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Nash G, Blennerhassett J B & Pontoppidan H. Pulmonary lesions associated with oxygen therapy and artificial ventilation. *N. Engl. J. Med.* **276**:368-74, 1967.
[Depts. Pathology, James Homer Wright Labs., Anesthesia Labs., and Respiratory Unit, Harvard Med. Sch., Massachusetts Gen. Hosp., Boston, MA]

Characteristic pathological changes were found in the lungs of a group of patients who died after prolonged mechanical ventilation. The alterations did not correlate with duration of mechanical ventilation but appeared to be associated with prolonged inhalation of high concentrations of oxygen. Pulmonary oxygen toxicity was implicated as a possible cause of morbidity and mortality in patients treated with mechanical ventilators. [The *SCI*® indicates that this paper has been cited in over 380 publications since 1967.]

Gerald Nash
Divisions of Anatomic Pathology
and Pulmonary Medicine
Cedars-Sinai Medical Center
Los Angeles, CA 90048

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"In 1965, as a first-year resident in pathology at the Massachusetts General Hospital, I became intrigued with a problem that was troubling my clinical colleagues who were caring for patients requiring mechanical ventilation. They were puzzled by the occasional development of a progressive deterioration of pulmonary function that was apparently unrelated to the patient's underlying disease. The patients typically did well for a few days, then developed a progressive reduction in pulmonary compliance and vital capacity. They could not be weaned from the ventilator, and they eventually died of respiratory failure. Some physicians at the Massachusetts General Hospital believed that the mechanical ventilator was somehow the culprit, and they referred to the problem as the 'respirator lung syndrome.' H. Pontoppidan, of the Respiratory Unit, thought that the ventilator was being accused unjustly, and he was keenly interested in unraveling the mystery.

"J.B. Blennerhassett and I, in the Department of Pathology, were struck by unusual gross and microscopic appearances of the lungs of patients who died of this syndrome. With the enthusiastic support of Pontoppidan, we decided to compare the morphological findings of a group of patients who died in the Respiratory Unit with a control autopsy population. We found three major differences that characterized the study group: heavy lungs, hyaline membranes, and early interstitial fibrosis. These changes did not correlate with duration of mechanical ventilation, but they appeared to be related to prolonged inhalation of high concentrations of oxygen. Moreover, a review of the literature revealed that the lesions of pulmonary oxygen toxicity as described in animals were similar to those seen in our patients. We concluded that some of our patients with the so-called respirator lung syndrome probably had succumbed to oxygen toxicity.

"At the time this study was performed, oxygen was routinely administered in this country without concern for its possible toxic effects on the lung, and many patients were undoubtedly given toxic levels unnecessarily. This paper warned the medical community that pulmonary oxygen toxicity could develop during therapy for acute respiratory failure. We also recommended that the inspired oxygen concentration should be monitored, and if toxic concentrations must be given to sustain life, the dose should be lowered as soon as possible.

"After publication of this paper and others on the same topic, there was general acceptance of the notion that oxygen is potentially dangerous and its administration should be closely monitored. The paper helped pave the way to a more judicious use of the gas, and in the process it became highly cited. The subject has been recently reviewed by Deneke and Fanburg.[1] Another reason the paper is so highly cited is that it contains the first description of the evolution of a common, nonspecific morphological reaction of the lung to a variety of deleterious agents in addition to oxygen. The lesion is now well recognized and is known as 'diffuse alveolar damage.' "[2]

1. **Deneke S M & Fanburg B L.** Normobaric oxygen toxicity of the lung. *N. Engl. J. Med.* **303**:76-86, 1980.
2. **Katzenstein A A, Bloor C M & Leibow A A.** Diffuse alveolar damage—the role of oxygen, shock, and related factors. *Amer. J. Pathol.* 85:210-24, 1976. (Cited 105 times.)

