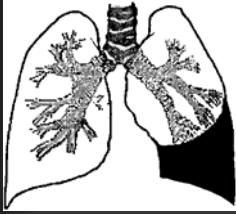


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Physiology of the Pleura: Lessons from the Elephant

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What is the only mammal without a pleural cavity? This might be a good question to ask a student on a ward round when a patient with pleural disease is being discussed. The answer is the elephant. As long ago as 1681 Mullen¹ dissected an elephant 'accidentally burnt in Dublin on Fryday [sic], June 17' and reported that the pleura 'were so joyned that there was not one place where you might see a natural separation of them'. Many other descriptions have since been reported although it is interesting that the fetal elephant has a normal pleural space² which is obliterated late in gestation. Several explanations have been suggested for this anatomical peculiarity which is seen in both the Asian and African elephant but none is convincing. It is a 300 year old puzzle.



Fig 1.
Elephants breathing through their trunks while swimming near Chobe, Botswana.
Photograph by R. Saxon.

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Another unique feature of the elephant is that it is the only animal that can snorkel at a considerable depth. This was first described by Aristotle³ some 2,300 years ago when he noted that the animals have 'been furnished by nature with their lengthened nostril; and, whenever they have to traverse the water they lift this up above the surface' to breathe through it. There are many accounts of elephants crossing rivers or lakes by walking on the bottom while the tip of the trunk just protrudes above the surface of the water. For example, Tennent⁴ wrote 'In crossing deep rivers .. [the

elephant] generally prefers to sink till no part of his huge body is visible except the tip of his trunk through which he breathes.' Elephants are also strong swimmers (Fig 1) and there are reports of them swimming for hours at a time while breathing through their trunks. Many biologists believe that the elephant has an aquatic ancestry⁵ and it is possible that the trunk evolved to enable it to snorkel while living in water with obvious survival advantages. In fact there is evidence that the elephant (order *Proboscidea*) and the sea cows (*Sirenia*) share a common ancestor.

What are the physiological consequences of snorkeling at depth? This results in very large pressure differences in the immediate vicinity of the lung⁶ as shown in Fig 2. This is drawn assuming that the bottom of the elephant lung is 2 m below the surface of the water where the pressure is approximately 150 mmHg above atmospheric. All the systemic vascular pressures will increase by this amount because if this were not the case no perfusion of the tissues would be possible. However the pressure in the alveoli is close to atmospheric because they are connected to the surface by a tube. Therefore near the outer surface of the lung the pressure changes abruptly from 0 to 150 mmHg and this creates the basic dilemma faced by the pleural membranes.

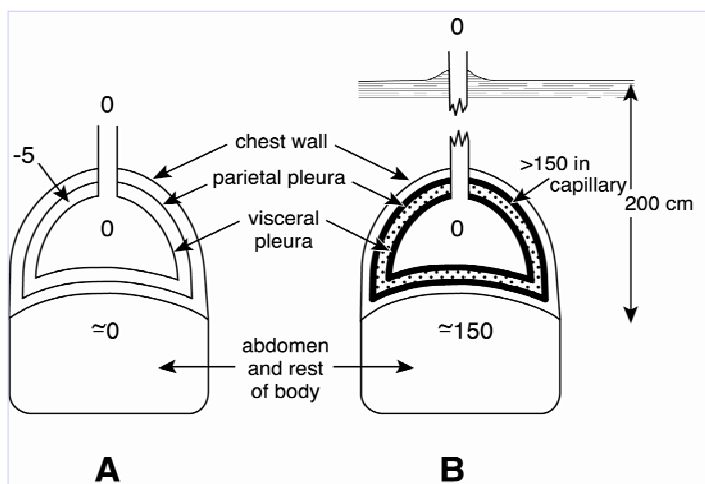


Fig 2. Distribution of pressures (mmHg) near the lung for terrestrial mammals (A) and for a snorkeling elephant (B) where the bottom of the lung is 2 m below the water surface.

The most vulnerable structure appears to be the parietal pleura. Normally its capillaries which are close to the surface provide the transudate which becomes the pleural fluid. These vessels are supplied by the systemic circulation, and so in a snorkeling elephant the pressure in the small veins must exceed 150 mmHg and the capillary pressure will be even higher. However the pressure just outside the capillaries in the pleural space would be close to alveolar pressure, that is atmospheric, if a space existed. Clearly under these conditions the capillaries would either rupture, or the great imbalance of the Starling forces would cause a massive transudation.

