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Pulmonary oxygen toxicity is modulated by its paramagnetic property

A preliminary report from studies of developmental biophysics *

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Abstract:

Molecular interaction can be determined from biological experiments [MARM 2011, #415, p. 252]. Atomic attributes can be shown to be determinative in whole animal experiments under appropriate circumstances [MARM 2012, #225, p. 169]. The dynamics of replenishing gas interchange in the distal air spaces of the mammalian lung, and at the atmosphere-lung interface, are shown by differences in the extent of pulmonary lesions after the induction of respiratory distress and changes in the mix of the gases inhaled [*Biol.Neonat*. 20:140-158, 1972]. Such effects have significant biological and pathogenetic consequences. Hyaline membrane disease (HMD) is a common and sometimes lethal disorder, especially in premature newborns [*Clin.Med*. 72:477-490, 1965; *Int.J.Clin.Pharmacol*. 5:20-25, 1971].

There is significant evidence the lesions can be induced by oxygen enrichment [*New Eng.J.Med*. 277:833-837, 1967; *Lab.Invest.* 21:439-448, 1969]. Bilateral cervical vagotomy (BCV) is a standard method of inducing ventilatory distress which leads to HMD [*J.Exp.Med.* 66:397-404, 1937; *Biol.Neonat.* 6:340-360, 1964; *Biol.Neonat.* 11:61-86, 1967]. This model has relatively short median (2.50-7.22 hours) and mean (3.54-13.63 hours) post-BCV life spans [*Lab.Invest.* 21:439-448, 1969], making it difficult to identify subtle but important effects which might change the result. Thus, a slower model inducing ventilatory distress, previously studied, was again employed, thoracic restraint (TR). In this model, quarter inch soft cloth adhesive tape is tightened around the lower rib cage of newborn rabbits, reducing the segmental thoracic circumference by 10%, and then placing them [1] in a 480 ml clear plastic chamber with 100% oxygen running at 1.0L/min, or [2] in an identical chamber resting on four adherent donut magnets with a varied field up to +1200 gauss. Parallel experiments were done using young adult female white mice to eliminate the effect of ventilatory distress induced by TR.

Diatomic oxygen is the only gas in the inhalant mixtures noted which is inherently paramagnetic.

Studies have considered the effects of magnetic fields on flame combustion which is a chemical reaction involving oxygen [*IEEE Trans.Mag*. 21:2077-2079, 1985; *IEEE Trans.Mag*. 23:2752-2754, 1987; *J.Appl.Phys*. 69:2734-2736, 1991; *Combus.Flame* 93:207-214, 1993]; oxygenation in capillaries [*Int.J.Math. Anal*. 4:1697-1706, 2010]; and also on organic photochemical reactions [*Acc.Chem.Res.* 13:369-377, 1980], which, taken together, indicate magnetic influences on the flow and orientation of oxygen as gas and in solution. Two principal objective results from these experiments demonstrate an effect of the magnetic field on the whole animal and on the extent of lung injury. The newborn rabbit survival in pure 100% oxygen was 58.56 ± 3.19 hours versus 82.89 ± 4.91 hours in magnetized oxygen ($p < 0.0001$); the difference in gross lung injury was 47.46 ± 6.51 per cent versus 99.57 ± 0.43 per cent respectively ($p<0.0001$). The adult female mice in pure 100% mean survival was 53.71 ± 5.40 hours versus 64.57 ± 2.93 hours in magnetized oxygen ($p \approx 0.015$); the respective percentages of lung injury were 61.67 ± 10.91 and 55.75 ± 10.45 (n.s.). But, when the result is considered on the basis of rate of lung injury per hour, magnetized oxygen is much slower. The rates for newborn rabbits were, (magnetized oxygen) 1.3728%/hour and (plain oxygen), 1.7969%/hour, a ratio of 1.3088, or 24.6% slower. In mice the rates were 0.8634%/hour and 1.2617%/hour respectively, a ratio of 1.462, or 31.5% slower.

A variable magnetic field added to whole animal models of pulmonary oxygen toxicity changes the outcome in two overt ways: [1] survival is enhanced, but despite this, [2] the rate of formation of lung injury is reduced by 24% in newborn rabbits and by 31% in young adult female white mice. Thus, the toxic effect of oxygen is reduced systemically and in the lung by low strength magnetic field effects on inhaled paramagnetic 100% oxygen.

