NOMINATION FOR THE EDWARD LIVINGSTON TRUDEAU MEDAL – 2004

[Note: Jack died before the Awards Committee met. Even so they requested a resubmission the following year, which was extraordinary]

John T. Reeves M.D.

1. Major Scientific Contributions

John T. Reeves has made major scientific contributions in area of hypoxia, the lung circulation, and the oxygen transport system. Specific areas of investigation include control of the fetal, neonatal and adult pulmonary circulations and the effects of high altitude.

THE PULMONARY CIRCULATION

Control of the pulmonary circulation. More than four decades ago, while Dr. Reeves was a research fellow with Dr. Robert Grover, the two of them, with veterinary scientists of Colorado State University, conducted the first prospective studies to induce chronic pulmonary hypertension. In those days, except for its weak reaction to hypoxia, the lung circulation was thought devoid of intrinsic control. And apart from the rare medical curiosity of primary pulmonary hypertension, elevated pressures were limited to patients with chronic heart disease or those with destruction of the lung parenchyma. However, this conventional wisdom was not adequate to explain why otherwise healthy cattle in Colorado should die of right heart failure at high altitude. Reeves and Grover suggested the possibility that a chronically hypoxic environment might induce severe pulmonary arteriolar constriction which would overwhelm the right ventricle. In such case, the lung would not host a merely passive circulation, but rather one capable of profound, occasionally even fatal, intrinsic control.

When they brought cattle from low altitude to 3,000m in Colorado, serial cardiac catheterizations over the next six months showed progressive pulmonary hypertension leading to right heart failure. Postmortem examination showed marked pulmonary arteriolar narrowing. Two years later, a repeat study showed that at a higher altitude the rate of pressure rise accelerated, that polycythemia was not a contributor, and that other species were less susceptible than cattle. A surprise finding was that when the cattle acutely breathed 100% oxygen, pulmonary arterial pressure remained severely elevated; some weeks at low altitude were required to restore pressure to normal. Obviously, chronic hypoxic pulmonary hypertension was more than sustained acute hypoxic vasoconstriction. And the lung circulation was not just a passive organ.

Because young calves often died of heart failure at altitude, Reeves began to study responses to hypoxia in the lung circulations of newborn calves. He found they had large acute pressor responses to hypoxia and that in chronic hypoxia they rapidly developed severe hypertension. He suggested that the "teleological purpose" of hypoxic pulmonary vasoconstriction might be survival of the fetus and newborn rather than matching of perfusion to ventilation in the adult as had been thought. Fetal hypoxia would constrict pulmonary arteries and shunt blood away from the useless lungs to the placenta. At birth, breathing well oxygenated air would help dilate the lung circulation to sustain life. If so, hypoxic vasoconstriction after birth would be a vestige of that in the fetus, but would likely show a variable decrease with age among individuals.

To understand better the integrated physiological responses of the fetus, Reeves took a sabbatical (1967-'68) with the father of fetal and neonatal physiology, Geoffrey Dawes in Oxford. His studies with Dawes showed that augmented fetal hypoxia, not only caused pulmonary vasoconstriction, but also induced, via the chemoreceptors and the neural sympathetics, systemic vasoconstriction in other non-essential fetal organs and this response preserved flow to more essential tissue such as placenta, heart, and brain. He drew on this experience in his later studies of the adreno-sympathetics in humans at high altitude.

As a result of his work in the newborn calf and his experience with Dawes, Reeves attracted to the laboratory young clinicians, including a pediatrician, Kurt Stenmark. Their idea, developed from Reeves's prior work, was simple - the newborn was not a miniature adult, but had unique characteristics of its lung arteries, including the marked capacity for vasoconstriction. Their strategy was to place a newborn calf at an altitude high enough to induce hypoxemia equal to that of fetal life, and when they did so life threatening pulmonary hypertension developed within two weeks. Also the cytoskeletal architecture of the right ventricular cardiac myocyte showed extensive damage, not present in adult right heart failure. But it was the remarkable histological change in the lung arterioles that led to their subsequent work in vascular cell biology.

