemic lupus erythematosus associated with pulmonary hypertension (as well as other conditions associated with pulmonary hypertension) before we say that chronic IV epoprostenol is appropriate therapy for these patients based on overall risk-benefit considerations. Whether there will be increased adverse events in patients with collagen vascular disease treated with chronic epoprostenol compared with primary pulmonary hypertension patients remains unknown. The experience of Humbert et al[13,15] suggests less efficacy and increased adverse events in patients with pulmonary hypertension associated with collagen vascular diseases compared with primary pulmonary hypertension patients (reported by McLaughlin et al[14]). Patients with a relative degree of immunosuppression due to the collagen vascular disease and its medical management have an increased risk of infection. In addition to catheter-related infections (as observed in primary pulmonary hypertension patients[14]), Humbert et al[13] reported severe sepsis unrelated to the drug delivery system, including 3 of 17 patients (18%) developing fatal cutaneous infections. In addition, 4 of the 17 patients (24%) were anticardiolipin positive with no history of thromboembolic disease; 2 of these patients developed sepsis-related thrombosis after initiation of epoprostenol. Their reported high complication rate underscores our need for an improved delivery system of epoprostenol or its analogs.[19,20] This rate of fatal infections as well as catheter-related thromboses is uncommon in primary pulmonary hypertension.

More recently, Sitbon et al[16] observed significantly less efficacy with long-term epoprostenol in 25 patients with pulmonary hypertension associated with connective tissue diseases compared with 132 primary pulmonary hypertension patients: the 1-, 2-, and 3-year survival rates were 56% vs 83%, 50% vs 75%, and 21% vs 70%, respectively. This poor outcome occurred despite clinical and hemodynamic improvement at 6 weeks after initiation of chronic IV epoprostenol.[13] Coughlan et al[17] also recently reported a significantly poorer outcome with sclero-

derma-associated pulmonary hypertension compared with primary pulmonary hypertension. As compared with significant decreases in pulmonary artery pressure in primary pulmonary hypertension patients treated with chronic IV epoprostenol, Coughlan and colleagues[17] did not observe significant improvement in pulmonary hypertension nor prognostic benefit in the scleroderma patients treated with chronic epoprostenol. Furthermore, the improvement in pulmonary vascular resistance had no influence on overall survival in their series of 35 patients with scleroderma-associated pulmonary hypertension. These data reinforce our need for continued caution as we consider treating more and more patients with chronic IV epoprostenol. These recent reports also demonstrate our need for longer follow-up with more patients before we "assume" that chronic IV epoprostenol will be as efficacious for patients whose pulmonary hypertension is associated with collagen vascular disease as it is for patients with primary pulmonary hypertension. We need to remember what Hippocrates said and continue to "pay attention to experience and reason together."

In summary, although the pathologic changes in the lung appear to be similar in patients with pulmonary hypertension associated with systemic lupus erythematosus and patients with primary pulmonary hypertension, I do not believe we can say at this time that the pathogenesis and pathophysiology in these two groups of patients is the same and therefore the response with various medical therapies including continuous IV epoprostenol will be the same. A difference in pathogenesis is suggested by a case report[20] demonstrating improvement in pulmonary hypertension with immunosuppression, *eg*, prednisone and cyclophosphamide, in a patient with lupus. Significant improvement has been observed (M. Humbert, MD; personal communication; August, 1999) in several other lupus patients treated with immunosuppressive therapy, *ie*, specifically cyclophosphamide. Further investigation is needed to explore this therapeutic option. If we suspect that primary pulmonary hypertension or pulmonary vascular disease associated with collagen vascular disease results from an "unknown" injury in immunogenetically susceptible individuals, the "injury" may be different for systemic lupus erythematosus patients than for other groups of patients who develop similar pulmonary vascular changes in their lungs, *eg* pulmonary hypertension associated with congenital heart disease, scleroderma, portal hypertension, or HIV, etc. Unfortunately, it does not appear likely that a randomized clinical trial will be performed with chronic epoprostenol in patients who have associated conditions other than the "scleroderma spectrum of disease," which has already been carried out with demonstrated efficacy.[18] We therefore need to carefully and critically evaluate our patients and, after instituting therapy, continue to follow all patients closely. As we do this, we need to remain cautious regarding initiating continuous IV epoprostenol in patients in whom adverse events may be greater than previously reported in patients with primary pulmonary hypertension. Unfortunately, despite the demonstrated efficacy of epoprostenol in primary pulmonary hypertension, as we gain more and more experience with this therapeutic modality, we often are only delaying an inevitable fatal outcome for many patients with primary pulmonary hypertension. Although we should continue to treat patients with chronic epoprostenol, we need to remain cautious regarding their long-term outlook.

