Oxygen therapy and pulmonary fibroplasia: A review and case reports

by David Teo Ah Chew
MBBS (S'pore)
Department of Anaesthesiology

and Anthony Leong Siew Yin
MBBS (Malaya)
Department of Pathology

Faculty of Medicine,
University of Malaya,
Kuala Lumpur.

Introduction

THE ADMINISTRATION and prolonged use of oxygen in inspired tensions above that of air has been employed in various fields, e.g. deep sea-diving, space research, and, in the medical field, in radiotherapy and intensive care of infants and adults.

Oxygen, although essential to life, also seems toxic to all living cells. The toxic effect depends on the partial pressure and individual species sensitivity (Bean, 1965). At very high pressure of over 3 atmospheres (hyperbaric), clinical signs and symptoms of oxygen toxicity usually become apparent initially in the nervous and respiratory systems, although because the basic disturbance is at the cellular level, all systems are affected eventually.

The early signs and symptoms of oxygen poisoning are (1) facial pallor, (2) fibrillation of lips (3) sweating, and (4) bradycardia. (Slacks, 1967). Warning signs and symptoms include visual, acoustic, olfactory, gustatory and respiratory changes. Convulsions may occur. At lower oxygen pressure, the lungs appear to react first.

At atmospheric pressure, administration of 98.5 – 99.5% oxygen to a series of 34 normal subjects continuously for 24 hours resulted in 30 of them suffering from retrosternal soreness which became sharp and severe during inspiration. (Comroe et al, 1945). That the breathing of oxygen in high percentage (more than 80%) for prolonged periods consistently resulted in pulmonary changes and sometimes in retrolental fibroplasia in the newborn has been reported in various centres. These cases are usually newborn infants with respiratory distress syndrome (Hyaline membrane disease) which initially requires a high percentage of inspired oxygen in order to maintain the arterial oxygen tension within the physiological range. These pulmonary changes are usually termed pulmonary fibroplasia by various workers, or pulmonary respiratory syndrome (Lancet, 1967).

The pathological features of hyaline membrane disease are known to change with the duration of the illness, and it is rare to find any membrane after four to five days (Lancet 1: 1969). In contrast, lungs of infants kept alive with artificial ventilation showed slowly healing and persistent membranes for as long as ten days, followed by mucosal metaplasia, histiocytic invasion and fibrosis. Patchy fibrosis, thickening of alveolar wall, and distortion of alveolar architecture have been characteristic findings in lung biopsy specimens and necropsy materials from infants requi-

ring respiratory therapy.

Pulmonary fibroplasia is not confined to cases with respiratory distress syndrome. Cases have been described in which many of the patients have had no respiratory or cardiac disease before the use of the ventilator (Nash et al 1967; Pusey et al 1969). Pusey reported a series of 51 newborn infants with respiratory failure treated with artificial positive pressure ventilation, and 11 of 16 infants ventilated for over six days. Five of the 11 infants had initial clinical and radiographic features different from hyaline membrane disease. Nash et al reported post-mortem examinations of 70 patients who were artificially ventilated and many showed characteristic pulmonary changes. These patients' underlying diseases vary from acute myocardial infarction, bronchopneumonia, emphysema to post-operative cardiac surgery.

Although most of the reports on the occurrence of pulmonary fibroplasia are associated with the use of inspired oxygen of more than 80%, there are also reports of characteristic pathological changes with inspired oxygen of less than 80%. Nash et al, in their series, used inspired oxygen varying from 21 – 100% and Pusey et al, in their series, have three infants with pulmonary changes in which inspired oxygen was below 80%.

We describe below two infants, one with respiratory distress syndrome and the other with neonatal tetanus, who developed pulmonary changes, including fibrosis, in spite of inspired oxygen concentration being below 80%.