Lung vascular cell biology. What had particularly excited Reeves and Stenmark were the extensive changes in the adventitia of the small lung arteries. Early activation of the adventitia in rats at high altitude was known, but in these high altitude calves, the magnitude and the character of the changes were new. It was not just that the adventitia was thickened; there were great whorls of connective tissue, new vessels, edema, red cell "extravasation," impressive expansion of the vaso vasorum, and many breaks in the external elastic lamina, with disorganization of the sub-adjacent medial smooth muscle. The arterial wall was not just a series of layers, but rather an integrated organ, in which the adventitia might play a dominant role. And the hypoxemic newborn calf offered a unique animal model to study the process.

The fibroblast was a good place to start and Stenmark, with Reeves's assistance, was developing a laboratory to study it. First it was necessary to know what happened during normal development. In collaboration with Bob Mecham of Washington University, they found unexpectedly that during development of the fetal calf, pulmonary arterial fibroblasts were markedly proliferative and simultaneously synthetic, a versatility not found in adult cells. The proliferating fibroblasts produced copious amounts of elastin in a carefully orchestrated developmental pattern. Soon after birth, the elaboration of elastin nearly ceased, but the capacity for proliferation, characteristic of the newborn, persisted. When young calves developed pulmonary hypertension at high altitude, the versatile phenotype reappeared, and the cells again became both highly synthetic and highly proliferative. These new findings raised new questions.

Possibly pluripotential fetal-like cells could continue to reside in the adventitia after birth and, when stimulated, these sub-populations could proliferate and assume fetal-like characteristics. One stimulus could be vascular leak. Reeves had shown that leak of protein into the pulmonary arterial wall preceded the anatomic changes. In 1988 he took a sabbatical with Dr. Geoffrey Laurent, Chief of Cardio-Pulmonary Biochemistry in the National Heart and Lung Institute in London. His idea was that if the vascular wall were injured, then plasma proteins could leak into the wall, clot, stimulate fibroblasts to replicate, and initiate wall thickening. Working with Andy Gray, a post-doctoral fellow in Laurent's laboratory, they found that the clotting factors, thrombin and fibrinogen acting alone, each increased growth rate in lung fibroblasts. However, a far greater proliferative response resulted from a fragment of the Bb chain of fibrinogen, which following clotting remained in solution and acted on fibroblasts through their calreticulin receptor. These studies are continuing in Laurent's laboratory.

Another stimulus to the fibroblast could be hypoxia. Mita Das working with Stenmark and Reeves, showed in cloned individual neonatal adventitial fibroblasts their remarkable variability in proliferation with hypoxia. It seems likely that sub-populations of fetal-like fibroblasts persist or can be induced to become activated in the pulmonary arterial adventitia after birth.

Another possibility was that in response to injury, circulating cells could enter the adventitia, perhaps via the bronchial circulation. Four decades ago when Reeves put newborn calves into an altitude chamber, he found that growth of the pulmonary arterial circulation was stunted, but the bronchial circulation expanded. Because of the presence of bronchial collaterals, he could even record aortic pressure through a catheter wedged in the pulmonary artery. Later, he and Stenmark, showed the very large increase in the volume of vasa vasorum within the adventitia of the small pulmonary arteries of hypoxic calves. Whether the great increase in the volume of adventitia in pulmonary hypertension stimulates growth of the vasa vasorum or vice-versa is under investigation. Stenmark, Reeves, and colleagues are now pursuing the hypothesis that circulating stem cells may be brought to the arteriolar adventitia by the expanded bronchial circulation, and these may contribute to the diversity of cells residing there.

These concepts and this work over the last decade have evolved in Stenmark's laboratory, where Reeves still violates University rules by parking his bicycle in the lab. But the roles have changed; Stenmark is now the chief, and Reeves is the fellow. However, taken together, these studies stimulated by, or with the participation of, Reeves have pointed to the adventitial fibroblast as an important, but hitherto relatively neglected, player in the vascular changes in chronic pulmonary hypertension. Reeves helped initiate the field of chronic hypoxic pulmonary hypertension and he has provided a substantial amount of the description which has led to subsequent work in the field. His investigations developed important fetal and neonatal aspects of hypoxic pulmonary hypertension, and he stimulated many of the cellular investigations into the mechanisms involved. While these studies have provided background for ongoing work in laboratories around the world, perhaps more important was that through them, Reeves stimulated and encouraged young investigators.