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Benefits of Cardiac Rehabilitation and Exercise Training

We and others[1–4] have demonstrated the benefits of cardiac rehabilitation and exercise training programs on coronary risk factors, including lipids, obesity indices, exercise capacity, and adverse psychological factors (especially depression and hostility), as well as significant reductions in hospitalization costs and overall cardiac morbidity and mortality. These benefits have been noted in several subgroups of patients, including elderly, female, and obese patients, those with high or low baseline exercise capacity, as well as diabetic patients.[1,2,5–11] The report in this issue of *CHEST* by Dylewicz et al (see page 47) extends these benefits to glucose metabolism and insulin resistance following exercise training in patients after bypass.

Although the program used by Dylewicz et al was very short (only 3 weeks, compared to the usual 12-week phase II cardiac rehabilitation and exercise training programs), they still demonstrate significant improvements in work capacity. Numerous studies indicate that parameters of exercise capacity and fitness predict the risk of major cardiac events and mortality, and changes in fitness over time are also very predictive of subsequent risk.[1,2,12–14] These data may be particularly applicable to groups with lower baseline exercise capacity, such as elderly,[5,6] female,[7] and diabetic patients,[11] as well as those with adverse psychological profiles.[11,15–18]

Substantial data indicate that a large majority of coronary patients have an insulin resistance syndrome, characterized by impaired glucose metabolism, hypertension, abdominal obesity, hypertriglyceridemia, and low levels of high-density lipoprotein (HDL) cholesterol.[2] We have previously demonstrated that diabetic coronary patients not only have lower exercise capacity than nondiabetics, they also have more hypertension, obesity, and higher triglycerides and lower levels of HDL cholesterol.[11] The improvements in glucose metabolism and insulin resistance, as noted in the present report with only 3 weeks of exercise training, further support data that exercise training improves insulin sensitivity in a broad range of coronary patients, with or without definite diabetes.

Cardiac rehabilitation and exercise training usually result in small but statistically significant improvements in lipids.[1,2,5–11,15–21] Although only total cholesterol significantly fell in the short-term study by Dylewicz et al, most of our studies show more significant improvements during the 12-week programs, especially in reducing triglycerides and increasing levels of HDL cholesterol.[1,2,5–11,15–21] Although most studies show only small reductions in low-density lipoprotein (LDL) cholesterol, LDL heterogeneity may improve with exercise training, which may transform the LDL particle from a small, dense (pattern B), and more easily oxidized and atherogenic LDL into a larger and more fluffy (pattern A) LDL, which is less atherogenic.[21,22]

The impact of obesity in cardiovascular disease is now being appropriately and increasingly recognized by many major societies, including the American Heart Association.[23] The prevalence of obesity in patients with coronary artery disease approaches 40%, and obesity has adverse effects on many coronary risk factors, including adverse effects on plasma lipids (especially increasing levels of triglycerides and reducing levels of HDL cholesterol), raising arterial pressure and left ventricular hypertrophy (even independent of arterial pressure), possibly reducing exercise capacity, and worsening insulin

sensitivity.[2,8,9,23] In addition to all of these effects, data indicate that obesity is an independent coronary risk factor.[24] Studies of cardiac rehabilitation and exercise training generally report small but statistically significant improvements in obesity indices (such as weight, body mass indices, and percent body fat).[1,2,6–11] In fact, obese patients who lost ≥ 5% body weight with cardiac rehabilitation had significantly greater improvements in all of their lipid parameters and exercise capacity compared to obese patients who failed to lose weight.[9]

