Adventures in Gas Exchange

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Donald W. Seldin was the new chairman of the Department of Medicine at the University of Texas Southwestern Medical School when I arrived as a first-year medicine resident at Parkland Hospital in Dallas in July 1952. I had no plans to enter an academic career nor any concept of what it meant to do so. Seldin was relentless in his demands for excellence from the house staff, and we dreaded the embarrassment of his criticisms. However, he occasionally lowered his gruff facade and allowed the gentler, more human side of his nature to surface. There was the time that, as a volunteer experimental subject, I received an intravenous solution contaminated with pyrogens. I developed chills, high fever, and hypotension as I lay on a floor mattress in the laboratory. Seldin was called by two panicked student research fellows, and I remember him pacing worriedly around me giving orders as I lay prostrate on the floor and saying with genuine concern: “What if this had happened to a patient?” Residents, of course, were expendable in those days. But I recovered and became chief resident at the end of that first year. I attained this position not because of my excellence but because I was the only senior resident left. Yet Don Seldin did inspire us to excel and to make the most of our capabilities. One of the student fellows I worked with is presently a dean at Southwestern; the other is chairman of medicine at the University of California at San Francisco.

It was Seldin who convinced me that I could achieve a place in academic medicine and was capable of doing research. I spent a year of pulmonary fellowship with William F. Miller in Dallas before going to the University of Pennsylvania Graduate...
School of Medicine for further training in Julius Comroe's department. At Pennsylvania, I was placed under the expert tutelage of Robert E. Forster, with whom I had many wonderful and animated discussions. Bob Forster set me to the task of developing a technique for simultaneously measuring pulmonary capillary blood flow ($Q_c$), tissue volume ($V_t$), and CO diffusing capacity ($D_{Lco}$) during rest and exercise. I spent 2 months in the library; 4 months learning the behavioral idiosyncrasies of the mass spectrometer, infrared analyzers, and Brush recorders; 3 months setting up the technique; and 3 months gathering data. But in that short time I learned vital techniques and had seeds of ideas implanted that were to continually shape my career.

I have often wondered why so many funny things happened in those early days. I think it was because we were all so new to research and to the techniques that we were trying to master. Put more directly, we didn't know what we were doing. For instance, there was the time that John Rankin wanted to show off his Donald Duck voice to the two female technicians in the next laboratory. He took a deep breath of 100% helium and ran into the hall but never made it to their laboratory. He awoke on the floor with the two technicians frantically trying to revive him; John learned that a deep breath of 100% helium couldn't supply enough oxygen to get him to the next lab. Then there was the time Myron Stein and Phil Kimbel were learning how to measure pulmonary blood flow with Arthur Dubois' plethysmographic technique, using Bill Spicer as a subject. The steel whole-body plethysmograph was fit with a speaker for voice communication and a small, round glass porthole for visual communication. Bill Spicer had inhaled an inspiratory capacity of 80% nitrous oxide and was holding his breath for the blood flow measurement. Phil and Myron, struggling with unfamiliar electronic circuitry, kept saying to Bill, "Hold it. Hold it. Hold it just a little longer!" as Bill Spicer's head slowly slipped beneath the porthole window. The two investigators suddenly remembered that nitrous oxide is an anesthetic. When they opened the plethysmograph door, Bill slipped out onto the floor. Another funny incident illustrating our early problems with handling gases and plumbing occurred after I had returned to Dallas. It involved Harold Lawson, who later would also train under Robert Forster. Harold was filling a "bag-in-a-box system" consisting of a 30-gallon steel drum containing a standard weather balloon. I was in the next laboratory and was startled by a terrific explosion. I rushed next door and found Harold on the floor and the steel drum on the other side of the room with its seam ripped open. Harold had closed the spirometer port too early, thinking that any overpressure would be relieved by the small cork plug in the cylinder head of the drum popping out. The seam of the cylinder head had been ripped out while the cork remained undisturbed. He had forgotten the story of the little Dutch boy who had saved the city of Haarlem by holding back the entire North Sea using his small arm to plug a leak in the dike.

After returning to Dallas, I wanted to set up Bob Forster's method for measuring $Q_c$ and $D_{Lco}$ at the University of Texas and to determine whether we could use the method to derive useful information about oxygen transport in normal subjects or in patients. Norman Staub, also at the University of Pennsylvania at that time, had measured the kinetics of oxygen uptake by red cells and made it possible to translate measurements of CO diffusing capacity into terms of oxygen transport using the Roughton-Forster equation.

