Whatever the underlying mechanisms of morphine-induced dyspnea relief, the clinically relevant message of the study of Banzett and colleagues is that morphine may be a promising compound for the relief of air hunger, the most typical variant of dyspnea (9). Most importantly, this study presents a new, promising, well-controlled experimental model that may substantially improve testing of therapeutic intervention for dyspnea, which, given the high prevalence and the stressful nature of this symptom, remains a crucial issue.

Author Disclosure: Author Disclosures are available with the text of this article at www.atsjournals.org.

Claudine Peiffer, M.D., Ph.D.
Physiologie-EFR
Hopital Robert Debré
Paris, France

References

1. Banzett R, Moosavi S. Dyspnea and pain: similarities and contrasts between two very unpleasant sensations. *APS* 2001;11:1–8.
2. Von Leupoldt A, Sommer T, Kegat S, Baumann HJ, Klose H, Dahme B, Büchel C. Dyspnea and pain share emotion-related brain network. *Neuroimage* 2009;48:200–206.
3. Lansing RW, Gracely RH, Banzett RB. The multiple dimensions of dyspnea: review and hypotheses. *Respir Physiol Neurobiol* 2009;167:53–60.
4. O'Neill PA, Stark RD, Morton PB. Do prostaglandins have a role in breathlessness? *Am Rev Respir Dis* 1985;132:22–24.
5. Santiago TV, Edelman NH. Opioids and breathing. *J Appl Physiol* 1985; 59:1675–1685.
6. Mahler DA, Murray JA, Waterman LA, Ward J, Kraemer WJ, Zhang X, Baird JC. Endogenous opioids modify dyspnoea during treadmill exercise in patients with COPD. *Eur Respir J* 2009;33: 771–777.
7. Gifford AH, Mahler DA, Waterman LA, Ward J, Kraemer WJ, Kupchak BR, Baird JC. Neuromodulatory effect of endogenous opioids on the intensity and unpleasantness of breathlessness during resistive load breathing in COPD. *COPD* 2011;8:160–166.
8. Jennings AL, Davies AN, Higgins JP, Gibbs JS, Broadley KE. A systematic review of the use of opioids in the management of dyspnoea. *Thorax* 2002;57:939–944.
9. Banzett RB, Adams L, O'Donnell CR, Gilman SA, Lansing RW, Schwartzstein RM. Using laboratory models to test treatment: morphine reduces dyspnea and hypercapnic ventilatory response. *Am J Respir Crit Care Med* 2011;184:920–927.
10. Stark RD. Dyspnoea: assessment and pharmacological manipulation. *Eur Respir J* 1988;1:280–287.
11. Stark RD, Morton PB, Sharman P, Percival PG, Lewis JA. Effects of codeine on the respiratory responses to exercise in healthy subjects. *Br J Clin Pharmacol* 1983;15:355–359.
12. Supinski G, Dimarco A, Bark H, Chapman K, Clary S, Altose M. Effect of codeine on the sensations elicited by loaded breathing. *Am Rev Respir Dis* 1990;141:1516–1521.
13. O'Donnell DE, Banzett RB, Carrieri-Kohlman V, Casaburi R, Davenport PW, Gandevia SC, Gelb AF, Mahler DA, Webb KA. Pathophysiology of dyspnea in chronic obstructive pulmonary disease: a roundtable. *Proc Am Thorac Soc* 2007;4:145–168.

DOI: 10.1164/rccm.201108-1463ED

Progressive Endobronchial Premalignancy: Marked by Original CIN

In the United States, over 220,000 new cases of lung cancer were diagnosed in 2010, with over 157,000 deaths (1). The 5-year survival of lung cancer has improved from 9% to 16% over the past 50 years, a hard-fought but profoundly disappointing advance. Early detection and prevention are likely to lead to the majority of the decrease in cancer mortality in the future. In this respect, the recent publication of the results of the National Lung Screening Trial, demonstrating a 20.3% reduction in lung cancer mortality in the low-dose computed tomography (CT) arm, is a landmark that may lead to significant improvement in lung cancer survival, provided we are able to implement screening in a cost-effective manner and minimize harm from diagnostic workup (2).

While there is now a clear lung cancer mortality benefit to low-dose CT based early detection strategies in high-risk groups, bronchoscopic surveillance of the central airways has lagged behind. It is widely believed that the detection and treatment of preneoplastic lesions in accessible epithelial organs (the skin, cervix, and colon) reduces cancer mortality. In the lung, the complex airway anatomy and the undifferentiated appearance of preneoplasia have slowed progress on the clinical detection of this biomarker. Autofluorescence bronchoscopy significantly improves the detection rate of preneoplastic lesions, raising sensitivity by 3- to 4-fold over white light bronchoscopy and making a focus on treatment of preneoplasia more feasible (3). However, the natural history of airway preneoplasia is poorly defined, and it has not been clear which lesions warrant detection and treatment (4, 5). Histologic dysplasia (at least short of carcinoma in situ [CIS]) is not a strong predictor of lung cancer risk at a specific bronchial site. While this finding supports the American College of Chest Physician guidelines of bronchoscopic follow-up of severe dysplasia or CIS in the central airways, many would advocate local treatment for CIS that does not regress after initial biopsy (6).