Material and Methods

The two infants were admitted to the Intensive Care Unit of the University Hospital, the first a few hours after delivery for respiratory distress and post-operative supportive ventilation, and the second for respiratory distress following neonatal tetanus. Both were treated with intravenous fluid; sodium bicarbonate when necessary, antibiotics according to sensitivity reports of cultures from nasal and tracheal secretions; physiotherapy and tracheo-bronchial toilet as often as necessary; vitamin supplements; and intermittent positive pressure ventilation, using the Engstrom ventilator. The adequacy of ventilation was judged clinically by the infants' colour, by auscultation and chest movement and by correlation with micro-Astrup studies. Chest X-rays were taken when indicated to assess the position of the nasotracheal tube, the progress of any consolidation and the occurrence of any pulmonary atelectasis or pneumothorax. The infants' temperatures were kept to 37°C and humidification was achieved by using ultrasonic nebulizer. The general management was undertaken jointly with the surgeon, the paediatrician and the physiotherapist.

Case I – b/o N.K.L.

The infant, the first of a twin, was vertex delivered on 13.7.70 following spontaneous labour at 36 weeks' gestation, (birth weight of 3.17 kgm). She breathed spontaneously and Apgar score at 1.0 minute was 5. She had macroglossia, facial plethora and an exomphalous measuring 20 cm. in diameter. There was mild grunting with intercostal recession, and her respiratory status progressively deteriorated. She had to be intubated and artificially ventilated. The exomphalous was repaired and post-operatively, she was ventilated in I.C.U. (Engstrom ventilator). The ventilation pressure varied between 15 – 34 cm H_2O, using Jackson Rees portex nasotracheal tube, internal diameter of 3.0 mm. The inspired oxygen concentration was initially at 50%, but gradually decreased to 35% by the 23rd day of ventilation.

Several attempts were made to wean her off the ventilator but failed. She developed spontaneous tension pneumothorax on five occasions during her two admissions to I.C.U., the first occasion being five days after I.P.P.V. On all occasions, the tension pneumothorax was drained. The infant was finally weaned off the ventilator completely, 35 days after I.P.P.V. and continued to have oxygen therapy, using the Isolette incubator.

Six days after weaning off the ventilator, the baby developed respiratory and cardiac arrest in the paediatric ward, necessitating treatment with I.P.P.V. in I.C.U. after resuscitation. Inspired oxygen concentration was never above 48% at this stage. She never recovered respiratory independence and finally succumbed, 56 days after delivery.

Necropsy

At autopsy, the infant was found to have multiple congenital abnormalities, the major ones being an exomphalons (with partial surgical repair) associated with organomegaly (liver 160 gm. with Riedel's lobe and kidneys 52 gm. each), multiple small muscular ventricular defects in the heart and malrotation of intestines.

The right and left lungs weighed 40 gm. and 25 gm. respectively. The apical portions were aerated

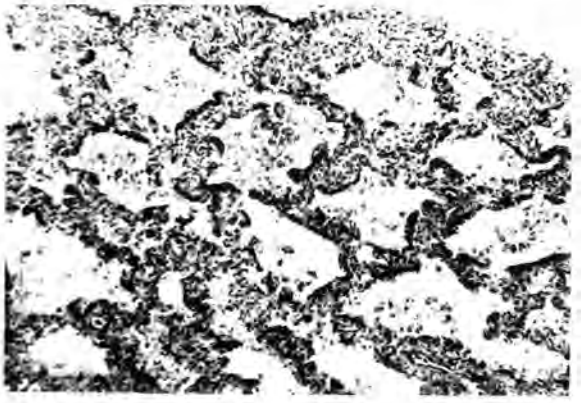


Fig. 1

(Magnification x 150. Van Gieson stain.) This section shows the increased elastic tissue as black in the thickened alveolar walls.

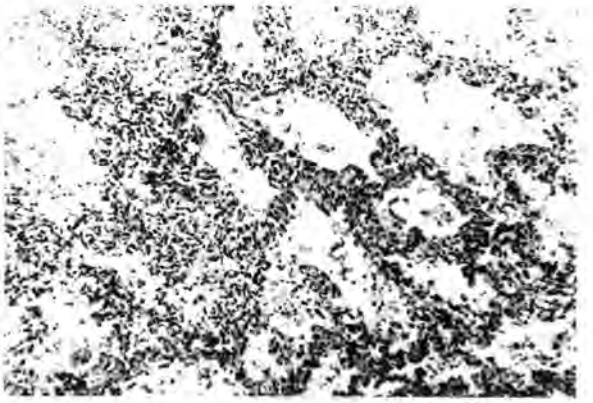


Fig. 2

(Magnification x 150. Haematoxylin/Eozin stain.) Shows the thickened alveolar septae with intra-alveolar macrophages, shed-off septal cells, and initial interstitial fibrosis.

and pink-tan in colour but both basal portions were dark red-purple with small areas of consolidation. There was no evidence of tension pneumothorax or of embolisation.