HIGH ALTITUDE

In the late 1950's Reeves began his studies of oxygen transport by asking whether and how leg blood flow might contribute to regulation of cardiac output in normal man. In resting supine subjects including himself, he found relatively high leg blood flow and high oxygen levels in the femoral venous blood. With mild supine leg exercise, the cardiac output was hardly changed and the leg just extracted more oxygen from the blood it received. However, the oxygen extraction from femoral blood was nearly complete in some subjects simply on going from lying to standing. When these subjects walked, an increase in leg blood flow was necessary to increase oxygen supply to the exercising leg. These early studies indicated the complex circulatory integration necessary for normal activity and provided the background for his studies at altitude.

Up until the 1960s it had been assumed that the increase in arterial oxygen content which accompanied altitude acclimatization would result in a higher maximal oxygen uptake than was possible on arrival. However in a series of papers, Reeves and collaborators showed that maximal oxygen uptake did not increase with acclimatization. Although with altitude residence, increases in ventilation and hemoglobin caused a higher arterial oxygen content than on arrival, maximal cardiac output fell, so that maximal oxygen uptake remained unchanged. The addition of CO_2 to the air during acclimatization allowed the cardiac output to be sustained at the sea level value, but now this was offset by a lower arterial oxygenation. For maximal exercise at altitude, it was as though there was a "bottleneck" in oxygen transport at the level of pulmonary ventilation and lung diffusion, which supported the then recent findings from the “Silver Hut” in Nepal.

Ventilation at altitude. This "bottleneck" in oxygen transport was shown by Reeves and collaborators in Operation Everest II (OE II), a project conceived by Charles Houston and conducted in 1985 in the U.S. Army chambers in Natick, MA. Normal volunteers were decompressed to permit measurements of oxygen transport in controlled environments from sea level to the equivalent of the summit of Mt. Everest. From OE II maximal exercise data, Reeves showed a maximal ventilation of ~200 L/min for all altitudes including sea level, and suggested in each instance, ventilation had reached its limit. As barometric pressure fell with altitude, so were there in nearly exact proportion decreases in the calculated number of oxygen molecules brought to the alveolus and in the measured maximal oxygen uptake. The finding was that ventilation brought approximately the same calculated number of oxygen molecules to the alveolus for each L/min of oxygen uptake, regardless of altitude or exercise intensity, indicating a near constant ventilatory oxygen transport relative to demand. At increasing altitude where there were fewer oxygen molecules in the air, more of this "thin air" had to be ventilated which caused the PCO_2 to fall and the pH to rise. Yet even under the extreme hypoxemia at the "summit" of Mt. Everest, renal compensation was sufficient to maintain a directly measured arterial pH of 7.56.

Heart and pulmonary circulation at altitude. Salient findings in OE II were that the heart functioned well, and better than the brain or lung, during severe hypoxemia on the "summit." From the OE II heart catheterization data, Reeves developed the concept that during exercise at sea level, increased left heart filling pressures passively dilated a distensible pulmonary circulation. However, after three weeks of increasing altitude, even a minimal increase in vascular resistance caused the locus for pulmonary vascular control to shift dramatically from the left heart to the pulmonary arterioles. Three factors now contributed to malfunction of the lung circulation during exercise: an increase in arteriolar resistance, loss of the increase in left ventricular filling pressures, and less distensibility of the pulmonary vessels. In terms of understanding the control of the lung circulation during exercise, Reeves had developed a novel integrated model.