Molecular analysis of premalignant lesions has been ongoing since the early 1990s, and overall patterns of progressive chromosomal instability (CIN) in lung squamous cell carcinogenesis have been proposed (4). Salaun and coworkers reported that, in a series of patients with severe dysplasia or CIS, chromosome 3p loss of heterozygosity, as demonstrated by PCR analysis of microdissected formalin fixed paraffin-embedded lesions, is significantly associated with progression to invasive cancer (7). However, these studies offer only a limited analysis of possible changes to the premalignant genome.

In this issue of the *Journal*, van Boerdonk and colleagues (pp 948) report a search for CIN in the genome of microdissected dysplastic epithelium obtained from squamous metaplasia lesions. Multiple regions of genome copy number gain and loss, the indelible stains of CIN, were found in five of the six subjects with progressive bronchial lesions and subsequently diagnosed invasive squamous cell lung cancer (8). There are several remarkable aspects to this report. First, to obtain these six biopsies, the investigators performed 1,238 autofluorescence bronchoscopies over 12 years in a very high-risk cohort of 474 subjects followed at their institution. In addition, at each of the

Author Contributions: Editorial conception and design, Y.E.M. and C.D.C.; initial draft of editorial, Y.E.M.; comments and revisions, C.D.C.

Supported by NCI Specialized Program of Research Excellence in Lung Cancer, CA 58187, and by an Early Detection Award from the LUNGevity Foundation.

4,170 endobronchial sites biopsied in these subjects, the investigators acquired and banked a frozen biopsy in addition to the routine formalin-fixed, paraffin-embedded specimen. Each of the six nested case and 23 control biopsies were carefully microdissected, leaving only the genomes of dysplastic epithelial cells to contribute to the assay output. Finally, they employed array comparative genomic hybridization (CGH), using a platform that quantifies over 40,000 chromosomal loci, to analyze these precious specimens. In this way van Boerdonk and colleagues signifcantly build on and extend the work of Salaun and coworkers, in which three genetic loci were analyzed. DNA copy number alterations, particularly at chromosomes 3p, 3q, 9p, and 17p, were significantly more frequent among cases than among control subjects. Control subjects were selected to exhibit similar squamous metaplasia at baseline, but no cancer diagnosis on follow up.

There are several limitations to this study. First, 5 of the 6 cases (and 9 of 23 control subjects) had a history of respiratory tract cancer, so it is possible that the lesions analyzed represented recurrent, rather than incident, lung cancer. This concern is particularly salient for two subjects who had been treated with radiotherapy for invasive cancer at the site of the new squamous cell lung cancer. In the remaining four cases, the new tumor arose at a distant site, making recurrence less likely. This distinction between CIN originating in the neoplastic field and CIN inherited from the parent tumor is important for models of the natural history of lung carcinogenesis, but the wages of CIN seem apparent: four of the five subjects exhibiting cytogenetically abnormal lesions (and five of the six with incident lung cancer) died of lung cancer over the next 21 to 68 months. This highlights the question of how effective bronchoscopic early detection and local treatment were in this setting.

The work described above is focused on the likelihood of progression to invasive cancer at a specific site. We are clearly a long way from a clinically applicable approach, except perhaps for highly advanced dysplasias. There is, however, significant evidence that global damage to the respiratory epithelium is a biomarker of lung cancer risk. Slaughter and colleagues first described the field cancerization concept in 1953, when two or more independent squamous cell carcinomas were described in 88 of 783 patients with oral cancer (9). In addition, widespread dysplastic epithelial changes were found in these subjects. These diffuse premalignant changes in patients with lung cancer are likely due to a combination of genetic susceptibility, exposure of the entire respiratory epithelium to the multiple carcinogens present in tobacco smoke, and the expansion and dispersal of clones of mutant respiratory epithelial cells, as has been demonstrated for both p53 and EGFR mutant preneoplastic cells (10, 11). The hypothesis that the presence of premalignant epithelial cells harboring DNA copy number alterations reflects risk of lung cancer at some site (but not necessarily the site in which the analysis was undertaken) is supported by previous studies using fluorescence *in situ* hybridization (FISH) to detect chromosomal aneusomy in sputum and dysplastic biopsies, as well as spectral karyotyping of cultured bronchial epithelial cells, in which clonal chromosomal abnormalities parallel lung cancer risk factors (12–15). These approaches are limited by the small number of chromosomal locations that can be interrogated by FISH. We expect that the use of higher-resolution methods, including CGH, will improve our ability to define lung cancer risk, with potential application to both bronchoscopic and low-dose CT early detection strategies.