Because we wanted to test whether $D_{Lco}$ could predict limits of oxygen exchange by diffusion, we planned to exploit conditions in which oxygen transport in the human lung would be stressed to its limit, i.e., combinations of exercise, pneum-
Pneumonectomy in Humans

Studies began with humans and only later involved animals. Chris DeGraff, then at the University of Texas, knew of a thoracic surgeon in San Antonio who had been doing extensive lung resections on patients with pulmonary tuberculosis. We contacted the surgeon and arranged to study a group of his patients who had undergone from 45 to 66% lung resections. In the spring of 1963, with the help of Carleton B. Chapman and funding from the U.S. Air Force, we moved our laboratory to Willford Hall, the air force hospital in San Antonio, and arranged to use their cardiac cath lab. In Dallas, Jere Mitchell and Carlton Chapman had collected data suggesting that in average humans maximal oxygen consumption is limited by cardiac output and peripheral oxygen extraction, not by gas exchange.

The hypotheses we tested were that, after pneumonectomy: (1) Exercise will become limited by gas exchange because of the loss of capillary bed and alveolar surface area; and (2) We should be able to predict the limitation imposed from measured \( DL_{CO} \), membrane diffusing capacity (\( DM_{CO} \)), and pulmonary capillary blood volume (\( Vc \)).

Demographics and maximal oxygen intake of the 8 patients studied after lung resections are shown in Table 1. Six subjects were female. Average age was 34, ranging from 27 to 47, and the average amount of lung remaining was 40.6%, ranging from 55 to 33%. Average time since surgery was 2 years.

Maximal oxygen intake was significantly reduced, almost in proportion to the amount of lung removed; the average was 47% of predicted normal. Contrary to expectations, however, these patients were not limited by gas exchange but, rather, appeared to be limited by a low maximal cardiac output. At peak exercise they reached 83% of their age-predicted maximal heart rate. Yet arterial oxygen saturation fell only from an average of 95% at rest to 90% at peak exercise. Diffusing capacity was not reduced as much as expected from the amount of lung removed (Table 2), suggesting a significant compensatory increase of \( DL_{CO} \) in the remaining lung. When this reduction in \( DL_{CO} \) was translated into an expected reduction in oxygen transport, it was insuffi-

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### Table 1
Demographics and maximal oxygen intake after lung resection in humans

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Lung (% predicted normal)</th>
<th>Maximal ( O_2 ) Uptake (ml/min)/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS</td>
<td>F</td>
<td>27</td>
<td>166</td>
<td>48.4</td>
<td>55</td>
<td>19.8 (47)</td>
</tr>
<tr>
<td>BW</td>
<td>F</td>
<td>29</td>
<td>163</td>
<td>54.4</td>
<td>45</td>
<td>22.9 (55)</td>
</tr>
<tr>
<td>MG</td>
<td>F</td>
<td>41</td>
<td>150</td>
<td>40.9</td>
<td>42</td>
<td>24.1 (68)</td>
</tr>
<tr>
<td>CY</td>
<td>M</td>
<td>32</td>
<td>170</td>
<td>61.8</td>
<td>39</td>
<td>21.3 (42)</td>
</tr>
<tr>
<td>MC</td>
<td>F</td>
<td>29</td>
<td>159</td>
<td>57.3</td>
<td>36</td>
<td>18.3 (44)</td>
</tr>
<tr>
<td>RT</td>
<td>M</td>
<td>36</td>
<td>172</td>
<td>54.5</td>
<td>36</td>
<td>16.5 (34)</td>
</tr>
<tr>
<td>AB</td>
<td>F</td>
<td>29</td>
<td>167</td>
<td>40.4</td>
<td>36</td>
<td>17.9 (43)</td>
</tr>
<tr>
<td>RH</td>
<td>F</td>
<td>47</td>
<td>153</td>
<td>59.5</td>
<td>33</td>
<td>13.4 (41)</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>33.8</td>
<td>162.5</td>
<td>52.2</td>
<td>40.6</td>
<td>19.3 (46.8)</td>
</tr>
</tbody>
</table>