Metabolism at altitude. Traditional wisdom has been that at sea level, heavy exercise switches on muscle anerobic metabolism, where energy is obtained by breakdown of muscle glycogen into the waste product, lactic acid. Inconsistent with that view were remarkable findings on the "summit" of Mount Everest in OE II, where subjects with extreme arterial hypoxemia (PaO_2 = 26 mm Hg), had nearly normal lactate levels in their blood, normal amounts of glycogen in their skeletal muscles, and with maximal exercise, they accumulated less muscle lactate and showed less glycogen depletion than at sea level. Skeletal muscle might be far more tolerant of hypoxemia than had been supposed. Reeves dedicated four summers to study exercise metabolism on Pikes Peak, and he recruited experts including Brooks, Butterfield, Grover, Mazzeo, Sutton, Wagner, Wolfel, and Young. The studies utilized state of the art calibrated diets, steady state exercise, stable isotope

kinetics, catheterization of femoral artery and vein, and muscle biopsies. They found that after an initial burst of muscle lactate release during exercise at altitude, the muscle began to consume lactate at a rate approximately equal to its production, even when the PO_2 of the venous blood draining the muscle fell as low as 5 mmHg. For metabolic fuel, the exercising muscle at altitude showed a greater dependence on circulating glucose than at sea level. These studies suggested that skeletal muscle maintains oxidative metabolism even near anoxia and questioned the concept that normally exercising muscle produces lactate as a result of anerobic metabolism.

Autonomics and hypoxia. Reeves's studies on the autonomic nervous system and the adrenergics have spanned decades and several categories - the fetus and newborn, cold, the hypoxic heart, pulmonary hypertension, ventilation, and acclimatization to altitude. But his interest was heightened about two decades ago in studies of volunteers who had beta-adrenergic blockade while exercising on Pikes Peak. He had expected that relative bradycardia would impair maximal oxygen uptake at altitude. He found slower heart rates, but not lower maximal oxygen uptakes. The surprising findings led to a detailed examination (with Mazzeo) of the sympatho-adrenal system following altitude exposure. They found that the blood and urine levels of epinephrine increased immediately on arrival on Pikes Peak, but an increase in levels of norepinephrine was delayed several days. By one week, epinephrine levels were falling but norepinephrine levels were still rising. Increases in heart rate and metabolic rate accompanied the increases in epinephrine, while an increase in systemic arterial pressure and a decrease in blood volume accompanied the increase in norepinephrine. The two limbs of the sympatho-adrenal system had different activation patterns, which resulted in complex effects on oxygen transport during acclimatization. Of particular interest was a strong correlation between the increase in ventilation during acclimatization and the increase in norepinephrine levels, but cause and effect were not studied. These were new findings and all of them have provided clues for human adaptation to altitude, which deserve further study.

These highlights have been selected from Reeves's research career, to indicate the breadth of his contributions to respiration-related research. The contributions have been seminal to the lung circulation of the fetus, newborn and adult, particularly in the development of pulmonary hypertension. His high altitude research has been key to the areas of circulation and respiration, including metabolism and the adreno-sympathetics.

2. Accomplishments as a teacher and significant accomplishments of his trainees.

Reeves is a recognized teacher, popular with undergraduate medical students. His teaching awards have come from combining an understanding of pathophysiology, an emphasis on the basic concepts, and humor derived from his youth in Appalachia. His being named a Thomas Jefferson

Scholar of the University of Colorado resulted from his teaching, research, his assistance in developing family medicine in Ukraine, and from his publication of a small paperback he wrote to stimulate his daughter's reading of the classics.