Evolution's solution has been to replace the normally delicate parietal pleura membrane with a sheet of dense connective tissue⁷ (Fig 3). The visceral pleura is also vulnerable and is also greatly thickened. In the absence of a mechanism to provide the normal lubricating pleural fluid, these two pleural sheets are separated by loose connective tissue that allows sliding of the lung over the chest wall. Probably the mobility is less than in other mammals where a pleural space exists, but we know from studies on patients who have had a pleurodesis for recurrent spontaneous pneumothorax that the resulting impairment of ventilatory capacity is relatively minor.

Finally we have recently come across additional evidence for the vulnerability of the parietal pleura in the elephant. Studies of fetal elephants at a very early stage of lung development show an extraordinary thickening of the endothoracic fascia which will become the parietal pleura². This appearance is strikingly different from that observed in other mammals and is consistent with the hypothesis of a long history of snorkeling in the elephant's aquatic ancestors.

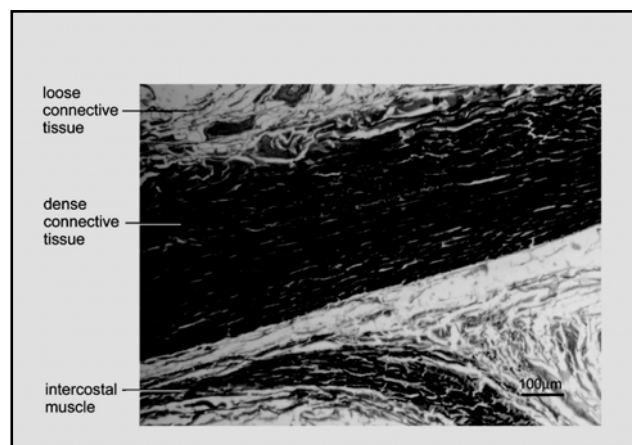


Fig 3. Parietal pleura from an African elephant. The normally delicate pleural membrane has been replaced by a layer of dense connective tissue. The loose connective tissue above this replaces the normal pleural space. Courtesy of R.E. Brown, J.B. Butler, and S.H. Loring⁷.

¹ Mullen A. *An Anatomical Account of the Elephant Accidentally Burnt in Dublin on Fryday, June 17, in the Year 1681, 1682*; London: Printed for Sam Smith.

² West JB, Fu Z, Gaeth AP, Short RV. Fetal lung development in the elephant reflects the adaptations required for snorkeling in adult life. *Respir Physiol Neurobiol* 2003; 138:325-33.

³ Aristotle. *De Partibus Animalium*. 1911; Oxford: Clarendon Press.

⁴ Tennent JE. *Ceylon*. 1860; London: Longman Green.

⁵ Gaeth AP, Short RV, Renfree MB. The developing renal, reproductive, and respiratory systems of the African elephant suggest an aquatic ancestry. *Proc Nat Acad Sci* 1999; 96:5555-8.

⁶ West JB. Snorkel breathing in the elephant explains the unique anatomy of its pleura. *Respir Physiol* 2001; 126:1-8.

⁷ Brown RE, Butler JP, Godleski JJ, Loring SH. The elephant's respiratory system: adaptations to gravitational stress. *Respir Physiol* 1997; 109:177-94.

Pemetrexed + Cisplatin Improves Survival and Quality of Life for Patients with Advanced Mesothelioma

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Malignant pleural mesothelioma (MPM) is the most common primary tumor of the pleura. The annual incidence is expected to rise worldwide until the year 2020, at which time asbestos abatement will have been in place in most countries for 20-40 years^{1,2}. Although the rate of new cases in the United States is beginning to decline, 2000-3000 new cases are still diagnosed each year.

Patients with MPM have a median survival of less than one year. Numerous cytotoxic agents (alone or in combination) have been evaluated, but no regimen has produced consistent response rates above 20%, or median survivals beyond 1 year³. For example, in 204 patients treated by the European Organization for Research and Treatment of Cancer from 1984 to 1993, using a variety of regimens, the median survival was 8.4 months from trial entry⁴, while in the case of 337 Cancer and Leukemia Group B patients from 1984 to 1994, the median survival from trial entry was 7.2 months⁵. There were virtually no phase III trials to suggest that single-agent chemotherapy was inferior (or superior) to combination chemotherapy. Promising phase II data published between 1999 and 2002 showed consistent activity of the gemcitabine + cisplatin combination (response rates 20-40% and median survival 10-12 months) and this combination, in turn, became an accepted treatment regimen⁶. The data-poor environment improved substantially with the recent publication of a 456 patient phase III trial⁷, which compared single-agent cisplatin (75mg/m²) to pemetrexed (500mg/m² i.v. bolus) plus the same dose of cisplatin in chemo-naïve patients with each regimen administered once every 3 weeks.