(Reproduced from reference 8.)
Table 2

Diffusing capacities and total lung capacities of patients after extensive lung resections as adults

<table>
<thead>
<tr>
<th>% Lung remaining</th>
<th>40.6 ± 6.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single breath $D_{LCO}$</td>
<td>52.4 ± 11.9*</td>
</tr>
<tr>
<td>Total lung capacity</td>
<td>55.1 ± 11.9*</td>
</tr>
<tr>
<td>Mean ± SD.</td>
<td>55.1±11.9*</td>
</tr>
<tr>
<td>*p &lt; 0.005 compared to % lung remaining.</td>
<td></td>
</tr>
</tbody>
</table>

(Reproduced from reference 8.)

Table 3

Diffusing capacities and total lung capacities of adults after pneumonectomy at a mean age of 6.6 years

<table>
<thead>
<tr>
<th>% lung remaining</th>
<th>48.8 ± 5.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single breath $D_{LCO}$</td>
<td>76.9 ± 15.1*</td>
</tr>
<tr>
<td>Total lung capacity</td>
<td>85.2 ± 17.1*</td>
</tr>
<tr>
<td>Mean ± SD.</td>
<td>55.1±11.9*</td>
</tr>
<tr>
<td>*p &lt; 0.01 compared with % lung remaining.</td>
<td></td>
</tr>
</tbody>
</table>

(Reproduced from reference 9.)

cient to explain the low maximal oxygen intake or the significant but modest fall in arterial oxygen saturation.

A similar compensatory increase of $D_{LCO}$ was reported by Giamonna in adults who had undergone pneumonectomy in childhood, which raised the possibility of enhanced alveolar capillary growth in the remaining lung (Table 3).

An alternate and equally plausible possibility, however, is that alveolar distension and increased blood flow in the remaining lung had recruited existing reserves of diffusing capacity. These findings stimulated our interest in the potential that might exist in children and adults for enhancement of lung growth.

High-Altitude Studies in Humans

It was recognized that diffusing capacity of the lung probably did not limit exercise at sea level but could do so at low alveolar oxygen tensions; thus the question arose whether prolonged residence at high altitude might stimulate lung growth. An adaptive increase in oxygen diffusing capacity had been reported among high-altitude natives in the Andes; however, this increase might reflect genetic selection that had occurred over centuries in this Indian population rather than any induction of lung growth. There was little opportunity in Texas for satisfying our interest in high-altitude adaptation. However, Carleton B. Chapman, then chief of cardiology in Dallas, learned from Dr. Gilbert Blount, chief of cardiology at the University of Colorado, that a young investigator in his division named Robert Grover was setting up a high-altitude research laboratory in Leadville, Colorado. Leadville is a mining community at 10,200 feet. The resident population is predominantly Caucasian, many of whose families had resided there for one to three generations. Hence, I contacted Bob Grover, who invited me to visit the laboratory and discuss possibilities for a collaborative study.

On my first visit, Bob arranged for me to ride up to Leadville from Denver with a new research fellow working with him from New York. We had to go over Loveland Pass at 12,000 feet because the Eisenhower Tunnel had not yet been built. The New Yorker became increasingly agitated as we left Denver because he was not accustomed to driving in the mountains. It was beginning to snow, and he began to suggest that we turn around or that I drive. At the top of the pass, now in a blizzard with visibility about 20 feet, he stopped the car and asked me to get out and determine which side of a tall red and white pole we should go on. The pole in fact marked the edge of the road and steep precipice, the bottom of which I could not see; it now became my job to lead the car
like a balky mule over this section of the pass, all the while reconsidering my commitment to high-altitude research. But we did not make it over the two crossings of the continental divide required to reach Leadville, and my subsequent collaboration with Bob Grover has extended over 26 years in spite of this early test of my fortitude.