Finally, we believe that behavioral and psychological factors, especially symptoms of depression and hostility, have largely been ignored by the medical and cardiology communities. We and others have demonstrated that depression symptoms are present in nearly 20% of coronary patients, and hostility symptoms are present in nearly 15%; these patients have more marked benefits following cardiac rehabilitation programs.[15–18] Since substantial data indicate that this psychological distress is a risk factor for coronary disease and affects the recovery process following coronary events, reductions in parameters of psychological distress should markedly improve coronary risk. We previously demonstrated that diabetic patients had a higher incidence of depression (26% vs 14%) compared to nondiabetics, and also had more somatization and lower scores for components of quality of life than nondiabetics.[11] Following cardiac rehabilitation, besides the benefits in insulin sensitivity described by Dylewicz et al and the benefits on coronary risk factors that we previously published,[11] the incidence of depression was reduced in diabetic patients by 67% and, ultimately, was equal to the 9% prevalence found in the nondiabetic group after rehabilitation. These diabetic patients also had marked benefits in anxiety, somatization, and quality of life components.

Therefore, we agree with Dylewicz et al regarding the benefits of cardiac rehabilitation and exercise training programs, especially when extended well beyond just 3 weeks, to markedly improve overall coronary risk in the secondary prevention of coronary artery disease. Greater efforts are needed to increase referrals, attendance, and "cost-effectiveness" of this underused but valuable therapy.[25]

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Treatment of Multifocal Atrial Tachycardia by Treatment of Pulmonary Insufficiency

Or Is it Vice Versa?

"He is the best physician who knows the worthlessness of the most medicines."

Benjamin Franklin, Poor Richard's Almanac

In this issue of *CHEST*, Ueng et al (see page 52) use radiofrequency energy to modify or control the ventricular response to multifocal atrial tachycardia (MAT) in the setting of COPD, for the most part avoiding drugs that might exacerbate lung or heart failure. Their 13 patients did not receive mechanical ventilation, they were not given very high doses of theophyline, and they did not have uncorrected blood gas disturbances. Ventricular rate was immediately reduced from an average of 145 beats/min to 89 beats/min (one patient later required a pacemaker; one required a second procedure). Symptoms and quality of life improved at 6-month follow-up, as did left ventricular ejection fraction. Serum theophyline levels, FEV_1, and FVC were unchanged, and do not explain the better quality of life or that most patients did not have recurrence of MAT, even transiently when searched for on a Holter monitor.

MAT presumably results from right atrial hypertension and distension, in turn resulting from pulmonary hypertension. At first glance, the latter is simply the result of the pulmonary disease. However, in the obstructive pulmonary disease population there is often concomitant left ventricular disease, whether from coronary artery disease, systemic hypertension, or aortic stenosis. Indeed, left ventricular failure frequently accompanies the MAT,[1–3] although hemodynamic and other functional data are largely lacking. Hazard and Burnett,[4] half of whose patients had clinical evidence of congestive heart failure, found the average pulmonary capillary wedge pressure to be elevated (15.5 + 2.1 mm Hg). Further, there is abnormal left ventricular filling in cor pulmonale.[5] Thus, elevated left ventricular diastolic and pulmonary capillary pressure can contribute to the pulmonary hypertension, ultimately expressed as MAT.

Moreover, there are two ways that MAT can contribute to elevation of left ventricular diastolic pressure and thereby to pulmonary hypertension (thereby facilitating MAT, a vicious cycle). First, tachycardia limits the portion of time spent in diastolic filling, especially elevating left atrial and pulmonary capillary pressure when filling is limited by left ventricular disease. Second, prolonged bouts of tachycardia can cause cardiomyopathy. In animals, sustained rapid pacing causes deterioration of ventricular function within a day, with end-stage heart failure within 3 to 5 weeks, largely reversible; in humans, reversal of cardiomyopathy with rate or rhythm control of chronic supraventricular tachycardia is not uncommon.[6]

If MAT indeed contributes to pulmonary dysfunction by these mechanisms, then control of the ventricular response to MAT should not only improve pulmonary symptoms, it should make paroxysms of the arrhythmia less frequent or sustained (interruption of the vicious cycle). Perhaps that is why Ueng et al saw few and transient episodes of MAT after radiofrequency modification of AV conduction. The trick is to control ventricular rate without hampering left ventricular or pulmonary function, which can be problematic with both beta- and calcium blockers; antiarrhythmic drugs notoriously worsen left ventricular function; amiodarone causes pulmonary fibrosis; and digitalis is insufficient when there is sympathetic stimulation.

