

# Correspondence

## The Molecular–Clinical Divorce

To the Editor:

Dr. Brody disagrees with the statement that “basic science and basic scientists have little relevance to clinical medicine” (1). I disagree too, and perhaps I failed to make that clear (2). The problem is the gap between the promises of basic discovery and the clinical trials that deliver the goods. Clinicians are definitely interested in the latter and not the former. Brody may well be right that “Gene expression profiles and bioinformatics . . . will revolutionize diagnosis, prognosis, and choice of treatment . . .”, but clinicians are not going to hold their breaths. Undoubtedly, they were excited when cystic fibrosis transmembrane regulator was cloned 18 years ago, but they are disappointed that it hasn’t done much for the present (3). To paraphrase Brody: the list of promises is long and growing. But patients and clinicians need more than promises.

This distinction between clinical relevance of basic science and what clinicians read in journals needs to be made crystal clear. No matter what the promise for the future, clinicians think that the messages being sent by molecular biologists have little pertinence to how they take care of their patients today. Clinicians are unlikely to read about molecular biology until a clinical trial proves relevant to his or her clinical practice. Dr. Brody points to the successful treatment of acquired immunodeficiency syndrome and later states that “clinicians will not be able to optimally apply scientific advances if they do not understand them.” But my guess is that clinicians, in applying the results of clinical trials, are appropriately providing combination therapy while understanding little or nothing about its molecular basis.

Molecular biologists claim that they have discovered the secrets of life. If you don’t believe me read the title of James Watson’s latest book. The search for these secrets was started by Schrödinger in his classical monograph “What Is Life?” (4). In it he predicted that a large molecule carrying a genetic code would explain heritable characteristics. But he also pointed out that that the living organism has the “astonishing gift of concentrating a stream of order on itself and thus escaping . . . decay into atomic chaos . . .,” meaning that we appear to violate the second law of thermodynamics. For Schrödinger, life held two secrets: the first was the genetic code, and the second was our stunning order. The code was broken by molecular biology; the origins of order remain largely a mystery. A clinician’s life is spent maintaining and restoring the order that represents health and we don’t even know how that order comes to be. We only know in general that it spontaneously develops in complex, non-linear, interacting, dynamic systems that consume energy and function far from thermodynamic equilibrium (5–7).

In view of the fact that we really understand only one of life’s secrets, Watson’s book might be more aptly titled “DNA: Half the Secret of Life.” Granting agencies do not seem to be interested in investigating the other half that involves the coordinated interaction of many component parts. This secret will not be unlocked by studying single molecules in isolation, but once understood it will be just as relevant to clinical practice as the first secret is. More promises! Enough already! But that’s what granting agencies gamble on.

PETER T. MACKLEM  
McGill University  
Montreal, Quebec, Canada

**Conflict of Interest Statement:** P.T.M. has no declared conflict of interest.

## References

1. Brody G. What we’ve got here is a failure to communicate. *Am J Respir Crit Care Med* 2003;168:415–416.
2. Macklem PT. Is cell and molecular biology divorcing from clinical practice? *Am J Respir Crit Care Med* 2003;167:1164–1165.
3. Rubin BK. Cystic fibrosis: bench to bedside 2003. *Can Respir J* 2003;10:161–164.
4. Schrödinger E. *What is life?* Cambridge, 1944.
5. Schulz SG. Homeostasis, Humpty Dumpty and integrative biology. *News Physiol Sci* 1996;11:238–246.
6. Prigogine II. Stengers. Order out of chaos. New York: Bantam Books; 1984.
7. Kauffman S. Origins of order. New York: Oxford University Press; 1993.

## Identifying Smokers at Risk of COPD and GOLD

To the Editor:

In their article, Vestbo and Lange (1) discuss the concept of identifying subjects at risk for COPD. They wrote “The single-breath nitrogen test was regarded as a promising candidate in the 1970s and 1980s but turned out to be too unspecific for subsequent use in both epidemiology and clinical medicine. . . . This test, as well as others (e.g., mid-expiratory flows), may well be able to demonstrate small changes in the airways; however, these changes are not indicative of more serious changes taking place and thus they lack predictive value.” The authors are quoting our study (2) as supporting their assertion. In fact, the conclusion of our study is at variance with their assertion.

It is well known that although cigarette smoking is the cardinal cause of COPD, clinically overt disease develops in only a minority of smokers. Our objective was to identify high-risk smokers and to assess the prognostic significance of “small airways” tests. In a follow-up for 13 years of 56 former steelworkers, smokers and ex-smokers, two indices, FEV<sub>1</sub>/VC and the single-breath nitrogen test, identified at the start of the study those subjects who reached at its end FEV<sub>1</sub>/VC values as low, or lower than 45%. These values are observed in the clinical stages of the disease. It is worth mentioning that 13 years earlier all these subjects were active “blue collar” workers in their 50s. It appears that in a middle-aged smoker a decreased FEV<sub>1</sub>/VC ratio has no serious implication in itself. Only an associated increased single-breath nitrogen test adds the necessary information to predict a serious functional deterioration.