We moved our laboratory to St. Vincent’s Hospital at Leadville in the summer of 1964 and studied a sample of the Leadville population in collaboration with Bob Grover. Bob and his team had developed an excellent working relationship with Leadville residents, who also had concerns about health problems at high altitude. We studied a young group of lifelong residents of Leadville, 7 males and 6 females, ranging in age from 15 to 31 (mean = 20.8). These data were compared with measurements taken by the same methods at rest and exercise in 8 males and 6 females matched for body size and age raised near sea level and studied in Dallas (mean age = 18.0); prediction equations were derived for the relationships among single breath $DL_{CO}$ at peak inspiration, $DM_{CO}$, $Ve$, $Qc$, and total lung capacity (TLC). The 6 investigators also were studied in Dallas and after 6 weeks in Leadville to confirm reproducibility of the measurements in both locations. Results for the young Leadville subjects and results for the investigators studied both in Dallas and in Leadville are summarized in Table 4.7

$DL_{CO}$ was significantly higher by about 16% in Leadville residents than predicted based on sea level data from our own laboratory. This was due to a significantly higher membrane diffusing capacity ($DM_{CO}$) as well as pulmonary capillary blood volume ($Ve$). Total lung capacity was significantly larger (by about 11%) than predicted from sea level data, although spirometric data were not significantly different from sea level predictions.

The members of the investigative team from Dallas showed no significant changes in $DL_{CO}$, $DM_{CO}$, or $Ve$ or in lung volumes during the 6 weeks spent in Leadville. We concluded that Caucasians born and raised at 10,000 feet had significantly larger diffusing capacities and total lung capacities than Caucasian natives of sea level. We presumed that the differences were a consequence of enhanced lung growth induced environmentally. But in

<table>
<thead>
<tr>
<th>Table 4</th>
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</thead>
<tbody>
<tr>
<td>Single breath diffusing capacity and total lung capacity in 6-week sojourners and lifelong residents in Leadville, Colorado (3,100 m)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>$TLC^a$ (liters)</th>
<th>$DL_{CO}$ (ml/min)</th>
<th>$DM_{CO}$ (ml/min)</th>
<th>$Ve$ (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residents</td>
<td>20.8</td>
<td>6.25 (111)$^b$</td>
<td>39.1 (116)$^b$</td>
<td>82.8 (124)$^b$</td>
<td>102.0 (115)$^b$</td>
</tr>
<tr>
<td>(n = 13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparison with sea level predictions</td>
<td>$p &lt; 0.025$</td>
<td>$p &lt; 0.005$</td>
<td>$p &lt; 0.025$</td>
<td>$p &lt; 0.025$</td>
<td></td>
</tr>
<tr>
<td>Sojourners</td>
<td>27.0</td>
<td>7.59 (107)$^c$</td>
<td>36.1 (97)$^c$</td>
<td>76.3 (93)$^c$</td>
<td>83.0 (101)$^c$</td>
</tr>
<tr>
<td>(n = 6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparison with sea level predictions</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

Mean ± SEM.

$^a$TLC estimated by single-breath He dilution.

$^b$% of predicted based on matched Dallas resident of similar age and body size.

$^c$% of Dallas measurements.

(Reproduced from reference 7.)
the early 1970s Cerny et al.\textsuperscript{4} did a similar study in Leadville on newcomers to high altitude, one group that had arrived in Leadville as adolescents and another group that had arrived as adults and lived there for between 1 and 17 years (see Table 5).

The Cerny study was published in 1973.\textsuperscript{4} The investigators concluded that lung growth had occurred in adults and adolescents after a period of residence at high altitude. This casts a new light on interpretation of our own Leadville data. Either high altitude stimulates growth of the lung in adults as well as children, or other effects of acclimatization to high altitude independent of growth alters diffusing capacity measured at high altitude. For example, polycythemia and the associated increase in total blood volume might increase both membrane diffusing capacity and pulmonary capillary blood volume. The kinetics of red cell uptake of CO might be affected by acclimatization.

Hence, results in humans after pneumonectomy or after prolonged residence at high altitude had yielded confusing data from which firm conclusions were not possible. Although the data indicate that both lung resection and prolonged residence at high altitude evoke compensatory increases in lung volumes and diffusing capacities in children and adults, it is not possible to assign the observed changes to growth. In 1976 we decided to use dogs to obtain some answers. We chose beagles. Our questions are listed below:

1. What effect does prolonged residence at high altitude have on lung pressure volume relations, shape of the thorax, lung tissue volume, and diffusing capacity of mature beagles and of puppies?
2. What effect does pneumonectomy have on lung pressure volume relations, shape of the thorax, lung tissue volume, and diffusing capacity of mature beagles and of puppies?