However, returning to the rapid ventricular response to MAT, we postulate that MAT is facilitated by pulmonary dysfunction in turn exacerbated by the fast ventricular rate in MAT and by the drugs used for its control. Ueng et al describe a treatment that interrupts this vicious cycle. Radiofrequency modification of AV conduction during an episode of MAT improved quality of life in their patients disabled from obstructive pulmonary disease. In a sense, these were not paired

long-term observations on AV modification and each patient did not serve as his or her own control in terms of the ventricular response; rather, the arrhythmia went away. One could argue therefore that AV modification of the ventricular response to MAT could not explain patient improvement if in fact the MAT was no longer problematic. On the other hand, one can argue that modification of the ventricular response to the MAT actually eliminated the arrhythmia; otherwise, the rapid ventricular rates in response to MAT would have caused the arrhythmia to be sustained or recurrent because of exacerbated pulmonary hypertension secondary to tachycardia-induced left ventricular dysfunction. A simpler explanation for patient improvement would be the avoidance of drugs that are deleterious to pulmonary or ventricular function. Both explanations are simultaneously attractive, because radiofrequency modification of AV conduction both eliminates the need for drug control and is quite effective.

There are problems with accepting the results of Ueng et al, even if our explanation for the amelioration of MAT is held tenable. Their patients did not serve as their own controls in terms of MAT frequency, in that we do not know the arrhythmia frequency in the 6 months prior to the study. There were no controls denied AV modification, and perhaps better treatment of obstructive lung disease (study patients do tend to receive more attention) explains both improved symptoms and less MAT. But even so, the nagging question remains as to whether better pulmonary function resulted from elimination of MAT, and not vice versa.

The role of radiofrequency modification of AV conduction in refractory MAT therefore requires more controlled study for confirmation. For example, a control group would have antiarrhythmic or AV blocking drugs continued after the procedure in a double-blinded fashion. Comparison of pulmonary function, blood gases, potassium, and magnesium needs to be done in a structured design. Objective measures of function could include exercise performance, as a 6-min walk test. Perhaps the procedure should be extended to other obstructive pulmonary disease patients: those with MAT not refractory to potentially deleterious drugs, those with atrial fibrillation or flutter, or even those merely at risk for MAT. In summary, we need to study whether obstructive pulmonary disease responds to arrhythmia treatment, and not vice versa.

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Perfluorocarbon Fluid as a Mediator of Pulmonary Barotrauma

A Potential Hazard of Liquid Ventilation

In this issue of *CHEST* (see page 191), Ferreyra et al report their findings using partial liquid ventilation (PLV) in an animal model. This is a cutting-

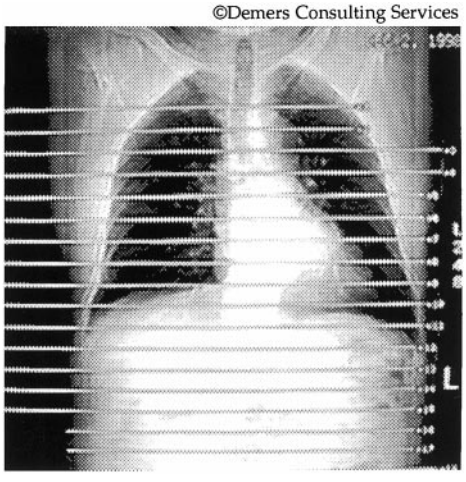

FIGURE 1. A posteroanterior chest radiograph taken in preparation for a CT scan.

edge technology, and the article makes for fascinating reading. The perfluorocarbon fluid used in this technique is hyperdense, having a specific gravity of 1.92. This attribute poses a potential hazard for human patients, owing to the elevated hydrostatic pressure that this extremely dense liquid is able to exert.