Microscopically, there was diffuse thickening of the alveolar septae with increase in elastic tissue and fine collagen fibres (Fig. 1). There was also congestion of alveolar capillaries with haemorrhage and some fibrinous material in some alveoli. In other areas, the alveoli were filled by foamy macrophages and shed-off septal cells (Fig. 2). There was squamous metaplasia of the epithelium lining the trachea. No evidence of pneumonia was present.

Case II – T.W.K.

This was a male infant referred to the University Hospital from another hospital at ten days of age with neonatal tetanus. He was home-delivered at full term and the umbilical cord cut with a pair of unclean scissors. Birthweight was unknown, but at ten days old, he weighed 3.17 kgm.

The baby was moderately dehydrated and jaundiced on admission, with severe spasms and respiratory distress. I.P.P.V., using Engstrom ventilator, was immediately instituted. Jackson Rees portex nasotracheal tube (internal diameter 3.0 mm.) was used, the inflation pressure varying between 14 – 32 cm H_2O throughout. Inspired oxygen concentration was 39% initially, tailing to 37% on 11th day of ventilation, but increasing to 42% subsequently due to consolidation of both apices of the lungs on the 14th day of ventilation.

On the 18th day of ventilation (26 days old), the baby suddenly developed bilateral tension pneumothorax with spreading subcutaneous emphysema. Resuscitation was done with drainage, but with supervention of cardiac arrest, resuscitation was unsuccessful.

Necropsy

At autopsy, there was extensive surgical emphysema over the head, shoulders and trunk extending into the upper portion of the thighs. The pericardial sac was distended by frothy clear fluid and two blebs, 2 x 4 mm. in size each, were present over the anterior pericardial surface.

There was bilateral tension penumothorax; about 1 ml. of air was released from each pleural cavity when they were pierced under water. The right lung weighed 33 gm. and the left 30 gm. Both lungs were collapsed, of a red-purple colour and sank in water. There were many blebs of 2 – 4 mm. size in the interlobular fissures of both lungs and larger bullae of 1 – 2.5 cm. diameter were present over the surface of the right lung.

Microscopically, there was atelectasis with prominent perivascular air spaces along major vessels and these spaces extended along interlobular connective tissue to the pleural surface. There was congestion of pulmonary vessels and alveolar capillaries, and the alveoli contained macrophages and shed-off septal cells (Fig. 3). The alveolar septae were thickened. No in-

Fig. 3

(Magnification x 150. Haematoxylin/Eosin stain.) Shows thickened alveolar septae and alveoli containing foamy macrophages and shed-off septal cells.

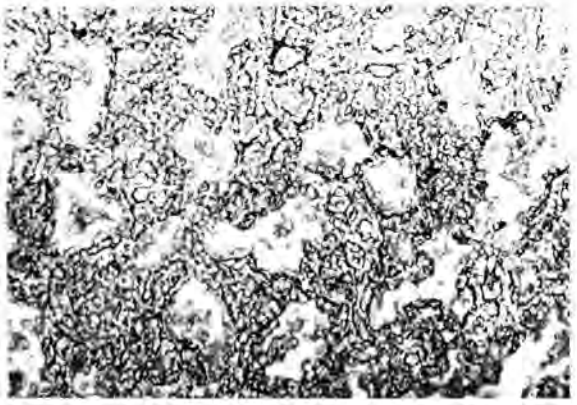


Fig. 4

(Magnification x 150. Reticulin stain.) Demonstrates the increased reticulin in the prominently thickened alveolar walls.

crease of collagen was demonstrable but reticulin was definitely increased (Fig. 4). Some bronchioles showed squamous metaplasia.