DAN STANESCU  
Université Catholique de Louvain  
Brussels, Belgium

## References

1. Vestbo J, Lange P. Can GOLD stage 0 provide information of prognostic value in chronic obstructive pulmonary disease? *Am J Respir Crit Care Med* 2002;166:329–332.
2. Stanescu D, Sanna A, Veriter C, Robert A. Identification of smokers susceptible to development of chronic airflow limitation. A 13-year follow-up. *Chest* 1998;114:416–425.

*Dr. Vestbo was given an opportunity to respond to this letter, but declined to do so.*

## Glucocorticoids in Preterm Infants and Discrepancies of Vascular Endothelial Growth Factor

To the Editor:

The importance of elucidating the regulation of vascular endothelial growth factor in the newborn lung and the interference of antenatal and postnatal glucocorticoids with this growth factor recently have been emphasized. Lassus and colleagues (1, 2) repeatedly found no significant differences in the ratios between vascular endothelial growth factor and secretory component of IgA in tracheal aspirate fluid analyzed in dexamethasone-treated or untreated preterm infants. In our experience (3), however, pulmonary levels of vascular endothelial growth factor in epithelial lining fluid significantly increased in the untreated as compared with the dexamethasone-treated group (at similar schedule and dose). In the same samples, transforming growth factor- $\beta$ 1 levels showed a similar profile, increasing during the study period in the untreated subjects ( $p < 0.05$ ), whereas a significant decrease ( $p < 0.05$ ) was observed in treated infants. Moreover, the values of transforming growth factor- $\beta$ 1 from three untreated subjects (30%), in whom severe bronchopulmonary dysplasia developed, were significantly greater ( $p < 0.05$ ) than those found in babies with mild or no bronchopulmonary dysplasia.

The behavior of vascular endothelial growth factor shown by Lassus and colleagues (1, 2) is surprising. In fact, it has been reported that its expression is downregulated *in vitro* by steroids in pulmonary fibroblasts (4) even if, *in vivo*, dexamethasone treatment increases its mRNA expression in developing mouse lung (5) and in newborn rabbits recovering from experimental lung injury. The unchanged values of the cytokine observed in the two study groups by Lassus and colleagues (2) conflict with the significant difference in the incidence of bronchopulmonary dysplasia between treated and untreated infants (2), as well as with the assertion that lower concentrations are associated with bronchopulmonary dysplasia (1, 2).

Vascular endothelial growth factor plays a crucial role in vascular development, and the reduction observed in our study could be interpreted as impaired microvascular repair of lung injury, but it has been demonstrated that activated human neutrophils also express this mediator (6). Therefore, its production may be central to the classic acute phase response to injury and chemoattraction of other leukocytes toward the injury source. In this way, the abolition of a spontaneous increase of vascular endothelial growth factor observed in the treated infants in our study could be interpreted as a positive effect of dexamethasone. Clarifying the possible mechanisms involved in both the development of bronchopulmonary dysplasia and the action of steroids may be crucial in preserving the beneficial effects and reducing short- and long-term side effects of postnatal steroid administration.

GIOVANNI VENTO

PIERO GIUSEPPE MATASSA

ETTORE CAPOLUONGO

LUCA TORTOROLO

COSTANTINO ROMAGNOLI

Università Cattolica S. Cuore  
Rome, Italy

FRANCO AMEGLIO

General Hospital "S. Giovanni Calibita"  
Fatebenefratelli/AFAR  
Rome, Italy

A, Andersson S. Pulmonary vascular endothelial growth factor and Flt-1 in fetuses, in acute and chronic lung disease, and in persistent pulmonary hypertension of the newborn. *Am J Respir Crit Care Med* 2001;164:1981–1987.

- Lassus P, Nupponen I, Kari A, Pohiavuori M, Andersson S. Early postnatal dexamethasone decreases Hepatocyte Growth Factor in tracheal aspirate fluid from premature infants. *Pediatrics* 2002;110:768–771.
- Vento G, Matassa PG, Ameglio F, Capoluongo E, Tortorolo L, Romagnoli C. Effects of early dexamethasone therapy on pulmonary fibrogenic mediators and respiratory mechanics in preterm infants. *Eur Cytokine Netw* 2002;13:207–214.
- Nauck M, Roth M, Tamm M, Eickelberg O, Wieland H, Stulz P, Perruchoud AP. Induction of vascular endothelial growth factor by platelet-activating factor and platelet-derived growth factor is downregulated by corticosteroids. *Am J Respir Cell Mol Biol* 1997;16:398–406.
- Bhatt AJ, Amin SB, Chess PR, Watkins RH, Maniscalco WM. Expression of vascular endothelial growth factor and Flk-1 in developing and glucocorticoid-treated mouse lung. *Pediatr Res* 2000;47:606–613.
- Webb NJ, Myers CR, Watson CJ, Bottomley MJ, Brenchley PE. Activated human neutrophils express vascular endothelial growth factor (VEGF). *Cytokine* 1998;10:254–257.