Consider a case wherein PLV might be employed for an adult patient in the erect posture. In order to illustrate the pattern of distribution of the instillate, we are going to employ the modified roentgenogram shown in Figure 1. This posteroanterior chest radiograph was obtained in preparation for a CT scan, for which horizontal lines are automatically scribed onto the radiograph at 1-cm intervals. As perfluorocarbon fluid is instilled into the airway, it will percolate into the most dependent regions of the lung. Ferreyra et al continued to instill perfluorocarbon into the endotracheal tube until it reached the level of the teeth of the (animal) subject. If this methodology were duplicated in an erect human subject, the pattern of perfluorocarbon distribution would resemble that shown in Figure 2. We have overdrawn a line at each of the centimeter markers, beginning at the lateral costophrenic sulcus, upward to the level of the main stem bronchi. This vertical distance is observed, in this case, to be 8 cm. The posterior sulcus lies below this level, but we have chosen the lateral sulcus as our zero point because it is easier to visualize on the chest radiograph. Perfluorocarbon would rise to the 8-cm level within the lungs, at which point additional fluid would rise within the endotracheal tube. This additional instillate would be prevented from entering the portion of each lung overlying the 8-cm scribe line because the newly loculated gas lying above each hilum would have no route of egress.

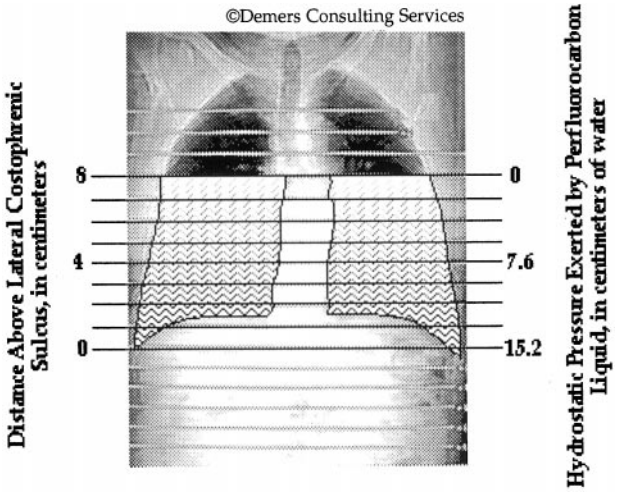

FIGURE 2. Pressure gradient ascribable to perfluorocarbon liquid after instillation.

Owing to the high density of the perfluorocarbon instillate, the hydrostatic pressure gradient would be far greater than that seen if an equal volume of water had been instilled. Hence, the alveoli at the level of the sulcus would be subjected to a pressure of approximately 15 cm H_2O. We have specified the resultant pressure gradient on an axis drawn along the right-hand margin of Figure 2.

Let us assume that a positive end-expiratory pressure (PEEP) of 10 cm H_2O were imposed upon the lungs at this point, in a manner analogous to the study of Ferreyra et al. This would result in an augmentation of pressure by that margin throughout the lung. Thus, the alveoli at the lung bases would be exposed to a pressure of approximately 25 cm H_2O at end-expiration, not the 10-cm level that the unwary clinician might assume would prevail if he or she failed to take the additional perfluorocarbon-related gradient into account. If a cyclical pressure were now to be imposed upon the lungs in order to undertake PLV, the gradients throughout the lung would escalate accordingly. Pressure fluctuations are propagated at the speed of sound through intrapulmonary gas, and at a marginally higher velocity through liquid. This translates to a speed of about one foot per millisecond. Because pressures are transmitted undiminished throughout the body of any liquid, we can anticipate that any variation in pressure occurring at the central airways will be reflected throughout the lungs almost instantaneously.