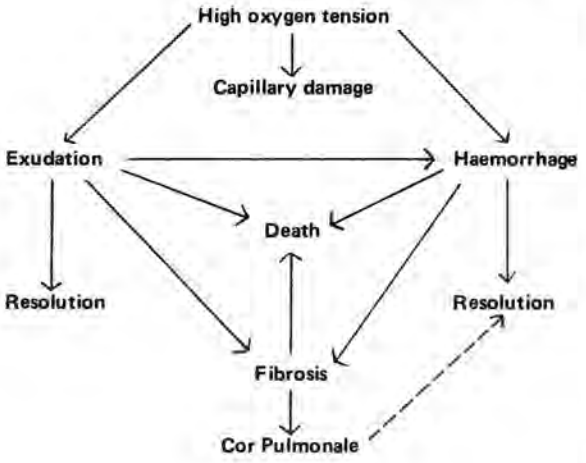
Discussion

That oxygen in high concentration (more than 80%) is toxic to the tissues is well documented by various workers. As early as 1897, Lorrain Smith concluded that oxygen at 41.6% of an atmosphere was well tolerated by mice, and at 70–80%, 50% of mice were dead at the end of one week. Kaplan et al (1969) also documented the oxygen toxicity in their work with monkeys. In man, most of the work on oxygen toxicity was either at increased atmospheric pressure or at ambient pressure with inspired oxygen concentration of more than 80%, and most of these centred around treatment in hyaline membrane disease. Recent reports have shown that pulmonary changes can occur at lower inspired oxygen concentration. Patients requiring respiratory therapy for pulmonary disease other than hyaline membrane disease also showed pulmonary changes, including diffuse interstitial fibrosis.

Northway et al (1967), from their clinical, radiological and pathological observations, have reconstructed the development of the pulmonary sequelae in which four stages were described, the radiological and pathological stages of which may overlap each other slightly. Stage I, within 2 – 3 days, a "period of acute respiratory distress syndrome" with increased pulmonary density and air bronchogram. There is hyaline membrane, atelectasis and metaplasia, and necrosis of bronchiolar mucosa. Stage II (4 – 10 days), a period of regeneration, with necrosis and repair of alveolar epithelium, persisting hyaline membrane, focal capillary basement thickening and bronchiolar eosinophilic deposition. Stage III (10 – 20 days), a transition period, with widespread bronchial mucosal metaplasia, moderate exudation of alveolar macrophages and histiocytes, emphysema, atelectasis and interseptal collagen deposition. Stage IV (more than one month), a period of chronic disease. Emphysema, atelectasis, increased macrophages and histiocytes, perimucosal fibrosis, widespread metaplasia, reticulin, collagen and elastin fibres in septal walls may all be present.

In both our patients, there is pathological evidence of emphysema, atelectasis, macrophagic infiltration and diffuse interstitial fibrosis in one (Figs. 1 and 2), with marked increase in reticulin in the other (Figures 3 and 4), the latter being the initial stage in the formation of fibrosis.

There are several reports in the literature which implicate high oxygen tension and oxygen toxicity, but due to many conflicting views, it is difficult to be certain of the factors which may play a role in the development of diffuse interstitial fibroplasia. Rowland and Newman (1969) have drawn up a scheme showing the effect of high oxygen tension on the lung as follows:



Northway et al postulated several possible mechanisms.

1. It is the result of pulmonary healing in infants with respiratory distress syndrome, who ordinarily do not survive.
2. It is the results from toxic effects of oxygen on the lungs superimposed upon pulmonary healing in infants with severe respiratory distress syndrome.
3. It results from the effects of pulmonary oxygen toxicity, healing severe respiratory distress syndrome, I.P.P.V. and poor bronchial drainage secondary to endotracheal intubation.

Respiratory Distress Syndrome

In the Pusey et al series, five infants, who developed diffuse interstitial fibrosis, did not have an initial diagnosis of respiratory distress syndrome; neither did the first of our cases. Our second infant had normal lungs initially. Nash et al reported cases of interstitial pulmonary fibrosis in patients who had no cardio-respiratory diseases to start off with. Thus the development of diffuse interstitial fibroplasia does not appear to be dependent on a specific pulmonary patho-physiology associated with respiratory distress syndrome.