From the Authors:

We thank Vento and coworkers for their comments on our articles (1, 2). In their letter they raise an interesting question concerning the regulation of pulmonary vascular endothelial growth factor (VEGF) by glucocorticoids.

It has been shown by several groups that glucocorticoids inhibit VEGF expression in various cell types *in vitro* (3–5). However, this effect has not been confirmed *in vivo*. We found, in our study in preterm infants, no differences in VEGF concentrations between those who received early postnatal dexamethasone and those who did not. However, D'Angio and colleagues (6) showed that, in preterm infants, postnatal dexamethasone was associated with greater pulmonary VEGF levels. In contrast, Vento and colleagues (7) found that postnatal glucocorticoids were associated with lower pulmonary VEGF in preterm infants.

The reasons for different results in these three studies remain enigmatic. One possibility is differences in patient materials, for example, with regard to gestational age and morbidity rates. The effect of glucocorticoids on VEGF may also be dose-dependent. The relation among glucocorticoids on VEGF is important, on the one hand because of the frequent, at least antenatal, use of glucocorticoids, on the other hand because VEGF seems to play a crucial role in pulmonary development and in development of bronchopulmonary dysplasia (BPD). Our group has previously shown that pulmonary VEGF levels increase steadily during the first postnatal days, and that an association exists between lower pulmonary VEGF levels and greater incidence of BPD (8). Bhatt and colleagues (9) found, in lung specimens obtained by autopsy in infants dying of BPD, decreased VEGF and Flt-1 expression in association with an arrest of alveolar development and with abnormal capillary development. It has been suggested by Abman (10) that because VEGF participates in normal pulmonary development, a decrease in pulmonary VEGF might interfere with normal alveolarization and participate in the arrest of lung development in infants developing BPD.

These data emphasize the importance of elucidating the regulation of VEGF in the newborn lung and the interference of antenatal and postnatal glucocorticoids with this growth factor.

PATRIK LASSUS

STURE ANDERSSON

Hospital for Children and Adolescents  
Helsinki University Central Hospital  
Helsinki, Finland

## References

- Lassus P, Turanlahti M, Heikkilä P, Andersson LC, Nupponen I, Sarnesto

**Conflict of Interest Statement:** P.L. has no declared conflict of interest; S.A. has no declared conflict of interest.

## References

1. Lassus P, Turanlahti M, Heikkilä P, Andersson LC, Nupponen I, Sarnesto A, Andersson S. Pulmonary vascular endothelial growth factor and Flt-1 in fetuses, in acute and chronic lung disease, and in persistent pulmonary hypertension of the newborn. *Am J Respir Crit Care Med* 2001;164:1981–1987.
2. Lassus P, Nupponen I, Kari A, Pohjavuori M, Andersson S. Early postnatal dexamethasone decreases hepatocyte growth factor in tracheal aspirate fluid from premature infants. *Pediatrics* 2002;110:768–771.
3. Nauck M, Roth M, Tamm M, Eickelberg O, Wieland H, Stulz P, Perruchoud AP. Induction of vascular endothelial growth factor by platelet-activating factor and platelet-derived growth factor is downregulated by corticosteroids. *Am J Respir Cell Mol Biol* 1997;16:398–406.
4. Horiuchi T, Weller P. Expression of vascular endothelial growth factor by human eosinophils: upregulation by granulocyte macrophage colony-stimulating factor and interleukin 5. *Am J Respir Cell Mol Biol* 1997;17:70–77.
5. Klekamp JG, Jarzecka K, Hoover RL, Summar ML, Redmond N, Perkett EA. Vascular endothelial growth factor is expressed in ovine pulmonary vascular smooth muscle cells in vitro and regulated by hypoxia and dexamethasone. *Pediatr Res* 1997;42:744–749.
6. D'Angio CT, Maniscalco WM, Ryan RM, Avissar NE, Basavegowda K, Sinkin RA. Vascular endothelial growth factor in pulmonary lavage fluid from premature infants: effects of age and postnatal dexamethasone. *Biol Neonate* 1999;76:266–273.
7. Vento G, Matassa PG, Ameglio F, Capoluongo E, Tortorolo L, Romagnoli C. Effects of early dexamethasone therapy on pulmonary fibrogenic mediators and respiratory mechanics in preterm infants. *Eur Cytokine Netw* 2002;13:207–214.
8. Lassus P, Ristimäki A, Ylikorkala O, Viinikka L, Andersson S. Vascular endothelial growth factor in human preterm lung. *Am J Respir Crit Care Med* 1999;159:1429–1433.
9. Bhatt AJ, Amin SB, Chess PR, Watkins RH, Maniscalco WM. Expression of vascular endothelial growth factor and Flk-1 in developing and glucocorticoid-treated mouse lung. *Pediatr Res* 2000;47:606–613.
10. Abman SH. Bronchopulmonary dysplasia: “a vascular hypothesis.” *Am J Respir Crit Care Med* 2001;164:1755–1756.