Finally, we will assume that a peak inspiratory pressure (PIP) of 30 cm H_2O were to be selected. This would be in keeping with current and widespread clinical practice, aimed at avoiding the excessive alveolar pressures that have been shown to be barotraumatic. In this situation, an additional increment of 20 cm H_2O would be superimposed cyclically upon the end-expiratory pressure as positive-pressure inflation supervened. In accordance with our previous analysis, a PIP of this magnitude would result in a peak alveolar pressure at the lung bases of approximately 45 cm H_2O. Obviously, the failure to account for the augmented alveolar pressures mediated by the presence of perfluorocarbon results in substantial escalations in pressure in dependent lung zones. To be sure, this factor is of such considerable magnitude that it is likely to completely nullify clinicians' strategies to limit PIP to levels designed to protect against barotrauma, and they would not even be aware that such efforts were being frustrated.

What might be done to avoid incurring excessive pressures during PLV secondary to the mechanism described here? To the extent that the prevailing pathology is confined to a specific segment of the lungs, clinicians would be well advised to orient that zone lowermost. Subsequent introduction of perfluo-

rocarbon will thus tend to selectively fill the impaired regions of the lung. In the best of situations, a unilateral disease process would be present, which would allow for the patient to be placed in the lateral decubitus position. This would be fortuitous, because the lateral dimension of the lung is considerably smaller than its vertical dimension. This would, in turn, result in an attenuated perfluorocarbon-related pressure head in comparison to that which would be obtained in the erect posture. Irrespective of the orientation of the patient, the clinical team would also do well to instill a volume of perfluorocarbon that will rise to a level that falls short of the entry point(s) of the airway(s) of the lung(s) that are subject to instillation. Determination of this point would, of course, be facilitated by the availability of a fluoroscope. Ensuring that the fluid level does not extend into the affected bronchus (or bronchi) would obviate the need to subsequently impose obligatory PEEP in order to enhance the distribution of tidal ventilation. Finally, the clinical team should consider limiting peak inspiratory pressure to a level that prevents excessive distention of the most dependent lung zones. If the fluoroscopically confirmed vertical dimension of the perfluorocarbon bolus residing in the lung(s) were, for example, 6 cm, the prevailing end-expiratory pressure at the base of this fluid column would be $(6 \times 1.9 =)$ 11 cm H_2O in the absence of PEEP. This would prompt the clinical team to restrict inspiratory pressures to ≤ 19 cm H_2O, if 30 cm H_2O were the selected target for maximum inflation pressure. The narrowed range of pressures thus imposed might obligate the clinical team to employ a technique that was developed for the express purpose of preventing barotrauma-permissive hypercapnia.

Readers might consider this litany of precautions to be quite elaborate, insofar as they necessitate the procurement of a fluoroscope, not to mention the requirement for additional bedside calculations. On the other hand, a decision to undertake PLV itself obliges us to employ technologic tools that are intrinsically elaborate. Implementation of a few additional precautions in such a high-tech environment does not appear to be too much to ask. In the longer term, it would be useful for pharmacophysiologists to identify an oxygen-bearing fluid with a lower specific gravity, ideally approaching that of water, than that exhibited by perfluorocarbon.

Almost 2 decades ago, Dr. Alfred Fishman[1] coined a catchy phrase that might be considered the pulmonologist's call to arms: "Down with the good lung!" The physiology that undergirds this axiom relates to the fact that (lesion-free) pulmonary parenchyma in dependent zones is considerably better ventilated, and vastly better perfused, than is parenchyma in nondependent zones. Exceptions to the "Fishman Rule" are rarely encountered,[2] but liquid ventilation constitutes one such exception. Earlier, we suggested that the lesion-containing portion of the lung be oriented downward in preparation for instilling perfluorocarbon simply because, in that portion of the lung(s) wherein instillate resides, ventilation (although not oxygenation) will be zero. And, because the fluid will "put the squeeze" on alveolar capillaries, perfusion will be marginal to absent. Perfluorocarbon-filled alveoli will thus resemble a so-called "silent unit," with the notable difference being that oxygenation will persist at a presumably brisk rate, despite the absence of the ventilation associated with bulk gas flow. Because they are almost silent, perhaps we should refer to these units as "reticent."

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What Exactly *Is* Flock Worker's Lung?