Prolonged use of high concentration of oxygen.

Oxygen is administered clinically to re-establish a patient's arterial oxygenation tension to a physiologically normal range, usually around 70–90 mmHg. The difference between the PIO2 (inspired oxygen tension) and PaO2 (arterial oxygen tension) is an index of either diffusion or ventilation-perfusion abnormality. Changes in magnitude of PIO2 – PaO2 difference have served as an additional clinical prognostic sign. Harris et al (1968) have closely monitored PIO2 as well as PaO2 in clinical situations where a very high PIO2 was required for 1 – 14 days in order to maintain PaO2 in the normal range. In spite of the necessarily high PIO2, they have not encountered an identifiable case of oxygen toxicity. They found that when employing machines with provisions for accurate oxygen addition, control of PIO2 is simple and reasonably accurate, but with venturi-mix pressure limited machines, PIO2 can vary between 50% to 95%, as Pusey et al found with the Bennett and the Bird Ventilator. Harris et al devised a formula for the dosing of oxygen as follows:

$$\dot{V} \text{ gen/min.} = 1.25\,\dot{V}\,\frac{(PB - PIO2)}{PB} = \text{Litres oxy-}$$

where $\dot{V}$ = minute ventilation of patient,
PB = existing barometric pressure,
PIO2 = Inspired oxygen concentration.

Tunstall et al (1968) reported 90 newborn infants treated by using volume cycled ventilator. None had "respirator lung syndrome" as reported in Lancet 1: 1967. Our two infants were both on volume cycled ventilators but both had pulmonary changes.

Respirator therapy and inspired oxygen concentration of 80–100% were common to all cases of pulmonary fibroplasia so far described, given continuously for at least 2 – 3 days. Much circumstantial evidence incriminates oxygen toxicity apart from its action in causing retrolental fibroplasia. In retrolental fibroplasia, Robertson et al (1968) found two cases in which the retinal PaO2 were more than 160 mmHg, and they arbitrarily fixed the level of PaO2 at 160 mmHg for retrolental fibroplasia to occur.

The implication that pulmonary fibrosis occurs as a result of prolonged use of high oxygen concentration is difficult to evaluate. Various animal studies with 100% oxygen have shown thickening of the alveolar septal walls attributed to capillary proliferation, thickening of capillary endothelium or pulmonary oedema, but interstitial fibroplasia has been demonstrated in only one study of adult monkeys where septal fibrosis was seen 31 days after exposure

to pure oxygen (Robinson et al, 1967), and in rats after exposure to 700 mmHg oxygen for up to ten days (Schaffaer et al. 1967). It is also interesting to know that complications of diffuse interstitial fibroplasia was not seen in pulmonary pathology in infants dying of hyaline membrane disease between 1944 and 1948, a period when 100% oxygen was widely used. And yet, in our two infants, PIO2 was never above 60% in one, and 42% in the other. Morgan (1968) concluded that no toxic threshold for oxygen exists, and that any increase in oxygen of inspired gas mixture is a threat, but when oxygen administration is limited to a few days, percentage of oxygen more than 70% is dangerously high.

Prolonged nasotracheal positive pressure artificial ventilator

This has been known to be associated with squamous metaplasia and, occasionally, necrosis of tracheal epithelium, thus interfering with ciliary activity. Also, positive pressure ventilation may force secretions back into distal air passages. Whether this could eventually cause interstitial pulmonary fibrosis is unknown.

Could the respirator per se be a contributing factor to the development of fibroplasia? It is well known that patients on ventilators have progressive decrease in lung compliance secondary to progressive atelectasis due to the absence of the intermittent "sigh reflex" (Bendixen et al, 1963). Infants ventilated via an endotracheal tube cannot inspire deeply or cry, thus limiting their tidal volume. To avoid this, our infants were hourly hyperinflated via the by-pass in the Engstrom, using modified Ayre's T-piece system after tracheo-bronchial secretions were removed. In the absence of this, could progressive atelectasis end up in diffuse interstitial fibroplasia? This is at present unknown.