Protocols are summarized below:

A. Intervention as adults
1. Six beagles, born and bred at sea level, were taken as adults to 10,200 feet and kept there for 3 years.
2. Six control beagles of the same age were kept at sea level.
3. Six adult beagles, born and raised at sea level, had a left pneumonectomy at sea level.

B. Intervention as puppies
1. Six beagle puppies, born at sea level, were taken to 10,200 feet at 2.5 months of age and were raised there until they were 16 months old.
2. Six control beagles were raised simultaneously at sea level.
3. Six beagles had a left pneumonectomy performed at 2.5 months of age and then were raised at sea level.

High-altitude data are presented first.\textsuperscript{15} Final studies were done after the beagles kept at high altitude had been returned to sea level for 6 to 9 months. This time interval allowed complete reacclimatization to sea level.

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**Table 5**

Effect of 1 to 17 years' residence at high altitude on $DL_{CO}$ in persons born at sea level

<table>
<thead>
<tr>
<th></th>
<th>Measured $ml/min$</th>
<th>Predicted $ml/min$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>torr</td>
<td>torr</td>
</tr>
<tr>
<td>Arrival as adults\textsuperscript{a} (n = 11)</td>
<td>49.0</td>
<td>42.6</td>
</tr>
<tr>
<td>Comparison with sea level predictions</td>
<td>$p &lt; 0.005$</td>
<td></td>
</tr>
<tr>
<td>Arrival as adolescents\textsuperscript{a} (n = 13)</td>
<td>42.8</td>
<td>34.1</td>
</tr>
<tr>
<td>Comparison with sea level predictions</td>
<td>$p &lt; 0.005$</td>
<td></td>
</tr>
</tbody>
</table>

(Reproduced from reference 4.)
The dogs were anesthetized with pentobarbital and intubated; an esophageal balloon was then placed in the lower 1/3 of the esophagus to take esophageal pressure measurements. A 1,500 ml super syringe was used to inflate the lungs with a volume of 15, 30, 45, 60, or 75 ml/kg of a gas mixture containing 9% helium. After mouth and esophageal pressures had stabilized, pressure measurements were recorded, and the dog was rebreathed with the gas mixture until helium concentration stabilized. Lung air volume was calculated from the inspired volume and helium dilution.

At a separate time, using a gas mixture containing 0.6% C₃H₄, 0.3% C¹⁸O, and 9% helium in a balance of either air or 100% oxygen, pulmonary capillary blood flow, CO diffusing capacity of the lung, and lung volume were measured simultaneously during rebreathing. Measurements were repeated at different lung volumes and at two different oxygen tensions to estimate membrane diffusing capacity and pulmonary capillary blood volume. For brevity, only the data obtained at the lower alveolar oxygen tension are presented here (Fig. 1).

Physiologic studies were done after blood volumes, hemoglobin concentrations, and pulmonary arterial pressure had returned to sea level values.¹⁰,¹⁵ The beagles raised at high altitude had significantly larger lung volumes and diffusing capacities at any given transpulmonary inflation pressure. Keeping adult beagles at high altitude for an extended period had no significant lasting effect on either lung volume or diffusing capacity.

At the termination of the study, the beagles were anesthetized with pentobarbital and intubated through a tracheostomy. The abdomen was opened and the lungs collapsed by rupture through the left hemidiaphragm. This was followed by tracheal instillation of 3% gluteraldehyde in phosphate buffer at a hydrostatic pressure of 30 cmH₂O. After fixation in situ, the lungs were removed and immersed in Carson’s 10% buffered formalin. The volume of each lung was measured by water displacement after fixation. Tissue blocks were taken for light microscopy from six predetermined areas of each lobe, three from the dorsal and three from the ventral aspects; imbedded in methacrylate; and sectioned for morphometric measurements. They are summarized in Table 6 for comparison with corresponding physiologic measurements.