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The clinical problem:

Epidemiology:

Isolated, even rare reports of a form of neonatal respiratory distress in the human newborn, more especially in the premature newborn, appeared from 1903 to the early 1940s, and progressively more attention was paid thereafter to the striking finding of an eosinophilic protein lining many of the terminal air spaces of the lung found at autopsy in these newborns. The current designated term for the lesion and the disorder comes from their descriptive appellation, *hyaline membrane disease* (HMD), first directly applied by W. C. Johnson in 1923 under the title of *Pneumonia in newborn infants resembling influenza* [*Proc.N.Y.Pathol.Soc*. 23:138, 1923]. His report was no doubt stimulated by the then concurrent interest in the lung lesions from the pandemic of influenza which began before the end of World War I [Figure 1]. Johnson and Meyer then reported a larger data base in which *hyaline membrane* was expressly used as a categorical referent [*Am.J.Obstet.Gynecol*. 9:151-167, 1925].

At first, some pathologists and pediatricians attributed the lesion and the outcome to the aspiration of vernix caseosa from the skin of the fetus through inhalation of amniotic fluid before or during birth. However, others came to realize that this was turning the matter upside down because vernix was mostly on term infants and they developed hyaline membrane disease far less often than the prematures. Careful studies later revealed that aspirated amniotic cellular debris could be found in lungs with hyaline membranes but when prominent they were precisely segregated in the lung which observation indicated portions of lung obstructed by the debris did not develop the lesion. This is one of several lines of evidence that respiration was necessary for the disease to develop. The prevalence by fetal maturity is shown in Table 1.

Through clinical evaluation it was appreciated that male newborns were more susceptible to the disorder and the sex ratio was more pronounced at term. This was quantified in the 1960s as shown in Table 2. This is a combination of data from two papers: *South Med.J.* 56:1018-1022, 1963 and *Virch.Arch.Pathol*. 341:259-270, 1966, plus 13 unreported term cases from University of Florida and Johns Hopkins Hospital, Baltimore. Although it is generally recognized that the fetal weight rises as gestation proceeds, the progression is not expressly linear, with more variation in the first third of the third trimester (circa 27-31 weeks menstrual age). When a larger sampling of cases is

arranged by increasing birth weight, a distinctive differential pattern for male and female infants appears. This is shown in Table 3.

The table indicates a very similar frequency between male and female fetuses in the weight range of 1001-1500 grams at birth. The rate for females declines dramatically from there to term whilst that for males rises to a near plateau after 1500 grams. This resembles the pattern of growth of Leydig cells, which then involute almost immediately after birth. The masculinization of the male fetus occurs early, with a peak of testosterone reportedly around midgestation [*J. Endocrinol.* 56:621-622, 1973; *J.Steroid Biochem*. 5:207-210, 1974]. Interestingly, the slightly over four fold prevalence found in term infants, shown in Table 2, is replicated in the smallest infants by weight, 500-100 grams at birth. At minimum, the pattern is very suggestive of the influence of both placental hormonal production and testicular secretion of testosterone.

Clinical scenario:

The clinical appearance of these infants is one of occasional respiratory distress or difficulty in onset of respiration at birth but many have a short interval of apparent normal breathing before evident distress occurs. This is generally manifested by enhanced excursions of the diaphragm and a tendency toward tachypnea, an increased rate of breathing per minute. The upper chest and ribs often show retractions during the excursion of the diaphragm. The heart rate also rises. Dusky discoloration of the skin is the first sign of cyanosis and the determination of blood gas values will demonstrate both hypoxemia and carbon dioxide retention, initially defined as respiratory acidosis. As the infant struggles with this compelling pathophysiology, a draw down of hepatic, cardiac, and skeletal muscle reserves of glycogen leads to metabolic acidosis. The data noted above as to distribution by birth weight and sex of infant are from a time frame wherein little was done for the infant beyond some general supportive measures. The intravenous buffering methods begun by Usher [*Ped.Clin.N.Amer*. 8:525-528, 1961] had more general application after the mid-1960s. The addition of enriched oxygen in the air breathed began in Chicago in the 1930s and has been shown to be an important if not the controlling factor in pathogenesis [*Exp.Mol.Pathol*. 92:140-154, 2012]. Ready recognition of a rising frequency of HMD in neonatal autopsies followed directly upon the introduction of therapeutic oxygen to the program of care for premature newborns. The x-ray often shows a diffuse ground-glass appearance to the lung with dilated air filled bronchi, the so-called air bronchogram [*Radiology* 93:339-343, 1969].