Could high inflation pressure used to ventilate the lungs of infants lead to metaplasia and fibroplasia? In prolonged ventilation of newborn infants, Tunstall et al (1968) recommended that the ventilation pressure should not be above 20 cm H_2O and the ideal size of naso-tracheal tube is one that allows a slight audible leak back past the larynx when this pressure is applied. Infants with respiratory distress syndrome necessarily require a higher ventilation pressure. Becher and Koppe (1969), in their series of 14 babies with hyaline membrane disease, had eight fatalities and all these had high ventilation pressure – 50 cm H_2O on the average, with high oxygen concentration. Five of the six babies who survived were treated with relatively low pressures of 35 cm H_2O. In both our infants, the ventilation pressure in one varied from 15 – 34 cm H_2O and in the other 14 – 32 cm H_2O, a pressure considered "low" by Becker and Koppe.

Reduction of surfactant.

Loss or reduction of surfactant secondary to over distension of alveoli may result in atelectasis, but this does not appear to be implicated in the formation of pulmonary fibroplasia. Hawker et al (1967) reported normal surface tension measurements on lungs of five infants dying from diffuse interstitial fibroplasia after prolonged respiratory therapy. They inferred the presence of surfactant from findings of low surface tension of lung extracts. Apparently, the effect of oxygen toxicity on respiratory tract is not mediated through surfactant.

Conclusion

It is apparent from the various reports and conflicting opinions, that the direct factor causing pulmonary changes in patients under treatment with oxygen and I.P.P.V. has not been established, though oxygen itself in high concentration appears to be one of the factors. Even here, some workers do not think that it is causally related to the appearance of diffuse interstitial fibroplasia.

The mechanism of oxygen damage to the lung has not been fully elucidated, and the highest concentration of oxygen without toxic effect in the lungs is not yet known, but what is certain is that the use of 90 to 100% oxygen for a prolonged period is probably hazardous, and that careful monitoring of blood gas tensions is required when high oxygen tension is used (B.M.J. 1968). Pulmonary damage is not confined to patients ventilated with high oxygen concentration as our two infants have shown and reports in the literature have shown that it is possible even in lower concentrations.

The practice of oxygen therapy is to administer oxygen in a concentration that results in an arterial oxygen tension of 70 – 120 mmHg, sufficient to give a 95 to 99% saturation of arterial blood (Nash et al, Harris et al). This treatment often entails the use of a high concentration of inspired oxygen, including 100% oxygen. Nash et al have emphasised that such therapy is not withheld for fear of possible toxic effects on the lungs or other organs. However, the inspired oxygen concentration should be reduced as

soon as is possible, to a level compatible with adequate function of vital organs. Other measures to improve oxygenation of the body, thereby permitting a decrease in the alveolar PO2, such as fastidious tracheal toilet and correction of pulmonary oedema or congestion; treatment of anaemia and acidosis; reduction of fever, should also be utilised (Hyde and Fischer, 1969).

Summary

Oxygen therapy, at atmospheric pressure with inspired concentration above and below 80%, are reviewed. Two cases are reported of infants subjected to I.P.P.V. via Engstrom ventilator, with PIO2 below 80%, and the postmortem finding of pulmonary changes (fibroplasia). These changes, and their causal relationship to oxygen and other factors, are discussed, together with the review of reported series in the literature. It is emphasised that (1) pulmonary changes can occur with PIO2 greater than that of air (21%), and (2) the administration of oxygen as such is not withheld for fear of possible changes in the lungs, but the oxygen concentration should be reduced as soon as is permissible.

Acknowledgement

We wish to thank Dr. A.E. Delilkan for his encouragement and guidance in the preparation of this paper; to Mr. Milton G. Sirimanne for his laboratory investigations; and Miss S. Dawood for secretarial work.