The scientific contributions and successes of those whom Reeves trained, in part or in toto, came not only from his own research ideas, but more importantly from an encouraging environment based on the example of Dr. Robert Grover, who had trained him. Some of the outstanding contributions from trainees his can be listed. In the mid 1970s McMurtry showed that hypoxia directly induced pulmonary vasoconstriction by stimulating calcium entry into the smooth muscle cell. Weir found that the calcium entered the smooth muscle cell as a result of depolarization following closure of potassium channels. Moore reported that both low maternal hypoxic ventilatory responsiveness and impaired vasodilation of arteries which supply the uterus combined to cause low birth weight at high altitude. Tucker showed that hypoxia and/or cold caused pulmonary veno-constriction, in part from increased sympathetic neural activity. Stenmark found that adventitial fibroblasts were essential to hypoxic remodeling of lung arteries. Wagner has demonstrated how blood flow is controlled in its passage through the pulmonary microcirculation. Newman has been a leader in identifying a genetic basis for primary pulmonary hypertension. Abman and Kinsella demonstrated that nitric oxide was the treatment of choice for newborn pulmonary hypertension. Rounds is the immediate past President of the American Thoracic Society. Peacock established the Pulmonary Hypertension Center for Scotland. Burghuber has become director of a clinical respiratory center and President of the Austrian Society of Pulmonology. Aldashev was appointed Director of the Cardiovascular Institute of Kyrghystan. Todd Carpenter, Mita Das, W. A Droszcz (Warsaw), Anthony Durmowicz, James Fasules, Mark Gillespie, Andrew Gray (London), Peter Hackett, Eric Hoffman, Thomas Hyers, Meir Kryger, Takiyuki Kuriyama (Chiba), Johannes Mlczoch (Vienna), Nicholas Morrell (Cambridge, UK), Benjamin Walker, Mary Weiser-Evans, Norbert Voelkel, and Stacy Zamudio all have had outstanding careers and all have scientific descendants of their own.

Fellows and their positions

Fellow	Title	Address
Aldashev, A	Professor, Director	National Center for Cardiology and Internal Medicine, Bishkek, Kyrgyzstan
Asano, K	Assistant Professor, Physiology	Yamagada School of Medicine, Japan
Bender, PR	Assistant Clinical Professor, Emergency Medicine	Kaiser Permanente, Denver
Burghuber, OC	Chairman, Department of Internal Medicine	Korneuburg Hospital, Austria
Capen, RL	Professor & Chair, Biology	Colorado College, Colorado Springs, CO
Carpenter, TC	Assistant Professor, Pediatrics	University of Colorado Health Sciences Center
Cruz JC	Professor Emeritus, Anesthesia	University of Ohio, Toledo
Daoud, F	Cardiologist, Cincinnati	
Das, M	Assistant Professor, Pediatrics	University of Colorado Health Sciences Center
Dobyns, Emily	Associate Professor, Pediatrics, Director of Clinical Training	University of Colorado Health Sciences Center
Doekel, RC	Cardiologist, Nashville	
Droszcz, WA	Professor and Chair, Pulmonology	University of Warsaw, Poland
Durmowicz, AG	Associate Professor, Pediatrics	Washington, University, St. Louis
Fasules, JW	Professor, Pediatrics	University of Arkansas, Little Rock
Fedderson, CO	Associate Professor, Medicine	Phillips University of Marburg, Germany
Frid, M	Instructor, Pediatrics	Researcher, Lung Development Laboratory, UCHSC, Denver, CO
Gheen, KM	Private Practice, Pediatrics	
Gillespie, MG	Professor and Chairman, Pharmacology	University of Southern Alabama, Mobile
Gray, AJ	University College of London	Medicine, Division of Cardiopulmonary Biochemistry
Hackett, PH	Associate Clinical Professor, Surgery	University of Colorado Health Sciences, Denver
Herget, J	Professor and Head, Physiology, Dean of the Faculty	2nd Medical Faculty, Charles University, Prague, Czech Republic
Hiser, W	Cardiologist, Wyoming	
Hoffman, EA	Professor, Radiology and Physiology	University of Iowa, Iowa City
Huang, S-Y (deceased)	Assistant Professor Anesthesia	University of Colorado Health Sciences Center, Denver
Hyers, TM	Professor, Medicine, Physiology, Head Pulmonary Division	St. Louis University, St. Louis, MO
Johnson, TS	Associate Professor, Medicine	University Southern Alabama, Mobile
Kryger, M	Professor, Medicine, Physiology, Head, Pulmonary Division	University of Manitoba, Winnipeg
Kuriyama, T	Professor and Chairman, Pulmonary Medicine	Chiba University, Chiba, Japan
Lemler, M	Assistant Professor, Pediatrics	University of Texas, Dallas
Looga, R	Professor Emeritus, Physiology	University of Tartu, Estonia
McMurtry, IF	Professor, Medicine, Physiology, Head of CVP Laboratory	University of Colorado Health Sciences Center
Mlczoch, J	Professor, Head of Cardiology	University of Vienna, Austria

