ANIMAL MODEL OF HUMAN DISEASE

Oxygen Toxicity

Animal Model: Oxygen Toxicity in Nonhuman Primates

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Biologic Features

This paper deals with pulmonary oxygen toxicity in nonhuman primates after they have breathed concentrations of oxygen known to produce disease in man.[1-5] This disease was studied in several species of nonhuman primates;[6-8] baboons (*Papio* sp) were considered the animal model of choice because of the similarity of their pathologic response to that seen in man. Similar pathologic features were also observed in rhesus monkeys (*Macaca mulatta*) and cynomolgus monkeys (*Macaca irus fascicularis*); baboons were preferred, however, for the study of oxygen toxicity, as both of the *Macaca* species more frequently have naturally occurring pulmonary lesions from infestations of lung mites.[8]

Baboons and *Macaca* sp breathing 100% oxygen at normobaric pressure progress to an acute stage of oxygen toxicity in 2 to 4 days and, in those that survive, to a subacute phase in 7 to 12 days. If the animals are retained in this environment, death ensues in 20 to 22 days. Arterial partial pressures of oxygen remain at high levels until the later stages of the disease. Terminally, exchange of respiratory gases decreases significantly, and the animals become progressively anorectic, cyanotic and dyspneic, and they eventually die.

Toxicity of 100% oxygen at normobaric pressure is manifested as exudative changes in the lung during the acute stage and as proliferative changes during the subacute stage. In the animals that die after 7 to 10 days' exposure there is often a terminal exudation of edematous fluid in addition to the proliferative changes.[6-8] Initially, massive exudation of

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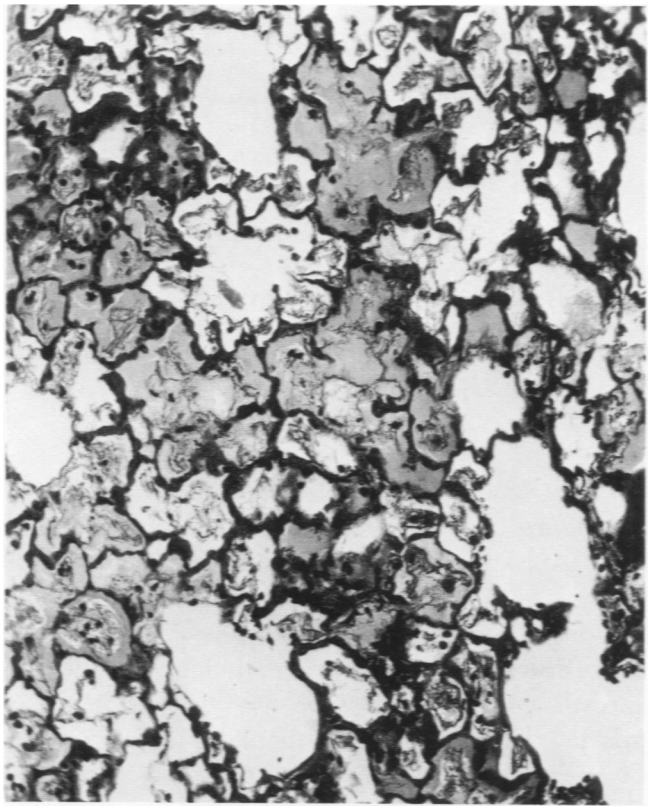

Fig 1—Lung of a baboon exposed for 7 days to 100% oxygen at normobaric pressure. Alveolar edema is resolving, forming fibrinous strands. Septa are thickened, and alveolar lining cells are enlarged and numerous (H&E, × 165).

edema fluid into the alveoli occurs after 2 to 4 days' exposure, resulting in marked distention of the lymphatic channels. Alveolar septal edema also is pronounced. If the exudation is not overwhelming, resolution begins, hyaline membranes form, and there is variable influx of inflammatory cells (Figure 1). The proliferative phase becomes recognizable by light microscopy after 5 to 7 days' exposure as a decided increase in the number of type 2 pneumocytes. By 12 days the alveoli are almost completely lined by the large type 2 cells, increasing the thickness of the blood–air barrier by four to five times (Figure 2). Early interstitial fibrosis is evident, and subacute inflammation of the septa may be focal or diffuse.

With additional exposure the proliferation of alveolar lining cells continues, interstitial inflammation becomes severe (Figure 3), and acute exudation and hemorrhage may occur terminally after about 3 weeks' exposure.