The gross lesion:

The gross pathological appearance of the lung, as well as the microscopic picture in HMD is best seen in case material from before the modern era of intensive therapy. In the human the lung is more or less uniformly involved as shown in Figure 2. The intense congestion or hyperemia gives an external appearance like that of the liver (*hepatization*) with a turgor or firmness also similar to that of the liver. The lungs almost always sink directly when placed in formalin solutions as the amount of air in the bronchi is insufficient to provide buoyancy. Following fixation as a whole the lung often reveals rib indentations on the lateral curved surfaces, indicative of pressure expansion of the lung against a collapsing thorax (Figure 2). Almost without exception, in human newborns, both lungs are equally and totally converted to the grossly apparent lesion.

The microscopic lesion:

In her books on the pathology of the fetus and newborn [1952, 1961, 1976], Edith L. Potter, M.D., Ph.D., longtime chief pathologist at the Chicago Lying In Hospital, emphasized four components to the lesion complex of hyaline membrane disease: [1] resorptive atelectasis, [2] vascular congestion, [3] pulmonary edema, and [4] hyaline membrane formation. The possibility these were the confluence of two different lines of pathogenesis was later discussed in a brief commentary [*Arch.Pathol*. 100:345-346, 1975] by the present author. The suggestion was that atelectasis, whilst possibly a result of a particular linked etiology in the first steps of pathogenesis, was likely the result of a different line of injury while the other three aspects were closely linked in pathogenesis through

the vascular dynamics of the matter. The importance of cardiovascular factors was emphasized in 1959 [*Arch.Pathol*. 68:49-57, 1959] by the observation that a cardiac anomaly in premature newborns, interatrial septal defect, was associated with a 3-fold higher frequency of hyaline membrane disease, 79.5% versus 25.5% ($\chi^2 = 40.354$, $p<<0.0001$). An analysis of the lung findings revealed the highest co-prevalence was between pulmonary edema and hyaline membrane formation (93.2%) in the cases with interatrial septal defect; the other findings were in the high 70% range. By contrast, in premature newborns without cardiac malformations, the co-prevalence for edema and membranes was 58.8%; the other features were in the low 30% range. The control group also reflected a higher prevalence of hyaline membrane formation when the birth weight was above 1000 grams, 35.0% versus 17.0% for those weighing 500-1000 grams. The differences in appearance of the proximal and distal forms of lung lesion in HMD are shown in Figure 3.

The relationship between the four principal findings in the classic newborn rabbit model was studied quantitatively in a medical student research project at the University of Florida [Cunningham, J.J., 1963]. When recently revisited, by use of cumulative quantitative plots, a clear pattern was discerned, with congestion consistently the most prominent finding, followed by atelectasis, edema, and then membrane formation. On an elapsed time plot a near exponential upswing occurred for both congestion and atelectasis from 5 to 10 hours post-BCV, thence a more linear secondary rise to the end of the run at 18 hours. Both edema and membrane formation showed a similar but lesser pattern from 6 hours to 12.5 hours with an effective plateau afterwards (Figure 4). An antihistamine, diphenhydramine (Benadryl), given either before or after the vagotomy, shifted the results but not the essential relationship of the four findings.

Potter also emphasized the dominant component microscopically was the *congestion*, usually considered pathologically as a passive process or event. That it might better be termed as *hyperemia*, an active process, was revisited in a recent paper [*Exp.Mol.Pathol*. 89:36-45, 2011] which pointed out the high volume of blood thus present in the pulmonary circulation brought with it considerable amounts of the enzyme catalase, a part of the anti-oxygen defensive repertory first chronicled by Winternitz and Meloy in 1908 [*J.Exp.Med.* 10:759-781, 1908].