Moore, LG	Professor , Medicine, Anthropology, Director, Women's Health Research	University of Colorado, Denver and Health Sciences, Campuses
Morganroth, ML	Pulmonologist, Oregon	
Morrell, Nicholas	Associate Professor, Medicine	Cambridge University, UK
Newman, JH	Professor, Medicine, Physiology	Vanderbilt University, Nashville, Tennessee
Orton, EC	Associate Professor, Surgery	Colorado State University, Fort Collins, CO
Peacock, AJ	Professor & Head, Pulmonary Medicine, Director, Pulmonary Hypertension Center, Scotland	University of Glasgow, Scotland
Redding, GJ	Professor, Head, Pediatric Pulmonary	University of Washington, Seattle
Roberts, AC	Director	Boulder Sports Medicine: Consultant to professional teams
Rounds, SS	Professor, Medicine and Pathology, Vice President, American Thoracic Society	Brown University Medical School, Providence
Scoggin, CH	President & CEO, MedRock Corp	Biotech firm in Boulder, CO
Selland, MA	Cardiologist	Anchorage, AL
Shelub, I	Cardiologist	San Francisco, CA
Stenmark, KR	Professor, Head Pediatric Critical Care, Director SCOR Program	University of Colorado Health Sciences Center
Stiebellehner, L	Assistant Professor, Pulmonary Medicine	University of Vienna, Austria
Sugita, T	President, Chiba Hospital	Chiba, Japan
Sun, S-F	Emeritus Director	High Altitude Medical Institute, Lhasa, Tibet
Tucker, A	Professor of Physiology, Associate Dean, University Vice Chancellor	Colorado State University, Fort Collins
Turkevitch, D	Artist	Grand Rapids, MI
Van Benthuysen, KM	Cardiologist	Denver
van Grondelle, A	Dept of Biomedical Engineering	Rensselaer Polytechnic Institute, Troy, NY
Voelkel, NF	Professor, Medicine, Head, Pulmonary Hypertension Center	University of Colorado Health Sciences Center, Denver
Wagner, WW	Professor, Physiology, Anesthesia, Head Pulmonary Research Laboratory	Indiana University, Indianapolis, IN
Walker, BR	Professor, Cell Biology and Physiology	University of New Mexico, Albuquerque
Weir, EK	Professor, Medicine, Head Cardiology	Veterans Administration University of Minnesota, Minneapolis
Weiser-Evans, Mary	Assistant Professor, Pediatrics	University of Colorado Health Sciences Center
Weiser, Phillip	Director, Pulmonary Diagnostics & Rehabilitation	Medical College of Pennsylvania, Philadelphia
Zamudio, S	Assistant Professor, Obstetrics and Gynecology	New Jersey Medical College
Zuckerman, BD	Supervisor, Medical Devices Division	Federal Food Drug Administration, Washington, DC

3. Recognition received nationally and internationally.

National. For his contributions to the understanding of the pulmonary circulation, altitude and exercise, Reeves has given numerous invited lectures and received many awards. Important, but not mentioned in his CV, is his activity in stimulating and promoting formation in November 2002 of the Colorado Center for Altitude Medicine and Physiology at the University of Colorado Health Science Center. The Center recognizes that Colorado is the highest state in the nation. It addresses health and economic issues of altitude; encourages public education; and stimulates basic research into the effects of hypoxia. Collaborative links with Bolivia, China, Peru, and Ukraine have been established.