Pemetrexed (ALIMTA®, Eli Lilly, USA) is a novel anti-metabolite distinguished by its action against multiple folate-dependent enzymes needed for synthesis of purines and thymidine. Affected enzyme targets include thymidylate synthase, dihydrofolate reductase and glycinamide ribonucleotide formyltransferase. The cellular uptake of pemetrexed is enhanced by its high affinity for both reduced folate carrier and folate receptor. Once inside the cell, it is an excellent substrate for folylpoly- γ -glutamate synthase (FPGS) and the polyglutamated forms have increased cellular retention and potency⁸.

The phase III trial results showed that pemetrexed + cisplatin was clearly superior to the single-drug regimen as assessed by median survival time (Fig 1, 12.1 vs 9.3 months respectively, HR=0.77, $p=0.02$). One-year survival rates were

also higher in the pemetrexed + cisplatin group (50% vs 38%). Tumor response rates (as measured by an average 30% reduction in the thickness of the pleural rind at up to 9 points on the CT scan) were 41.3% in the combination arm vs 16.7% in the cisplatin arm ($p<0.001$)⁷. Time to disease progression, pulmonary function⁹ and quality of life¹⁰ also improved significantly in pemetrexed + cisplatin treated patients.

A retrospective analysis designed to identify baseline factors associated with severe pemetrexed-induced toxicity was completed during the early stages of the trial (117 patients enrolled). The multiple regression analysis that included 246 patients previously enrolled in phase I and phase II pemetrexed trials, showed that patients with high baseline plasma homocysteine had an increased risk of severe pemetrexed toxicity¹¹. Folic acid and vitamin B₁₂ (FA/B₁₂) were subsequently added to both treatment regimens to reduce some of the severe drug-induced toxicities. FA/B₁₂ supplementation significantly reduced the incidence of serious toxicities in this trial (Table 1), without reducing treatment potency⁷. Median survival times for patients who received full FA/B₁₂ supplementation (both before and throughout treatment) were 13.3 months for patients treated with pemetrexed + cisplatin and 10.0 months for patients treated with cisplatin alone (HR=0.75, $p=0.051$). Serious adverse events including drug related death, NCI-CTC grade 3/4 neutropenia, thrombocytopenia, nausea, and vomiting were more prevalent in the two-drug regimen compared to cisplatin alone. The relative risk of selected toxicities was calculated for both the intent-to-treat population and the fully supplemented subgroup (Table 1). These results indicate that pemetrexed + cisplatin with FA/B₁₂ supplementation, provides a superior risk-benefit ratio for MPM patients.

This trial had several important features that support the credibility and relevance of the results. The patient population was highly representative of typical clinical practice in terms of age, performance status and histology. The median survival for cisplatin-treated patients was consistent with (if not slightly better than) previous reports. The methods of response assessment by serial CT scan provide a good and reproducible model for future trials and the serial assessment of health-related quality of life and pulmonary function provided important supplemental information about the clinical benefits of pemetrexed + cisplatin therapy. These results not only establish pemetrexed + cisplatin therapy as the new standard of care for patients with advanced mesothelioma¹², but also provide an important foundation for exploration of this combination for induction chemotherapy with MPM patients with early stage disease.

¹ Peto J. et al. Br J Cancer 1999; 79:666-72.

² Price B. Ann. Epidemiol 1997; 145:211-8.

³ Ong ST, Vogelzang NJ: J Clin Oncol 1996; 14:1007-17.

⁴ Curran D, et al. J Clin Oncol, 1998; 16:145-52.

⁵ Herndon JE, et al. Chest 1998; 113:723-31.

⁶ Byrne MJ, et al: J Clin Oncol 1999; 17:25-30.

- ⁷ Vogelzang NJ, et al. J Clin Oncol 2003; 21:2636-44.
⁸ Rhee MS, et al. Cancer Chemother Pharmacol 1999; 44:427-32.
⁹ Pistolesi M, et al. Lung Cancer 2003; 41: S220 (abstr P-513).
¹⁰ Gralla RJ, et al. Proc Am Soc Clin Oncol 2003; 22:621 (abstr 2496).
¹¹ Vogelzang NJ, et al. Proc Am Soc Clin Oncol 2003; 22:657 (abstr 2644).
¹² Rusch VW. J Clin Oncol 2003; 21:2629-30.