Air space volume, alveolar surface areas, and septal tissue volumes measured by morphometry were significantly larger.
Table 6
Comparison of morphometric and physiologic data in beagles living at high altitude for extended intervals with controls near sea level

<table>
<thead>
<tr>
<th>Group</th>
<th>Adults</th>
<th>Puppies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>High Altitude</td>
</tr>
<tr>
<td><strong>Morphometric</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Air Vol. (ml/kg)</td>
<td>54.4 ± 5.5</td>
<td>51.9 ± 4.5</td>
</tr>
<tr>
<td>SA (m²/kg)</td>
<td>2.92 ± 0.30</td>
<td>2.55 ± 0.11</td>
</tr>
<tr>
<td>Vt (ml/kg)</td>
<td>14.5 ± 1.5</td>
<td>12.3 ± 0.9</td>
</tr>
<tr>
<td><strong>Physiologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRC (ml/kg)</td>
<td>37.6 ± 3.6</td>
<td>36.5 ± 2.6</td>
</tr>
<tr>
<td>Vt (ml/kg)</td>
<td>13.8 ± 1.3</td>
<td>14.5 ± 1.0</td>
</tr>
<tr>
<td>Vt-Vc (ml/kg)</td>
<td>12.4 ± 1.2</td>
<td>13.1 ± 0.9</td>
</tr>
</tbody>
</table>

Mean ± SEM.
Vt = tissue volume of fine parenchyma.
Vc = pulmonary capillary blood volume.
Vt-Vc = extravascular tissue volume.
*p < 0.05 in comparison with corresponding controls.
**0.05 < p < 0.1 in comparison with corresponding controls.

in the beagles raised from 2.5 months of age at altitude when compared to corresponding controls raised simultaneously at sea level. On the other hand, there were no significant differences in these same measurements between beagles kept for 3 years as adults at altitude compared with corresponding controls kept at sea level. Both morphometric and physiologic measurements indicate enhanced lung growth in the beagles raised at high altitude. These data are consistent with the interpretation that the higher lung volumes and diffusing capacities measured in lifetime residents of Leadville, Colorado, reflect a direct stimulation of lung growth in infancy and childhood. The findings of Cerny and coworkers⁴ of increased diffusing capacities in long-term residents who arrived in Leadville as adults may result from secondary effects causing greater recruitment of lung capillary surface, such as expanded blood volumes and increased hematocrits. These effects should be reversible on return to sea level.

The results from the pneumonectomy studies¹⁴ were more difficult to interpret because of the inherent difficulties of separating compensation by recruitment of existing reserves in the remaining lung-by-lung distension or increased blood flow from compensation by growth of new functional lung units.

Diffusing capacity was significantly reduced after pneumonectomy as an adult. After pneumonectomy, both lung volume and diffusing capacity of the remaining right lung were significantly greater than in the right lung of controls. Compensation appears to be greater in puppies than in adults. Morphometric and physiologic data yielded similar conclusions (see Table 7).

This data in Figure 2 and Table 7 indicate significant compensatory increases in lung volume, diffusing capacity, and fine septal tissue volume in the remaining lung of beagles after a left pneumonectomy is performed either as an adult or as a 2.5-month-old puppy; however, compensation is not complete, i.e., functional measurements do not return to normal. Compensation tends to be greater in beagles after pneumonectomy as a
Table 7
Comparison of morphometric and physiologic data: right lung of beagles after left pneumonectomy as adults or as puppies versus the right lung of corresponding controls

<table>
<thead>
<tr>
<th>Group</th>
<th>Adults</th>
<th>Pneumonectomy</th>
<th>Puppies</th>
<th>Controls</th>
<th>Pneumonectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphometric</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Air Vol. (ml/kg)</td>
<td>30.8 ± 3.1</td>
<td>45.2 ± 4.4*</td>
<td>24.4 ± 2.8</td>
<td>37.0 ± 4.3*</td>
<td></td>
</tr>
<tr>
<td>SA (m²/kg)</td>
<td>1.75 ± 0.19</td>
<td>2.30 ± 0.17*</td>
<td>1.58 ± 0.13</td>
<td>2.42 ± 0.15*</td>
<td></td>
</tr>
<tr>
<td>V₄ (ml/kg)</td>
<td>8.6 ± 1.0</td>
<td>13.0 ± 0.9*</td>
<td>7.0 ± 0.7</td>
<td>12.5 ± 0.7*</td>
<td></td>
</tr>
<tr>
<td>Physiologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRC (ml/kg)</td>
<td>21.7 ± 1.7</td>
<td>35.5 ± 5.3*</td>
<td>21.6 ± 1.2</td>
<td>34.5 ± 4.0*</td>
<td></td>
</tr>
<tr>
<td>V₄ (ml/kg)</td>
<td>8.3 ± 0.7</td>
<td>10.3 ± 1.0*</td>
<td>8.1 ± 0.3</td>
<td>13.1 ± 1.1*</td>
<td></td>
</tr>
<tr>
<td>V₄-Vc (ml/kg)</td>
<td>7.0 ± 0.6</td>
<td>7.7 ± 0.9</td>
<td>6.8 ± 0.3</td>
<td>10.6 ± 0.9*</td>
<td></td>
</tr>
</tbody>
</table>