International Activities. In 1980, Reeves was one of four Americans invited to participate in the High Altitude Section of the Beijing Symposium on Tibet, organized by the Peoples Republic of China to celebrate the opening of Tibet to international visitors. From that visit, resulted a 'China - Colorado bridge', over which numerous scientists and research teams, especially those led by Reeves and Moore, have continued to travel. Currently Reeves is assisting his colleagues in Xining, Qinghai by editing their papers for publication in English. He himself has had his books and articles translated into Russian, Spanish, Ukrainian, Italian and German and has, in addition, published his English papers in Japan and China.

Reeves has been a member of the Organizing Committee for the International Conferences on High Altitude Medicine, Matsumoto, Japan for the years 1987, 1992, and 1998, with numerous visits to Chiba, Japan from 1978 to 2001. He has facilitated visits by young Japanese scientists wanting to work in the U.S., arranging for them to with Weil, McMurtry, Voelkel, Wagner, and, at Vanderbilt, with Newman. In 1998 at an international conference in Japan, Reeves facilitated the organization of an International Working Group on Chronic Mountain Sickness (CMS), with Dr. Fabiola Leon-Velarde of Peru as chair. Through international collaboration, the group, which has met in Japan, Chile, Spain, and Canada, aims to better define the CMS and (as has occurred in South America) have it officially recognized as a health problem.

4. Impact on clinical medicine.

Primary pulmonary hypertension (PPH). Reeves's 1978 report of isoproteronol-induced pulmonary vasodilation sustained for nearly three years was the first successful long term drug treatment reported in PPH. While the drug was helpful in only an occasional patient, the report did offer hope that treatment was possible in a disease previously considered "untreatable." Four years later, with Rubin, Groves and scientists from Burroughs-Wellcome, Reeves participated in one of the first U.S. clinical trials of prostacyclin in PPH patients. In subsequent clinical research with Groves, Reeves and colleagues showed that intravenous prostacyclin was the "gold standard" to which other vasodilators such as hydralazine, calcium channel blockers, and the prostacyclin analogue, iloprost, should be compared. These studies provided much of the foundation research on which current treatment - long term continuous infusion of prostacylin or administration of its analogues - is based.

Persistent pulmonary hypertension of the newborn (PPHN). Having worked with Dawes and having spent years studying the fetal and newborn circulation, Reeves had an interest in PPHN, which in the 1970s was a highly fatal disorder. In 1983, he, with Stenmark, reported the presence of powerful vasoconstrictor substances in the lung lavage of infants with PPHN, findings compatible with sustained pulmonary vasoconstriction in the disease. In 1990, Reeves began assembling Colorado pediatric researchers to attack this clinical problem. A large program grant from the National Institutes of Health gave financial support. When two of the investigators, Abman and Kinsella, found substances with nitric oxide-like vasodilator effects in the lamb fetus, Reeves suggested that they give nitric oxide (NO) gas in the inhaled air to PPHN infants. Their success led to the initial report showing in 1992 that NO was effective treatment. The former highly invasive procedure - several days of heart-lung by pass - soon gave way to treatment with inhaled NO at Denver's Children's Hospital. Abman and Kinsella subsequently provided convincing, controlled, multicenter trials showing the efficacy of NO treatment, now standard world-wide. They also extended the NO treatment to infants who were premature, those with respiratory distress syndrome, and those with congenital diaphragmatic hernia. As a result of the activities of these and other investigators at The Children's Hospital, the SCOR program on PPHN organized by Dr. Reeves has had a major impact on the practice of perinatal medicine.

Impairment of vaso-reactivity. The other side of the coin from chronic vasoconstriction is chronic vasodilation. In 1972, Reeves showed that loss of pulmonary arterial tone and failure of hypoxic pulmonary vasoconstriction occurred in many patients with chronic liver cirrhosis. Flaccid lung arterioles could no longer direct blood flow to the well oxygenated alveoli, and large channels developed which bypassed the alveoli altogether and shunted blood directly from pulmonary artery to vein. Low pulmonary vascular resistance, hypoxemia, and high cardiac output resulted.

McMurtry and colleagues in the Colorado's CVP Laboratory are currently investigating the mechanisms involved.