The classical model:

The first detailed use of bilateral cervical vagtomy to induce pulmonary edema in adult rabbits was by Farber [*J.Exp.Med*. 66:405-411, 1937]. When the technique of Farber was replicated in newborn rabbits the complete profile of clinical distress and the gross and histopathology of HMD was produced on a varied scale of extent which was dependent in part on time of survival, sex of the animal, and birth weight [*Biol.Neonat*. 6:340-360, 1964; *Biol.Neonat*. 11:61-86, 1967]. This model served to elucidate two major attributes of oxygen as the initiating etiological agent of HMD. The first was that the interaction between oxygen and nitrogen was an effect of their relative percentage in the inhaled gas mixture and not their partial pressure [*Lab.Invest*. 21:439-448, 1969]. The apparent effect of partial pressure was determined to be an attribute of sea level physiology. This was established by differential percentage compositions at 0.2, 0.6, 1.0, and 3.0 ATA (Figure 5).

In contrast to the human disorder, in the newborn rabbit, the classical model for respiratory distress and hyaline membrane disease, bilateral cervical vagotomy (BCV), often has only a partial lesion, sometimes only unilateral (Figure 6), often delineated along lobar and lobular boundaries.

The classical model also demonstrated the effect of substituted other gases for nitrogen for the environment following BCV. Figure 7 compares helium (top curve) and sulfur hexafluoride (middle curve in red) to nitrogen (bottom black curve) over an oxygen range of 3% (left) to 21% (right).

This shows considerable difference in the extent of lung injury from oxygen between helium, nitrogen, and SF_6 as the diluent gas. The minimum injury is with 7% oxygen in nitrogen, indicative of considerable blocking effect. The 3-7% range covers the limit of hypoxia described by G. Avery [*Pediatrics* 32:801-807, 1963]. Avery concluded that *hypoxia* was not a cause of HMD. The work described here and the data plotted in Figure 7 confirm Avery's interpretation. The semilog scale used in this graph minimizes the decline in the lung effect at 7% oxygen in helium.

Subatmospheric oxygen tension:

A more thorough study of oxygen tensions below 21% included comparative experimental runs of newborn rabbits after BCV and some without. Consideration of various molecular/atomic attributes brought forth the role of outer electron shell saturations as a marker for potential covalent bonding between oxygen and the diluent gas. The likelihood these combinations or affiliations were just transitory nevertheless carried with it the equally transitory diversion or removal of oxygen from its effective contact with the gas:lung tissue boundary, especially since there was actually very little oxygen in either the 7% or the 3% mix. The effects of the diluent would then prevail, much as is shown in Figure 9. A specific study of 3% oxygen in hydrogen, nitrogen, SF_6, helium, and argon produced the graph shown in Figure 8, with the abscissa representing the percentage of saturation of the outmost shell of the gas (SF_6 calculated on an additive basis of the molecule).

A different way to plot this result is shown in Figure 9. The extent of lung injury following BCV and 3% oxygen is on the left ordinate and that when the animal was placed in the 3% oxygen mixture without prior vagotomy is on the right ordinate.

The minimum change comes to about 3% of pleural surface, exactly where the results from 3% oxygen in nitrogen are plotted. The effect of respiratory distress added to the effects of the gas mixture per se is thus seen by following each line from right to left, independent of which electron shell is the outmost for the diluent. From these considerations it was concluded that atomic attributes were necessarily involved and in a prior paper [*Biol.Neonat*. 20:140-158, 1972] various aspects were described and discussed, as shown here in Table 4.

One significant attribute was lacking from that paper and discussion. Of the principal gases studied hydrogen, helium, nitrogen, argon, and sulfur hexafluoride are diamagnetic while oxygen is ***paramagnetic***. Accordingly, supplemental experiments were run in the winter and early spring of 2012 making use of a slower animal model, thoracic restraint.

Derivative slow models for pathogenesis:

The use of neurectomies to disrupt the ventilatory function is not limited to bilateral vagotomy. The recurrent laryngeal nerves (BRLN) are retrograde branches of the vagus and independent study has shown the earlier part of the survival curve following BCV is due to the laryngeal effect of interruption of both BRLN [*Biol.Neonat*. 11:61-86, 1967]. The phrenic nerves and the external respiratory nerves of Bell also play important roles in ventilation. These methods, which will not be detailed here, do result in a slower onset of the effects of respiratory distress but both require invasive surgery to achieve the effect. Both methods have a considerable effect on the lower thorax at the end of the rib cage and a non-invasive method was designed to influence ventilation from this site, that of thoracic restraint.