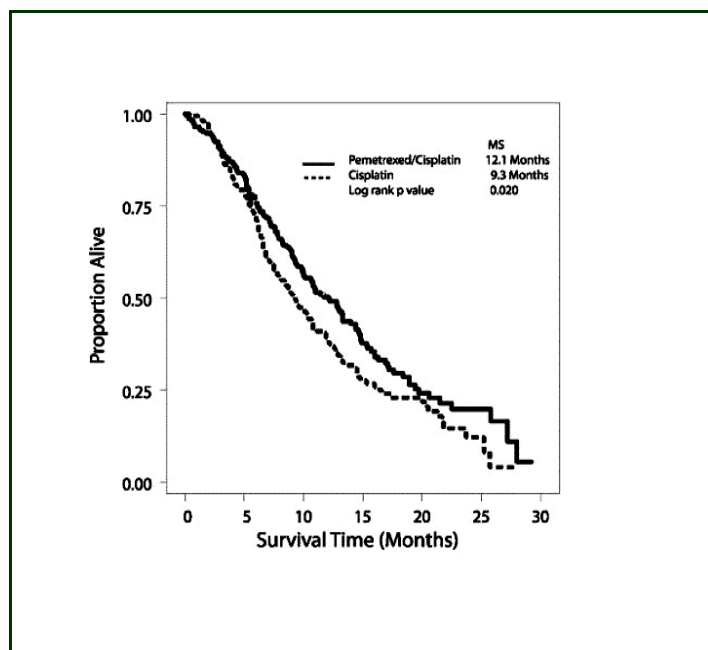


Figure 1. Kaplan-Meier estimates of overall survival time for all patients, intent to treat. (Reprinted with permission from the American Society of Clinical Oncology from Vogelzang NJ et al: Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003; 21:2636-44.)

	All patients, Intent to Treat (n=448)			Vitamin Supplemented Patients (n=331) †			
	P+C (226)	C (222)	RR	P+C (168)	C (163)	RR	Relat RR
SAE	51	16	3.1	35	15	2.3	0.72
N-penia	63	5	12.4	39	5	7.6	0.61
Nausea	33	14	2.3	20	9	2.2	0.93
Vomit	30	8	3.7	18	7	2.5	0.68

Table 1. Incidence and Relative Risk of Selected Toxicities
 † includes patients who received folic acid and vitamin B₁₂ supplements before and throughout treatment. SAE = drug-related serious adverse events; RR = Relative Risk between treatment groups; Relat. RR = relative risk for fully supplemented patients vs all patients. N-penia (neutropenia), nausea and vomiting referred to grade 3/4 events only.

Obituary: Prof Nai-Sang Wang

The pleural disease community lost one of its important researchers when Nai-San Wang MD PhD, died on October 21, 2003 at the age of 67. Dr Wang was one of the original advisors for the International Pleural Newsletter. Dr Wang was born in Taiwan and attended medical school at National Taiwan University in Taipei. He subsequently trained in the United States in anatomical pathology and concluded his training in pathology at McGill University, Canada where he earned a PhD in experimental pathology under the direction of Dr William Thurlbeck in 1971. After being on the faculty at McGill for 19 years, he moved to the University of California, Irvine where he was professor of pathology from 1990 to 1996. He then returned to Taiwan in 1996 to become Dean of the College of Medicine of the National Cheng Kung University in Tainan, Taiwan. In 2001, he became President of the Chungtai Institute of Health Sciences and Technology in Taipei, Taiwan.

Dr Wang was one of the few pathologists in the world whose primary interest was the pleura. Although he made many contributions in other areas of pulmonary diseases, his contributions to the pathology of the pleura are most remarkable. His articles in the mid 1970's describing the preformed stomas connecting the pleural cavity and the lymphatics in the parietal pleura (*Am Rev Respir Dis* 1975;111:12) and the regional differences of pleural mesothelial cells (*Am Rev Respir Dis* 1974;110:623) are classic papers describing the anatomy of the pleura that remain widely quoted 30 years later. His application of scanning electron microscopy to the pleura made these articles noteworthy. Dr Wang was also one of the first investigators to use electron microscopy for the diagnosis of mesothelioma. Furthermore, he contributed immensely to many published studies of experimental pleurodesis.

In addition to his academic accomplishments, Dr Wang was a perfect scholar – learned, diligent, yet always humble and polite. Much of his ground-breaking pleural research was performed with limited support, and he always encouraged young investigators not to be deterred by the scarcity of resources.

On a personal level, we enjoyed many tennis games together, which he always won. His great sense of humor will also be sorely missed.

Dr Wang, pleural pathologist, teacher, mentor, husband, father and friend has left a legacy and will be missed by many. Condolences may be sent to Mrs Ruey Suey Wang, 18 Zola Ct, Irvine, CA 92612, USA.

Richard W Light M.D.