References

1. Annotation: (1967). "Pulmonary Respiratory Syndrome". *Lancet.* 1: 992.
2. Bean, J.W.: (1965). "Factors influencing Clinical Oxygen Toxicity." *Ann. N.Y. Acad. Sci.* 117: 745.
3. Becker, M.J., and Koppe, J.G.: (1969). "Pulmonary structural Changes in Neonatal Hyaline Membrane Disease Treated With High Pressure Artificial Ventilation." *Thorax.* 24: 689.
4. Bendixen, H.H., Hedley-Whyte, J., and Laver, M.B. (1963). "Impaired Oxygenation in Surgical Patients During General Anaesthesia With Controlled Ventilation. A Concept of Atelectasis." *New Engl. J. Med.* 269: 991.
5. Comroe, J.M. Jr., Dripps, R.D., Dumke, P.R., and Demong, M: (1945). "Oxygen Toxicity: Effect of Inhalation of High Concentrations of Oxygen for Twenty-Four Hours On Normal Man at Sea Level and at Simulated altitude of 18,000 feet." *J.A.M.A.* 128: 710.
6. Harris, T.M., Gray, M., Petty, T.L., Mueller, R. (1968). "Monitoring Inspired Oxygen Pressure During Mechanical Ventilation". *J.A.M.A.* 206: 2885.
7. Hawker, J.M., Reynolds, E.O.R., Tahizadeh, A. (1967), "Pulmonary Surface Tension and Pathological Changes in Infants Dying After Respirator Treatment for Severe Hyaline Membrane Disease. *Lancet.* 2: 75.
8. Hyde, R.W., Fisher, A.B.: (1969). "Oxygen Therapy." *Ann. Intern. Med.* 71: 665.
9. Kaplan, H.P., Robinson, F.R., Kapanei, Y., Weibel, E.R.: (1969). "Pathogenesis and Reversibility of The Pulmonary Lesions of Oxygen Toxicity in Monkeys." *Lab. Invest.* 20: 94.
10. Leader: (1968). "Pulmonary Haemorrhage In The Newborn." *Brit. Med. J.*, 1: 397.
11. Leading Article. (1969). "Hyaline Membrane Disease, Oxygen and Pulmonary Fibroplasia." *Lancet.* 1: 32.
12. Lorrain Smith, J.: (1899). "Pathological Effects Due to Increase of Oxygen Tension in Air Breathed." *J. Physiol.* 24: 19.
13. Morgan, A.P. (1968). "The Pulmonary Toxicity of Oxygen." *Anaesthesiology,* 29: 570.
14. Nash, G., Blennerhassett, J.B., Pontoppidan, H.: (1967). "Pulmonary lesions Associated with Oxygen Therapy and Artificial Ventilation." *New Eng. J. Med.* 276: 368.
15. Northway, W.H. Jr., Rosaw, R.C., Porter, D.Y. (1967): "Pulmonary Disease Following Respirator Therapy of Hyaline Membrane Disease." *New. Eng. J. Med.* 276: 357.
16. Pusey, V.A., MacPherson, R.I., Chernick, V. (1969): "Pulmonary Fibroplasia Following Prolonged Artificial Ventilation of New-born Infants. *Canad. Med. Ass. J.* 100: 451.
17. Robertson, N.R.C., Gupta, J.M., Dahlenburg, G.W., Tizard, J.P.M.: (1968). "Oxygen Therapy In The Newborn." *Lancet.* 1: 323.
18. Robinson, F.R., Harper, D.T. Jr., Thomas, A.A., and Kaplan, H.P.: (1967). "Proliferative Pulmonary Lesions In Monkeys Exposed To High Concentrations of Oxygen." *Aerospace Med.* 38: 481.
19. Rowland, R., Newman, C.G.H.: (1969). "Pulmonary Complications of Oxygen Therapy." *J. Clin. Path.* 22: 192.
20. Schaffner, F., Felig, P., Trachtenberg, G. (1967): "Structure of Rat Lung After Protracted Oxygen Breathing." *Arch. Path.* 83: 99.
21. Slack, W.K. (1967). Recent Advances in Anaesthesia and Analgesia: Hyperbaric Oxygen. Churchill 10th Ed., p. 218.
22. Tunstall, M.E., Cater, J.I., Thomson, J.S., Mitchell, R.G. (1968). "Ventilating the Lungs of Newborn Infants For Prolonged Periods." *Arch. Dis. Childh.* 43: 486.