Of Mice and Men, or: A Pill for Emphysema?

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When John Steinbeck wrote his great novel *Of Mice and Men* (1937) he certainly did not intend to engage in the endless story of the proper choice of an experimental animal as an appropriate model of human pathophysiology. In fact, promising results of experiments on one species are often nullified by negative results in another species in an otherwise very similar experiment.

In their study published in this issue of *Respiration*, Lucey et al. [1, this issue of *Respiration*] took FVB mice, made them 'emphysematous' in order to study whether *all-trans* retinoic acid (ATRA) induces neogenesis of alveolar septa (septation) in dilated alveolar structures – and it didn't. This was disappointing since Massaro and Massaro [2] were more successful when experimenting with adult rats in a similar set-up: emphysema was produced by intratracheal instillation of porcine elastase; the treatment consisted of intraperitoneal injections of ATRA. In another study [3], the respective animals (Massaros and Massaros' very young rats) were investigated like Lucey et al.'s mice during a phase of rapid body growth. The rats rewarded their researchers by an almost complete reversal of the emphysematous changes by formation of new alveoli. Moreover, the authors cite another successful study, also on rats, in which a 50% restoration was obtained [4]. The FVB mice in the study by Lucey et al. [1] did not do them the same favor: there was no restoration of alveoli. Lucey et al. then looked for a response at

the level of cell biology – in vain! ATRA had an effect neither on mRNA expression for elastin, nor for collagen.

Here we have to deal with a negative study (on mice) as opposed to previous positive studies (on rats). We decided to present the former study to the readers of *Respiration* on several grounds:

(1) Obviously the choice of test animals is crucial for the outcome of a study. Even with a successful animal model, there is a long way towards applicability to humans.

(2) ATRA treatment was shown to enhance alveolar development (septation) in periods of rapid differentiation (late fetal or early postnatal period) not only in rats, but also in mice, particularly when septation had failed due to prematurity or steroid treatment [3]. When emphysematous models are used, the behavior of rats (responders to ATRA) and mice (nonresponders) is obviously different.

(3) ATRA treatment has a definite effect not only on alveolar development in young rats, but also on reseptation of emphysematous lungs of adult rats [2].

(4) Oral treatment with ATRA (Vesanoid®) has been successfully applied to patients with promyelocytic leukemia, accelerating cell differentiation and maturation. This may well play a role in activation of genes for alveolar septation.

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(5) It seems that oral ATRA is well tolerated by patients with emphysema [5]. So we should not hesitate to encourage research in humans, hoping for something like a pill for emphysema in the future.

What we lack at this point, however, are more studies on the effect of ATRA not only in young rodents, but also in adult or aged animals, be it rats, rabbits or mice. There is indeed just one ‘human model’: a breathless patient with advanced disease. And if it is true that ‘mice and men’ are a poor match, we might have to put up with the less charming solution of ‘rats and men’.

As we learned from recently published studies, a novel oral neutrophil elastase inhibitor is able to attenuate elastase-induced emphysema in rats [6], and an oral synthetic serine elastase inhibitor reduced cigarette-smoke-induced emphysema in guinea pigs [7].

In John Steinbeck’s novel, the dumb and good-hearted Lennie loves to pat a dead mouse in his pocket, longs for breeding rabbits, mourns over a dead puppy and must die because of the disaster that follows when he pats a woman’s hair. Let us hope that we are luckier in transferring our experience with animals to medicine – maybe with the ATRA pill for emphysema.

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