Kern and colleagues in this issue of *CHEST* (see page 251) report five new cases of interstitial lung disease among persons with histories of occupational exposure to rotary-cut nylon flock. In this case series, they report a spectrum of histopathology not principally associated with flock worker's lung, including desquamative interstitial pneumonia (DIP). Only one of the five case patients demonstrated histopathology that is viewed as stereotypical for flock worker's lung: lymphocytic bronchiolitis and peribronchiolitis with lymphoid nodules.[1,2] The authors now argue that a broader spectrum of histopathologic changes can result from flock inhalation than hitherto believed. This conclusion is in contrast with the more uniform pathologic picture that was presented in the seminal report on flock worker's lung that was published by these researchers in 1998.[1]

Notably, the case definition of flock worker's lung by Kern and colleagues is quite inclusive and conse-

quently readily accommodates the newly reported histopathologic incarnations. As outlined by this group, three findings are sufficient for a diagnosis of flock worker's lung: (1) persistent respiratory symptoms; (2) previous work in the flocking industry; (3) histologic evidence of interstitial lung disease that has no better explanation.[1] In contrast, a recent National Institute for Occupational Safety and Health (NIOSH)-sponsored workshop achieved consensus that flock-associated interstitial lung disease is characterized by the pathologic lesion first described by Kern and colleagues in their 1998 report, thereby distinguishing flock worker's lung from other known lung conditions.[2] The accuracy and usefulness of these two sets of diagnostic criteria can be debated. The NIOSH histopathologic diagnostic criterion may be more specific in identifying "true" cases of pulmonary disease that are caused by nylon flock. However, if, as Kern and colleagues argue in their current report, flock can indeed be causally linked with a broader spectrum of histopathologic changes, then the NIOSH definition may be insensitive in identifying all cases of lung disease caused by flock inhalation.

Terminology debates notwithstanding, the concept that respirable flock has the potential to be pathogenic should be accepted in view of the growing body of evidence linking exposure with disease.[1–4] That flock may cause lung injury in different ways in different persons should come as no surprise. Other respirable inorganic particles and fibers may cause protean manifestations of lung disease. For example, high-dose inhalation of crystalline silica particles may cause an acute form of diffuse alveolar injury characteristic of alveolar proteinosis. In contrast, lower-dose, chronic exposure to silica may result in scattered parenchymal nodules of whorled collagen. Similarly, asbestos exposure may cause a variety of pulmonary diseases that include interstitial fibrosis, bronchogenic carcinoma, and both benign and neoplastic pleural disease.

The pair of articles by Kern and colleagues on flock worker's lung adds to a growing body of evidence suggesting there may be no such thing as an "inert" respirable particle. Nylon now joins the synthetic abrasive carborundum (silicon carbide), rare earth metals, and other nonfibrous inorganic dusts once held to be inert,[5] but now viewed as capable of causing respiratory morbidity.[6–10] A wide variety of organic and inorganic fibers and particles, encountered either in the workplace or in ambient air, should now be accepted as being pathogenic when the susceptible individual is exposed to the "right" concentration for the "right" duration. Numerous studies have consistently demonstrated a significant association between ambient air particulate exposure in low concentration (relative to dusty occupational exposures settings) and morbidity.[11–16] Indeed, respirable range particulate matter is one of six common air pollutants for which national ambient air quality standards have been developed by the United States Environmental Protection Agency.

The hypothesis that inhalation of *any* type of particulate with a mass median aerodynamic diameter < 10 μm (and therefore capable of gaining entry into the lower respiratory tract), will cause adverse health effects has not been proved, however. Notably, there are reports that support the idea that adverse health effects caused by respirable particulates are, in fact, not generic responses; that is, substance *type* is of paramount importance in determining toxicity, and some substances may, indeed, be harmless. A recent series of experimental human exposure studies demonstrated that inhalation of one type of purified metal oxide particulate (zinc oxide) resulted in an exuberant pulmonary inflammatory response,[17,18] while inhalation of a different purified metal oxide particulate (magnesium oxide) in the same particulate size range and in comparable concentrations resulted in no measurable inflammatory response whatsoever.[19] These findings were subsequently reproduced in another laboratory.[20] The importance of particulate composition as a determinant of adverse health effects has been shown in other experimental models as well.[21–25]