Other pulmonary irritants such as ozone and nitrogen dioxide cause lesions similar to those described above for the acute stage, but proliferative lesions, particularly the extensive hyperplasia of the type 2 pneumocytes, have not been reported in nonhuman primates. This lack of

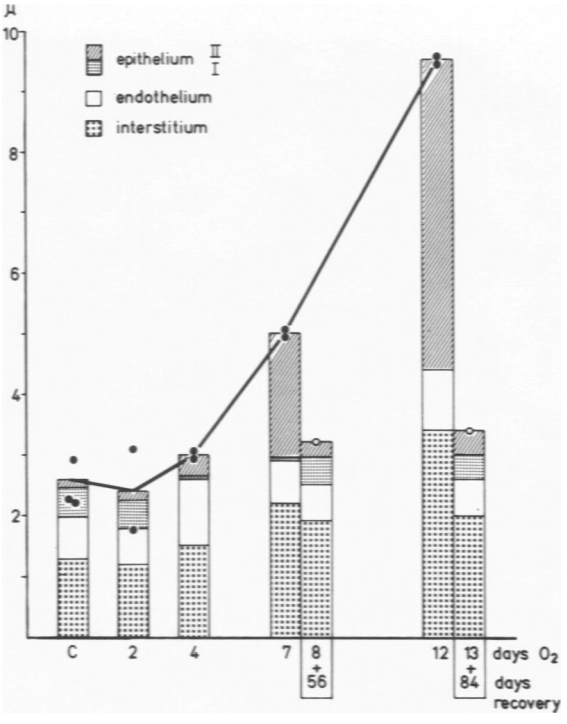

Fig 2—Change in arithmetic mean thickness of air–blood barrier of lungs of *Macaca mulatta* exposed to 100% oxygen at normobaric pressure. (Monkeys killed immediately after exposure, *solid circles;* Monkeys allowed to recover, *open circles;* control animals, *C*). (Lab Invest 20:101, 1969, used by permission).

cellular proliferation may be a factor of selecting the proper dose-time relationship with other irritants, since, in the simplest terms, oxygen as described above is a chemical irritant.

Comparisons with Human Disease

Although it is frequently difficult to distinguish lesions caused by therapeutic administration of oxygen from those caused by preexisting disease, retrospective studies have determined that both the exudative and proliferative lesions described above occur in human patients.[3,4] The lesions encountered in the so-called respirator lung syndrome are now considered to be the result of oxygen toxicity.[5]

Usefulness of Model

This nonhuman primate model has been important in elucidating the pathogenesis of oxygen toxicity and substantiating the theorized cause of similar lesions in the lungs of humans. Because the pathologic response of the lungs of these animals is more similar to that in man, compared to that in other animal species (dog, rat and mouse), investigators are encouraged to use the primate model in the further study of the biochemical mechanisms of oxygen toxicity which have not yet been well defined.[2,5]

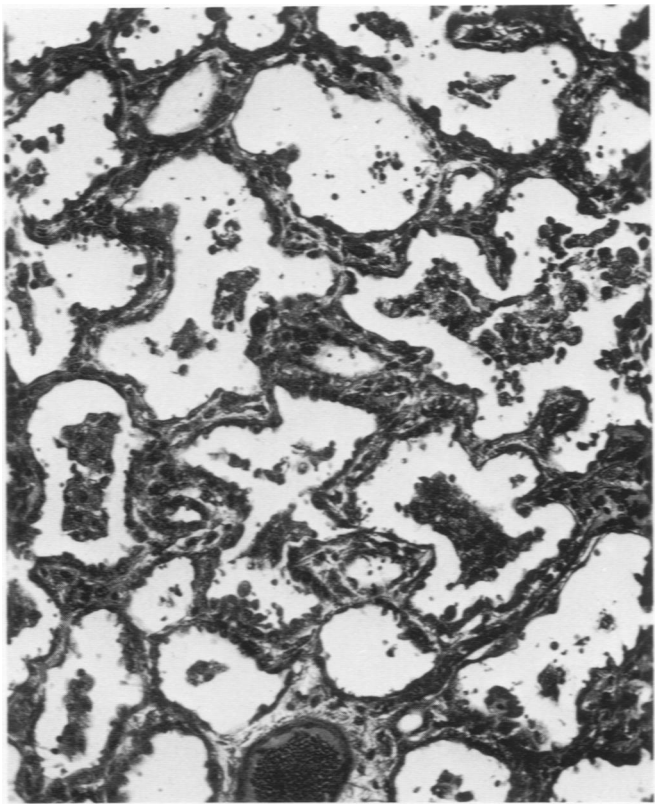

Fig 3—Lung of a *Macaca mulatta* exposed for 22 days to 100% oxygen at normobaric pressure. Septa are severely thickened with fluid, connective tissue and inflammatory cells. Alveolar lining cells are enlarged and numerous (H&E, × 170).

Availability

Baboons and *Macaca* sp are available in adequate numbers.

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