Mean ± SEM.
V₄ = tissue volume of fine parenchyma in morphometric studies and acetylene tissue volume by physiologic measurements.
Vc = pulmonary capillary blood volume.
V₄-Vc = extra vascular tissue volume.
*p < 0.05 in comparison with corresponding controls.
(Reproduced from reference 14.)

Figure 2. Lung volumes (upper panels) and CO diffusing capacities (lower panels) are plotted with respect to transpulmonary pressure in four groups of beagles. The four groups include beagles after left pneumonectomy as adults, adult beagles after left pneumonectomy as 2.5-month-old puppies, and their respective controls. Data from pneumonectomized animals are compared with respect to both lungs of the controls (left hand panels) and with respect to the right lung alone (right hand panels). The assumption is that the right lung normally constitutes 58% of the total air volume and contributes 58% of the total lung diffusing capacity. Total lung volumes were significantly reduced after pneumonectomy either as an adult or as a puppy.
puppy, and the significant increase in extravascular tissue volume in the puppies suggests that growth of the lung may have been enhanced. Nevertheless, the relative importance of functional compensation and growth remains uncertain in both immature and mature beagles.

To examine this issue further we developed methods to measure ventilation, oxygen consumption, pulmonary capillary blood flow, and CO diffusing capacity by a rebreathing technique in awake dogs during heavy treadmill exercise.\textsuperscript{1,2} We also constructed carotid artery loops in the dogs and inserted flow-directed catheters through the jugular vein into the pulmonary artery for blood sampling and pressure monitoring during heavy exercise.\textsuperscript{11,12} Our objectives were to measure maximal oxygen uptake in foxhounds before and after pneumonectomy, to determine the sources of exercise limitation, and to measure the upper limit of diffusing capacity during progressive increments of exercise. Our hypothesis was that we would be able to define an upper limit to the relationship between diffusing capacity and pulmonary blood flow or pulmonary arterial pressure at increasing work loads. A change in this limit might indicate the presence or absence of lung growth after pneumonectomy. Furthermore, if growth of the microvascular bed occurred after pneumonectomy, we should expect to see a change in the pressure flow relationship of the remaining pulmonary vasculature after pneumonectomy such that pressure would be lower than expected for any given flow. Our hypothesis regarding the recruitment of $DL_{co}$ is schematized in Figure 3.\textsuperscript{3}

A similar hypothesis can be developed for the pressure-flow relationship in the right lung before and after left pneumonectomy. What we found before and after left pneumonectomy in three adult foxhounds are shown in Figures 4 and 5.

The data presented in Figure 4 indicates that an upper limit to recruitment of $DL_{co}$ and presumably of microvascular bed was never reached even after pneumonectomy, when blood flow through the remaining lung reached levels 70%
Figure 4. In the upper panel $D_{LCO}$ increased in an almost linear fashion with respect to blood flow before pneumonectomy (unfilled circles, solid line). After pneumonectomy, $D_{LCO}$ was lower at any given level of pulmonary blood flow, and the slope of the relationship between $D_{LCO}$ and pulmonary blood flow was significantly less (filled circles, dashed line). An upper limit of $D_{LCO}$ was not reached either before or after pneumonectomy. In the lower panel the relationship between the $D_{LCO}$ and pulmonary blood flow to the right lung alone is compared before and after pneumonectomy. Data points after pneumonectomy are superimposed over the normal relationship at lower blood flows but deviate below the normal relationship at higher blood flows, suggesting either that an upper limit of $D_{LCO}$ was approached or that some structural distortion in the lung after pneumonectomy has impaired normal recruitment.

