A 37 year-old man was hospitalized for treatment of recurrent small bowel obstruction. He underwent laparoscopic surgery for lysis of intra-abdominal adhesions. Several days postoperatively he had a transient episode of hypoxemia and hypotension, which was attributed to a suspected venous air embolism from a central line manipulation. He recovered uneventfully and lung perfusion scans were normal. Neurology service was consulted because of the uncertainties surrounding the event, and two days later, at their request, transesophageal echocardiogram was performed with intravenous benzodiazepine sedation and was atraumatic and entirely normal. As the patient was being escorted via wheelchair back to his room, he was noted to be profoundly cyanotic, though otherwise in no apparent distress; respirations and pulses were normal. Pulse oximetry demonstrated O$_2$ saturation of 84%. With these persistent findings, emergency intubation was performed; the patient was ventilated with 100% O$_2$, and transferred to the SICU. Urgent cardiology consultation was requested.

Upon exam, the patient was well developed, awake, intubated, and on a 100% FI O$_2$ ventilator. He was markedly cyanotic, with hands and feet appearing slightly grayish blue in color. BP was 122/84, HR 93 regular, RR 16. Pulse oximetry measured 86%. No JVD was present and carotid upstrokes were normal. Upper extremity and lower extremity peripheral pulses were 3+ and symmetrical. Breath sounds were normal bilaterally. Cardiac auscultation was normal with no murmur, rub or S3. Abdomen was soft, not distended, non-tender, and surgical incision and ileostomy appeared normal. No edema was present. Arterial puncture for blood gas determination yielded very dark blood which was nonetheless pulsatile and which was sent for analysis. The result was surprising: pH 7.51, pCO$_2$ 24, pO$_2$ 547. After some cogitation and discussion, a tentative diagnosis was made.

Conditions of life during the first 2 billion years after its origin on earth were vastly different from what they are today. The early atmosphere was less than 1 part per billion O$_2$, and it was only through the persistent, abundant, photosynthetic splitting of water (largely by cyanobacteria) to extract hydrogen and release oxygen that the present O$_2$-rich atmosphere (fractional pressure O$_2$ = 21%) ultimately developed and stabilized during the next 2 billion years. This transformation was not without cost, however, to the multitudes of organisms that had thrived so well in an anoxic world. The oxygen that gradually accumulated over the eons of geologic time was reactive and destructive to metabolic systems that were not prepared to quickly deal with it. Anaerobic organisms are now marginalized to specific planetary niches or depend on sheltered symbiotic environments for their survival. The preponderant life forms in today’s world flourish in the oxygen produced and sustained by their photosynthetic brethren.

The dynamic processes that define life, however, illustrate the delicate balance that exists in safely handling and distributing oxygen. Erythrocytes comprise our most numerous cellular component – 5 million / mm$^3$ blood – 25% of all body cells. Each human erythrocyte contains about 280 million molecules of hemoglobin, which is a tetrameric protein. Molecular oxygen associates reversibly with iron contained in heme moieties, which reside in hydrophobic pockets in each of the four globin polypeptide chains. Hemoglobin is maximally (100%) saturated with O$_2$ at a pO$_2$ of 100 mmHg and is about 75% saturated at a p O$_2$ of 40 mmHg. Oxygen delivery in the peripheral tissues is thus approximately 5 ml O$_2$/100 ml blood flow [ 20 ml/dL (arterial) minus 15 ml/dL (venous) ]. Of note, 97% of the O$_2$-carrying capacity of blood is attributable to hemoglobin association; only 3% is dissolved in plasma and intracellular fluid.
As it associates with dissolved $O_2$ in the pulmonary alveolar capillaries, deoxyhemoglobin shares and partially transfers an iron atom electron from ferrous Fe$^{++}$ heme to $O_2$ to form oxyhemoglobin. To a great extent, this electron is retained by the heme iron when free $O_2$ dissociates in the peripheral tissues. A small portion of heme iron (about 3% each day), however, is stripped of an electron ("oxidized") when oxygen leaves hemoglobin as superoxide $O_2^-$.

Methemoglobin (hemoglobin that contains ferric Fe$^{+++}$ heme) is the other product of this disunion. Fe$^{+++}$ heme will not bind oxygen; the resonance state of the resulting molecule gives it a dark red color (similar to deoxy-Hgb); furthermore, oxygen release from ferrous heme moieties in the same Hgb molecule is impaired. Regeneration of hemoglobin from methemoglobin occurs by way of electron transfer to (i.e. "reduction" of) ferric heme by reductases, which, interestingly, derive from the outer mitochondrial membrane. Mitochondria have an ancient history of capitalizing on oxygen-dependent reactions and are themselves remnants of bacterial endosymbiosis at the dawn of eukaryotic life.

Methemoglobin accumulation imparts a clinically detectable slate blue color to the skin once absolute levels exceed 1.5 g/dL (10% of total Hgb). Several forms of hereditary methemoglobinemia exist, which result from relative deficiency of NADH-cytochrome b5 reductase. Acquired (or toxic) methemoglobinemia can be induced by a number of drugs and is caused by the accelerated oxidation of ferrous hemoglobin to produce methemoglobin. In our patient, the offending drug was suspected to have been benzocaine, which was sprayed into his pharynx to facilitate passage of the TEE probe. Treatment is intravenous administration of methylene blue (an electron receptor which facilitates an alternative enzymatic pathway of methemoglobin reduction) - 1 to 2 mg/kg over 5 minutes. Our patient received this therapy and his cyanosis promptly resolved.