Briefly, the thoracic circumference was measured by wrapping a string around it at the level of the xiphoid process and this distance was measured on soft half inch cloth adhesive tape. A transverse line was then marked at 90% of circumference and the tape was trimmed to twice this length. Just prior to placing the subject in the assigned chamber, the chest was wrapped snugly with the lower edge of the tape at the xiphoid and pulled so that a double layer was created compressing that zone of the thorax to 90% of original circumference. This did not overtly impede movement in the chambers and no immediate reaction was observed. The end result over time was similar to that following external respiratory neurectomy which has its physiologic effect through stabilization of the thorax against the force of downward excursion of the diaphragm. The original comparative series survival plots are shown in Figure 10, one series in air and the other in 100% oxygen.

The survival curves are essentially overlapping and present an ideal *slow motion process* from which a subtle effect, if there are any from a magnetic field, might be discerned. Table 5 contains the descriptive statistics of these runs.

The mean survivals were: air, 56.05 ± 4.48, and oxygen, 50.81 ± 3.27 hours, respectively, and the median survivals were: air, 63.5, and oxygen, 57.75 hours. The close approximation of mean and median survival in both subsets offered a fairly stable model for further study. And, clearly, these results again show worsening of the lesion from an increase in the per cent of oxygen breathed. The extent of lung injury from air exposure was 16.95 ± 4.19 per cent and from oxygen immersion, 38.97 ± 6.50 per cent.

The effect of a varied magnetic field on the thoracic restraint model in newborn rabbits:

Four 3.0 inch donut ceramic magnets were positioned in a quadrilateral format, #1 and #3 reversed as to magnetic pole from #2 and #4. This creates a stable magnetic platform on which comparable size clear plastic containers are placed and held firm by heavy duty strapping tape. Parallel subsets of newborn rabbits stressed by the thoracic restraint method were in oxygen flow chambers at 1.0 L/minute, with and without a magnetic field with a maximum of 1200 gauss (0.12 tesla). A subset of seven newborn rabbits in unmagnetized 100% oxygen was found to fit exactly with the result of the former experiments noted in Figure 10 and Table 5. They were then merged into a control set of 37 animals and compared with seven other newborn rabbits in a magnetic oxygen chamber. The combination of ventilatory distress, 100% oxygen, and a magnetic field yielded differences in survival time and lung injury. Table 6 shows some similarities and some differences.

The newborn rabbit survival in pure 100% oxygen was 58.56 ± 3.19 hours versus 82.89 ± 4.91 hours in magnetized oxygen ($p < 0.0001$); the difference in gross lung injury was 47.46 ± 6.51 per cent versus 99.57 ± 0.43 per cent respectively ($p < 0.0001$).

Superficially this suggests that providing oxygen in a magnetic field makes the lungs worse but on a per time unit basis the reaction is actually slower. The rate of accretion of lung injury for plain oxygen was 1.7969% per hour and for magnetized oxygen, 1.3728% per hour, a ratio of 0.764. When viewed from the opposite perspective, the rate for lung change during plain oxygen was 24.6% faster than in exposure to magnetized oxygen. The rate of weight loss is also different, despite the close fit of the final result: for plain oxygen, 0.563% per hour and for magnetized oxygen, 0.347% per hour, a ratio of 0.616. A 25% weight loss over these time frames is a marker for severe metabolic acidosis. These distinctions are shown clearly in a plot of survival in the two groups, Figure 11.

The effect of a varied magnetic field on young female white mice:

Since the magnetized subset was small it was determined to repeat the experiment using adult female white mice rather than waiting for another cycle of rabbit breeding. Again, one series was placed in chambers on a magnetic field similar to that noted above (Figure 12) and the second was not. This approach meant the onset of respiratory distress was induced by oxygen toxicity per se. The descriptive statistical result is shown in Table 7.

The mean survival for adult female mice in pure 100% was 53.71 ± 5.40 hours versus 64.57 ± 2.93 hours in magnetized oxygen ($p \approx 0.015$); the respective percentages of lung injury were 61.67 ± 10.91 and 55.75 ± 10.45 (n.s.).

Magnetized oxygen resulted in longer survival and less lung injury. When the result is considered on the basis of rate of lung injury per hour, magnetized oxygen is much slower. The comparative rates of lesion formation were: plain oxygen, 1.2617% per hour, and magnetized oxygen, 0.8634% per hour, the former a 46% faster effect; as a ratio the value is 0.6847. These effects and values compare reasonably with those for newborn rabbits. They are in the same direction and as ratios bracket the value of 0.7. A lesser formation of lung injury in adult female mice, as well as in newborn rabbits, is indicative of systemic effects of the magnetic field as well as some protection for the lung. The survival profile for adult female mice is also clear cut from the plot in Figure 13.