Figure 5. In the left panel, mean pulmonary artery (PA) pressure is plotted with respect to pulmonary blood flow before and after left pneumonectomy. In the right panel, mean pressure-flow relationships in the right lung are examined before and after pneumonectomy. Mean pulmonary arterial pressure is higher at any given blood flow after pneumonectomy than before, although the pressure-flow relationship in the right lung appeared unchanged.

tirely by normal recruitment of existing microvascular bed. Growth of new functional units in the lung need not be invoked to explain our results. These conclusions are reinforced by the lack of change in pressure-flow relationship in the remaining right lung after left pneumonectomy shown in Figure 5.

If new microvascular bed had been added, we would expect a lower PA pressure at any given flow. The lower slope of the relationship between $D_{LCO}$ and pulmonary blood flow after pneumonectomy

greater than that achieved before pneumonectomy. Furthermore, the compensatory increase in diffusing capacity after pneumonectomy could be explained entirely by normal recruitment of existing microvascular bed. Growth of new functional units in the lung need not be invoked to explain our results. These conclusions are reinforced by the lack of change in pressure-flow relationship in the remaining right lung after left pneumonectomy shown in Figure 5.

If new microvascular bed had been added, we would expect a lower PA pressure at any given flow. The lower slope of the relationship between $D_{LCO}$ and pulmonary blood flow after pneumonectomy...
suggests that an upper limit of recruitment may be approached at high blood flows through the remaining lung after left pneumonectomy. Left pneumonectomy removes only 42% of the lung in the dog. We are currently testing the hypothesis that the capacity for further recruitment of microvascular reserves might be exceeded after removal of the larger right lung (58% resection).

Previous estimates of DL_{co} by morphometry in dogs have been reported to be two to three times those measured by physiologic methods under anesthesia in the same dogs. On the other hand, measurements of DL_{co} in our foxhounds at heavy exercise before pneumonectomy are very close to those reported by Weibel and his coworkers in canids when normalized with respect to body weight (Figure 6).

Following completion of the physiologic studies in these 3 foxhounds, lungs were fixed by intratracheal instillation of buffered gluteraldehyde for morphometry as in the beagles. Morphometric studies have been performed by Connie C. W. Hsia in collaboration with Ewald Weibel at his laboratory in Bern, Switzerland; these results are now being prepared for publication. The morphometric data also suggest that the primary effect of left pneumonectomy was overdistension of the remaining lung rather than growth of new lung units. Despite a lack of evidence for structural growth, passive stretching and thinning of the alveolar-capillary membrane, by reducing the resistance to oxygen diffusion, could account for the significant functional compensation observed after pneumonectomy. The magnitudes of functional compensation estimated by physiologic and morphometric methods are similar.

Figure 6. A comparison of our physiologic measurements of DL_{co} in foxhounds at heavy exercise with morphometric estimates of DL_{co} in canids by Weibel et al. plotted with respect to body weight.

Figure 7. The relationship between DL_{co} and pulmonary blood flow in foxhounds after right pneumonectomy (pnx) compared with that in foxhounds after right thoracotomy without lung resection (Sham pnx). In the right panel, the slopes of the two relationships are not significantly different; hence, compensation is more effective after right pneumonectomy than after left.
Connie Hsia and her coworkers in my laboratory have now completed similar physiologic studies in foxhounds after right pneumonectomy, and she is presently working with Ewald Weibel to analyze the morphometric data on the lungs of this latter group of dogs. Contrary to our expectation, an upper limit to $D_{lCO}$ was not reached in the remaining lung at peak exercise after right pneumonectomy, in spite of an increase in blood flow equivalent to over 40 L/min in a normal dog with two lungs (Fig. 7).

Hence, unresolved questions still abound. Where do these apparently inexhaustible reserves of diffusing capacity exist in the lung? What are the mechanisms of recruitment, and can an upper limit ever be reached? Why aren’t unrecruited capillaries visible in morphometric studies, or, stated in a different way, why does the whole microvascular bed appear to be fully recruited after tracheal fixation? Are cells just stretched and thinned by overexpansion of the remaining lung, or does hyperplasia also occur in adults after pneumonectomy? Is there a critical level of lung stretch necessary to trigger the growth of cells? Does pneumonectomy enhance growth of the remaining lung in puppies, leading to more functional lung units at maturity?

Not only do the reserves of lung diffusing capacity appear to be inexhaustible, so do the questions derived from that one year I spent in Robert Forster’s laboratory, at least for one lifetime. I hope that the questions arising from investigations in my laboratory will also serve as an inexhaustible resource to those who have worked there.

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References