Pregnancy is associated with temporary impairment of systemic arterial vaso-reactivity. In animal experiments, Reeves, with Moore, demonstrated that estrogens were important for the low systemic arterial pressures and resistances, which were necessary for normal oxygen transport to the fetus. At high altitude an impairment of the normal pregnancy-related vasodilation (particularly in the arteries supplying the pregnant uterus) can occur and contribute to a low birth weight syndrome. Moore is continuing investigation of the mechanisms causing impaired systemic arterial vasodilation in pregnant women at high altitude.

Altitude illnesses. Reeves (with Scoggin and Grover) provided the first description of high altitude pulmonary edema (HAPE) in a resident high altitude population in North America. He also provided early demonstrations of the tendency for HAPE subjects to hypoventilate, to show mismatching of lung ventilation to perfusion, and to retain fluid. He showed that cold temperatures remarkably augmented the incidence of HAPE and that mild and moderate cases could be treated with oxygen and bed rest without need for evacuation. With Durmowicz, he reported the high incidence of associated viral illness in children who developed HAPE in Colorado. Following this lead and working with Carpenter, he showed that viral infections in juvenile rats augmented hypoxia-related lung water accumulation, and this in part reflected impaired ability of the lung to remove endothelin. With Hackett, he provided the first demonstration that persons with congenital unilateral absence of one pulmonary artery are markedly susceptible to HAPE. He also showed co-existence within some patients of pulmonary, cerebral and peripheral edema, suggesting a body-wide impairment of water handling at altitude.

Relating to acute mountain sickness (AMS) he showed that water loading of subjects or preventing the normal development of hypocapnia at altitude worsened headache. He found the disorder associated with fluid retention, hypoventilation, a reduced hypoxic ventilatory drive, and augmented hypoxic depression of ventilation. De-nitrogenation prior to arrival at altitude reduced AMS symptoms. He showed that the headache of AMS was not related to cerebral blood flow.

Regarding chronic mountain sickness (CMS), he showed that the hypoventilation was not due to over production of endogenous opiates. As a result of polycythemia, cerebral blood flow was reduced. He provided the first standards for pulmonary function in long-term altitude residents. From a review of world literature, he reported that differences in hemoglobin concentration attributed to age, gender, ethnicity, and locale, could be substantially eliminated by simply relating hemoglobin level to oxygen saturation, a finding which helps focus attention on oxygen transport.

The increased alpha neural activity at 4300m, as measured by nor epinephrine levels, was clinically relevant because it related to systemic arterial pressure, which sometimes approached systolic levels of 200 mm Hg even in normal volunteers. Possibly sympathetic activation is the

mechanism whereby persons with well controlled systemic hypertension at sea level, develop severe elevations of blood pressure on coming to altitude.

One of the main functions of the Pulmonary Circulation Assembly of the American Thoracic Society is the overseeing of the Grover Conference on the Pulmonary Circulation which he co-founded with Ken Weir 25 years ago. He has been on the Program Committee of that Conference since its inception and serves as President of the Pulmonary Circulation Foundation, which is involved with raising money to support the Grover Conference.

In summary, over nearly a half century, Dr. Reeves has had a full career in respiratory research, with important contributions in basic physiology and clinical medicine. The result has been a well-deserved national and international reputation. Of the 60 listed trainees, 15 have been from nine foreign countries in the continents of Europe and Asia, and 14 of the foreign trainees have continued in academic pursuits. Of the remaining 45 trainees from the USA, 33 or 73 % have remained in academic medicine. Of the total of 47 academics, 27 are full professors, 11 are department chairs, deans, or chancellor, and 28 are directors of research, clinical and/or training programs. These credentials make Dr. John T. Reeves an ideal and deserving candidate for the Trudeau medal.

Sincerely yours,

Wiltz W. Wagner, Jr., Ph.D.

Professor of Molecular and Cellular Pharmacology and Center for Lung Biology (Alabama)
V.K. Stoelting Professor of Medicine (Emeritus, Indiana)
Professor of Physiology, Biophysics, and Pediatrics (Emeritus, Indiana)