Pneumologists breathe easy

SIR—I have read with interest the article "Model Lung Breathes True"[1] and the quoted paper by two physicists, Bonsignori and Salvini, *Il Nuovo Cimento*[2], which is said to "contain an intriguing calculation of gas transport in the human lung of a kind that would normally have been found in a physiological journal". In fact, the results of similar calculations belong to standard physiological textbooks[3]. In my opinion, the paper of Bonsignori and Salvini is only relevant to the respiratory physiology of the early 1970s.

Whatever the model (in physiology as in physics), comparison with experimental observations is the crucial test. What Maddox has written[1], that "the outcome of the calculations is much what physiologists would expect", is not true. The authors simulated a simple experiment, called single breath nitrogen washout, consisting of an inspiration of oxygen followed by an exhalation. Most of the expired-N_2 concentration profile, the so-called alveolar plateau, is not flat, as would be expected if the lung is a perfect mixing chamber. (The slope of the alveolar plateau is one of the standard indices in pneumology and is explained to medical students in elementary textbooks.)

The model of Bonsignori and Salvini simulates a flat alveolar plateau and the authors say that "in experiments, the single breath washout curves have rather flat alveolar plateaus, indicating uniform mixing of the alveolar and inspired gases"[2]. It is well known, since the experiments of Krogh and Lindhard[4] at the beginning of the century, that this is not the case. In other words, the lung model of Bonsignori and Salvini does not breath true.

Maddox also quotes Bonsignori and Salvini as claiming to have improved on some of the approximations to which previous calculations have been subject. These improvements consist of: 1, using a better representation of the airway cross-section; 2, using a Taylor–Arris effective diffusion; and 3, discussing more appropriate boundary conditions. In a review on the subject[5], several references (probably not known by Bonsignori and Salvini) are given where all these points have been studied. None of these have significantly improved agreement between the model simulations and the experimental observations.

As Maddox says, the physiological data are striking, the total cross-section of airways increasing from a few square centimetres in the trachea to more than a square metre at the last generations of the bronchial tree. A major consequence of the lung geometry is that when we inspire at constant flow, the concentration profile of the inspired gases remains quasi-stationary, the convection flow of inspired gases towards the lung periphery being balanced by the diffusion flow of the residual (or alveolar) gases in the opposite direction[5]. This is the so-called diffusion front, equivalent to the stationary diffusion front in combustion science, when the combustion takes place in a tube with the appropriate convection velocity of gases.

A major development of models of gas mixing in the lung (not quoted by Bonsignori and Salvini) was the realization[5] in the 1970s that one of the most fragile assumptions in previous work consists of using the symmetrical Weibel model of the lung[6], which dates back to 1963. Not surprisingly, the first detailed asymmetrical model of the periphery of the human lung was recently published by Weibel's group[7]. Unexpected results appeared when a diffusion equation was written in an asymmetrical structure of ducts as a consequence of Fick's law of diffusion and matter balance in a branching tube: the flow of any gas in such a structure generates an inhomogeneous concentration distribution, even though the structure moves isotropically and homogeneously. This occurs in zones of the model that are subtended by branch points where the Péclet number (giving the relative contribution of convective to diffusive transport) is approximately unity. In the human lung during normal breathing, this corresponds to branch points subtending zones of the lung a few millimetres apart.

Simulated single-breath washout using these new models gives much better agreement with experimental observations than previous models[5]. This finding is of interest in that the single-breath washout, particularly when performed with tracer gases of different diffusivities such as He and SF_6, gives information on the structure of the very peripheral zones of the lung which are not accessible to traditional tests in pneumology nor even to modern imaging techniques such as positron emission tomography. To my knowledge, the description of gas transport in an asymmetrical lung model has no counterpart in physics or engineering, although it may have applications in the study of gas transport in porous media, or O_2 and CO_2 transport in some insect-built galleries, where the Péclet number may approach unity. It may also apply to the study of O_2 transport between capillaries and cells.

Physiology (which, in a way, is the physics of living beings) and physics were closely associated until the last century, and several discoveries in both fields were made by the same scientist. Boyle, Torricelli, Pascal, Hooke, Lavoisier, Laplace and Lagrange have contributed to the early development of respiratory physiology, and both Poiseuille and Fick were physicians. The bridge is much narrower today and the paper by Bonsignori and Salvini in *Il Nuovo Cimento* has the merit, as Maddox says, of establishing a new link. It also points out the necessity for the physicists who approach physiology to learn at least its elementary basis, if they want to avoid the trap of rediscovering the wheel. Bonsignori and Salvini promise a new paper where they will pay particular attention to the question of the boundary conditions in the model. If they do not in the meantime read the published literature, respiratory physiologists need not hold their breath awaiting future issues of *Il Nuovo Cimento*.

M. PAIVA
*Institute of Interdisciplinary Research,
Free University of Brussels,
Campus Erasme,
Route de Lennik, 808,
B 1070 Brussels,
Belgium*

1. Maddox, J. *Nature* **341**, 381 (1989).
2. Bonsignori, F. & Salvani, M. *Il nov. Cim.* **11D**, 1247–1263 (1989).
3. Engel, L.A. in *Handbook of Physiology* (American Physiological Society, Bethesda, Maryland, 1986).
4. Krogh, A. & Lindhard, J. *J. Physiol., Lond.* **51**, 59–90 (1917).
5. Paiva, M. & Engel, L.A. *Physiol. Rev.* **32**, 750–796 (1987).
6. Weibel, E.R. *Morphometry of the Human Lung* (Springer, Berlin, 1963).
7. Haefeli-Bleuer, B. & Weibel, E.R. *Anat. Rec.* **220**, 401–414 (1988).

PCR origins

SIR—We noted with interest the short note, entitled "DNA amplification" (*Nature* **341**, 570; 1989) which suggests that scientists who use PCR "dust off" the *Journal of Molecular Biology* from 1971, and read the paper by "H. Gobind Khorana and colleagues". Although the title and text of your note might suggest otherwise, the "lines of thought" and reference to experiments "in progress" in this 1971 article did not present a method that could be used to perform *in vitro* DNA amplification. The scientific community had to wait for such a method until, 14 years later, Kary Mullis invented the polymerase chain reaction (PCR).

Your readers might be interested to know that the articles written by Kary Mullis, Henry Erlich and their co-workers at Cetus describing the PCR method and its application have been cited in well over 1,000 publications since 1985. None of these publications cite the 1971 article to which you draw attention. Cetus is confident that Kary Mullis will continue to receive the recognition he deserves.

JEFFREY S. PRICE
*Cetus Corporation,
1400 Fifty-Third Street,
Emeryville,
California 94608, USA*