Author Disclosure: C.D.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. Y.E.M.'s institution has received grants from the LUNGevity Foundation; he has applied for patent along with his institution related to the prevention of cancer, but has received no income from this; he has received travel support from the International Association for the Study of Lung Cancer.

Christopher D. Coldren, Ph.D.
Division of Pulmonary Sciences and Critical Care Medicine
University of Colorado School of Medicine
Aurora, Colorado

York E. Miller, M.D.
Division of Pulmonary Sciences and Critical Care Medicine
University of Colorado School of Medicine
Aurora, Colorado
and
Denver Veterans Affairs Medical Center
Eastern Colorado Health Care System
Denver, Colorado

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics 2010. *CA Cancer J Clin* 2010;60:277–300.
2. Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, Gareen IF, Gatsonis C, Marcus PM, Sicks JD. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365:395–409.
3. Hirsch FR, Prindiville SA, Miller YE, Franklin WA, Dempsey EC, Murphy JR, Bunn PA Jr, Kennedy TC. Fluorescence versus white-light bronchoscopy for detection of preneoplastic lesions: a randomized study. *J Natl Cancer Inst* 2001;93:1385–1391.
4. Ishizumi T, McWilliams A, MacAulay C, Gazdar A, Lam S. Natural history of bronchial preinvasive lesions. *Cancer Metastasis Rev* 2010;29:5–14.
5. Breuer RH, Pasic A, Smit EF, van Vliet E, Vonk NA, Risse EJ, Postmus PE, Sutedja TG. The natural course of preneoplastic lesions in bronchial epithelium. *Clin Cancer Res* 2005;11:537–543.
6. Kennedy TC, McWilliams A, Edell E, Sutedja T, Downie G, Yung R, Gazdar A, Mathur PN. Bronchial intraepithelial neoplasia/early central airways lung cancer: ACCP evidence-based clinical practice guidelines. *Chest* 2007;132:221S–233S.
7. Salaun M, Sesboue R, Moreno-Swirc S, Metayer J, Bota S, Bourguignon J, Thiberville L. Molecular predictive factors for progression of high-grade preinvasive bronchial lesions. *Am J Respir Crit Care Med* 2008; 177:880–886.
8. van Boerdonk RA, Sutedja TG, Snijders PJ, Reinen E, Wilting SM, van de Wiel MA, Thunnissen FE, Duin S, Kooi C, Ylstra B, *et al.* DNA Copy Number Alterations in Endobronchial Squamous Metaplastic Lesions Predict Lung Cancer. *Am J Respir Crit Care Med* 2011;184:948–956.
9. Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. *Cancer* 1953;6:963–968.
10. Franklin WA, Gazdar AF, Haney J, Wistuba II, La Rosa FG, Kennedy T, Ritchey DM, Miller YE. Widely dispersed p53 mutation in respiratory epithelium: a novel mechanism for field carcinogenesis. *J Clin Invest* 1997;100:2133–2137.
11. Tang X, Varella-Garcia M, Xavier AC, Massarelli E, Ozburn N, Moran C, Wistuba II. Epidermal growth factor receptor abnormalities in the pathogenesis and progression of lung adenocarcinomas. *Cancer Prev Res (Phila Pa)* 2008;1:192–200.
12. Varella-Garcia M, Schulte AP, Wolf HJ, Feser WJ, Zeng C, Braudrick S, Yin X, Hirsch FR, Kennedy TC, Keith RL, *et al.* The detection of chromosomal aneusomy by fluorescence in situ hybridization in sputum predicts lung cancer incidence. *Cancer Prev Res (Phila Pa)* 2010;3:447–453.
13. Jonsson S, Varella-Garcia M, Miller YE, Wolf HJ, Byers T, Braudrick S, Kiatsimkul P, Lewis M, Kennedy TC, Keith RL, *et al.* Chromosomal aneusomy in bronchial high-grade lesions is associated with invasive lung cancer. *Am J Respir Crit Care Med* 2008;177:342–347.
14. Massion PP, Zou Y, Uner H, Kiatsimkul P, Wolf HJ, Baron AE, Byers T, Jonsson S, Lam S, Hirsch FR, *et al.* Recurrent genomic gains in preinvasive lesions as a biomarker of risk for lung cancer. *PLoS ONE* 2009;4:e5611.
15. Varella-Garcia M, Chen L, Powell RL, Hirsch FR, Kennedy TC, Keith R, Miller YE, Mitchell JD, Franklin WA. Spectral karyotyping detects chromosome damage in bronchial cells of smokers and patients with cancer. *Am J Respir Crit Care Med* 2007;176:505–512.

DOI: 10.1164/rccm.201108-1476ED