Discussion:

The previously demonstrated stochastic and competetive relationship between nitrogen and oxygen [Shanklin, *Lab.Invest*. 21:439-448, 1969] may be enhanced or modulated by the difference in magnetic properties of the two gases, in addition to their nearly equal size which provides for their interaction in space volume. Unsaturated hemoglobin, found in abundance in the pulmonary arterial flow, is also paramagnetic [Pauling and Coryell, *Proc.Nat.Acad.Sci.USA* 22:210-216, 1936], due to the oxidative state of unbound atoms of iron. This fact alone argues that the interaction between oxygen content of the terminal air space and the influx of unsaturated venous return has to be part of the action, thus also part of the problem. Indeed, the profound congestion or hyperemia which is the dominant aspect of the histological lesion of hyaline membrane disease might be considered a defensive action on the part of the organism, maximizing the amount of unsaturated hemoglobin by which to neutralize the adverse activity of oxygen which follows from its paramagnetic molecular state. The first volumetric surge of blood into the lung after birth is from reverse flow of low oxygen tension blood through the ductus arteriosus during the change from fetal vascular pO_2 values [*Exp.Mol.Pathol*. 89:36-45, 2010] to neonatal levels following effective onset of air breathing. The diversion of right ventricular outflow into the lungs, added to the reverse ductus flow, has an erectile effect, yielding some rigidity to pulmonary tissue. This factor is more significant in the premature infant because there is a progressive rise in pulmonary circulation towards term [*Am.Heart J.* 6:192-205, 1960], thus less of a change after birth.

The findings in adult female white mice which accrue from oxygen exposure alone call attention to the effects of increased intrathoracic oxygen tension on the vagus and phrenic nerves which traverse other structures en route to their organ and tissue plane destinations. It has been shown that increasing the oxygen surrounding the excised giant axon of the squid, *Loligo*, reduces the efficiency of nerve impulse transmission [*Biol.Bull*. 143:477-478, 1972]. Accordingly, the argument can be put forward that all of the symptoms and signs, the pathophysiologic effects, and pulmonary lesion formation can be attributed to the onset of air breathing and oxygen intake during the establishment of independent, extrauterine respiration, and that therapeutic oxygen enrichment of that adaptive exposure hastens the injury to the lung as well as generating a metabolic dependency on oxygen *per se* [*Exp.Mol.Pathol*. 89:36-45. 2010].

Summary and conclusions:

The experimental study of pulmonary oxygen toxicity has been both driven and informed by clinical scenarios which have often reflected the paradox of the necessity of oxygen for aerobic metabolism combined with adverse effects on the lung and other tissues. The pathophysiology of oxygen toxicity is complex and studies in whole animal models make use of the adaptations they undertake during the oxygen challenge and other forms of induced distress. The long term use of a basic tool, the bilateral cervical vagotomy model of Farber, when adapted to newborn rabbits, has been productive on several levels. The device of neural interruption in rabbits, as a model for humans, is assisted by the fact the respiratory innervation of both species is identical both as to location and in the branching of nerves as well as their neuromuscular and reflex functions. None of the extrinsic physical attributes of gases substituted for nitrogen, size, viscosity, or monoatomic/diatomic configuration, explain the behavior of oxygen beyond the percentage applied. A more fundamental aspect, the degree of saturation of the outermost electron shell, does explain the difference in extent of lung injury at subatmospheric oxygen tensions, invoking the paramagnetic quality of dioxygen. Direct testing of this concept in a varied magnetic field up to 1200 gauss demonstrates clear effects on the toxicity of oxygen to the lung and to the whole animal. Magnetized oxygen injures the lung but at a measurably slower rate, strongly suggestive of invoking the interplay of the paramagnetic property of oxygen through transient covalent bonding with the other gases with covalent properties. This includes hydrogen, nitrogen, and sulfur hexafluoride from the panel of five tested in the experiments described in this preliminary report. The noble gases, helium and argon, do not interfere with the adverse effects of oxygen on the lung, and in the whole animal model, on its adaptive metabolism.

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