There are a number of limitations to the current report by Kern and colleagues. This observational study does not provide any mechanistic insights into the lung damage that is associated with flock exposure. The paper does not extend our understanding of this newly identified disease by providing insights into susceptibility factors or biomarkers of exposure. Additionally, the case series is small and is subject to the biases of retrospective descriptive research. For instance, there is only limited information about other potential respirable exposures that were experienced by these blue-collar workers. There is no analysis of a possible dose-response relationship that might strengthen the association between exposure and morbidity. Finally, there are no experimental exposure data that strengthen the causal link between flock exposure and interstitial lung disease.

Nevertheless, this small case series serves to encourage the clinician to maintain a broad-minded view of flock worker's lung. Perhaps, the answer to the question, " What exactly *is* flock worker's lung?" should be a simple one: "It is lung disease (which, so far, has been interstitial) that is caused by nylon flock inhalation." Without biomarkers of exposure and

susceptibility, and without a marker of disease that is 100% accurate in detecting pulmonary disease caused by flock, diagnosis of this disorder will remain a clinical challenge requiring clinical acumen. Indeed, since it is not possible to perform a randomized human exposure experiment to study the effects of chronic exposure, our understanding about the relationship between flock inhalation and pulmonary disease in humans will necessarily remain, in part, inferential.

For the clinician facing a flock worker with respiratory disease, the same diagnostic principles apply to flock worker's lung that apply to other occupational lung diseases. Evidence that helps establish a causal relationship between exposure and disease includes the following: (1) data demonstrating pulmonary health before exposure to the toxicant in question; (2) historical and industrial hygiene data that help characterize the likely dose and duration of exposure to the toxicant; (3) assessment of other relevant toxicants; (4) data demonstrating that the onset and progression of lung damage are temporally related to the toxicant exposure; (5) stabilization, or ideally, resolution of lung disease following cessation of exposure; and (6) deterioration in respiratory health on reexposure, following improvement in health during an exposure-free period. The absence of some of this evidence, however, will not rule out a case of disease.

Most information that is relevant to an assessment of respiratory disease and its work-relatedness will be available from a careful medical history, the physical examination, pulmonary function testing, radiographic studies, industrial hygiene data, and perhaps BAL. Based on the findings in the current report by Kern and colleagues, however, the routine use of lung biopsy in defining and diagnosing flock worker's lung can now be questioned. Indeed, Kern and colleagues suggest that the triad of an abnormal distribution of cell types on BAL, restrictive lung function, and high-resolution CT findings of diffuse ground-glass opacity should serve as a surrogate for the histologic criterion.[1] The clinician will then need to ask, "How might a lung biopsy change what I do with this patient (since a variety of forms of pulmonary histopathologic changes may reflect lung damage due to flock inhalation)?" The lung biopsy may be more important in ruling out other causes of lung disease (*eg*, infection, neoplasm, sarcoidosis) than it is in ruling in flock worker's lung. Additionally, the lung biopsy may have value in guiding the management of interstitial lung disease, irrespective of etiology. For instance, histopathology showing DIP or bronchiolitis obliterans organizing pneumonia may support the use of corticosteroids as adjuvant therapy, in addition to removing the worker from the source of a suspected respiratory toxicant.

In sum, the current report by Kern and colleagues cautions us to keep an open mind with regard to the pathologic potential of flock and, indeed, all substances that are small enough to be inhaled deep into the lungs. The determinants of the pulmonary response to noxious stimuli are incompletely understood. The variable response seen among workers exposed to flock may be analogous to the variable individual response that is seen with other respirable toxicants, such as other particulates and fibers, cigarette smoke, and aeroallergens. As the articles by Kern and colleagues show, paradigms of newly recognized diseases are subject to critical review and must change as new findings emerge. The epidemiologist and clinical investigator will rightly demand unambiguous case definitions that readily distinguish a "case" from "not a case." The observant clinician, however, may be the first to recognize that the more rigorous the terminology used to describe health and illness, the more elusive a comprehensive understanding of those conditions may become.

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