Lung Injury from Oxygen in Lambs:

*The Role of Artificial Ventilation**

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Eighty to 100 per cent oxygen, breathed by lambs one or two weeks of age, is lethal after two to four days. Artificial ventilation did not aggravate or significantly ameliorate the pulmonary response. Lambs ventilated with air on respirators for comparable periods had no significant pulmonary damage. The cause of death of the oxygen-treated lambs was the pulmonary injury, characterized by edema. Studies of the excised lungs showed that the lesion was spotty, that the normal-appearing portions of the lung were normally distensible, and no significant alterations in pulmonary surfactant occurred. Several methods of assessment of the mechanical derangements are presented.

THE OCCURRENCE of bronchopulmonary dysplasia in the lungs of infants and adults treated with oxygen and positive-pressure respirators[1,2,3] has led to speculation about the possible role of artificial ventilation in the pathogenesis of this lung injury. Pulmonary oxygen toxicity in both adult animals and humans has been well documented[4-10] although few studies of oxygen toxicity in newborn animals have been reported.[11-14] The role of the respirator in the pathogenesis of the pulmonary lesion has been difficult to evaluate in humans because they have also had underlying pulmonary disease, which in itself could lead to the chronic changes described. In one study of adult dogs, designed to examine the roles of the respirator and prolonged endotracheal intubation in producing pulmonary changes associated with breathing 100 per cent oxygen, the lungs of oxygen-breathing animals showed significant damage after 25–30 hours, whereas the lungs of air-breathing animals were essentially normal.[15]

We have examined the effects of artificial ventilation in normal lambs approximately two weeks of age, exposed to 80+ per cent oxygen. The nature and severity of the pulmonary lesions were studied post-mortem by measurement of the static elastic properties of the lung, the pulmonary surfactant, and by histologic criteria.

Materials and Methods

Eighteen "mixed-breed" lambs were selected for the study. Eight were female, ten male. The lambs were divided into four treatment groups: 1) air breathing, no respirator; 2) air breathing with respirator; 3) oxygen breathing with respirator; 4) oxygen breathing, no respirator (table 1). The animals were anesthetized with sodium pentobarbital 20 mg/kg intraperitoneally and a femoral arterial cannula inserted. Silastic® † tracheostomy tubes (Aberdeen design) were placed in 13 animals, all of those on respirators, two of the five control lambs, and three of the five on oxygen alone.

The respirators used were two Harvard pumps®,‡ an Emerson infant ventilator® § and

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Received from the Departments of Pediatrics, Pathology, Medicine and Surgery; Johns Hopkins University School of Medicine, Baltimore, Maryland. Accepted for publication January 22, 1969. Supported in part by United States Public Health Service Grant HD 00281-08. Presented in part before the Society for Pediatric Research, May, 1968, and published in part in *Surgical Forum* 19: 265, 1968.

The views expressed herein are those of the authors and do not necessarily reflect the views of the U. S. Air Force or the Department of Defense.

† Dow-Corning Co., Midland, Michigan.

‡ Model 607, Harvard Instrument Co., Harvard, Mass.

§ Model 3-PV, J. H. Emerson Co., Cambridge, Mass.

TABLE 1. Clinical and Histologic Findings

Animals	Condition*	Survival (hours)	Cause of Death	Pa_{O_2} (Stage in experimental course)				P_{IO_2} Mean	*p*H** Mean	Pa_{CO_2} Mean	Edema	Alveolar Thickening	Congestion	Lymphatic dilation
				.1	.5	.8	.9							
Controls														
3	Tr		Sacrificed	82			82	142	7.35	37	0	0	0	0
4	Tr		Sacrificed	80			80	142	7.36	34	+	+	0	0
C_1			Sacrificed					142			−	−	−	−
C_2			Sacrificed	86				142	7.38	35	0	0	0	0
C_3			Sacrificed	85				142	7.40	40	0	0	0	0
Air and respirator														
5	EATr	101	Sacrificed	48	65	109	82	142	7.51	37.1	+	0	0	0
6	MATr	101	Sacrificed	95	116	85	—	142	7.58	13.1	0	0	0	0
10	HATr	70	Spontaneous***	103	109	109	82	142	7.48(7.54)	23.1(23)	+***	++***	++***	+***
11	HATr	73	Sacrificed	85	104	96	—	142	7.51	28.1	0	+	+	0
MEAN									7.52(7.53)	25.1(25)				
O_2 plus respirator														
1	HATr	55	Spontaneous	667	523	230	200	630	7.42(7.50)	28(28)	++	+++	+++	++
2	HATr	96	Spontaneous	463	389	383	26	637	7.49(7.60)	29(29)	++/+++	+++	+++	++/+++
12	MATr	19	Spontaneous	409	—	—	—	572	7.39(7.39)	43(43)	+++	+	+	0
13	EATr	68	Spontaneous	539	582	302	37	597	7.33(7.48)	28(21)	−	−	−	−
MEAN		59.5							7.41(7.50)	32(30)				
O_2 alone														
7	Tr	47	Spontaneous	—	—	—	—	657	—	—	+++	++	+++	+++
8		40	Spontaneous	—	—	—	—	638	7.36	44	+++	0	0	++
9		58	Spontaneous	339	271	339	261	644	7.31(7.38)	31(25)	+	+	+	0
14	TrA	9	Spontaneous	610	390	—	28	639	7.43	44	++	+	+	++
15	TrA	50	Spontaneous	451	215	168	87	656	7.42(7.35)	54(46)	0	+	0/+	0
MEAN		40.8							7.34(7.38)	43(40)				

* Tr = tracheostomy; E = Emerson infant ventilator; M = Mueller-Mörch respirator; H = Harvard pump; A = anesthesia.

** Values of *p*H and Pa_{CO_2} in parentheses represent means of gas values *before* the onset of clinical and chemical deterioration; values of *p*H and Pa_{CO_2} not in parentheses represent mean values over the entire experimental course.

*** Interstitial pneumonia.

a Mueller-Mörch respirator,¶ and were assigned among the groups as shown in table 1. The oxygen-treated animals were maintained in an environment of 80–100 per cent oxygen at one atmosphere. Oxygen-treated animals not on respirators received oxygen via tracheostomy, or, if unanesthetized, were permitted to move about in a chamber flooded with oxygen. All inspired gas was fully humidified at a room temperature of 23 C or, when the Emerson and Mueller-Mörch respirators were used, at 37 C. Respirator rates were set at 20–22/min and tidal volumes adjusted to maintain arterial *p*H between 7.45 and 7.65 to simulate the clinical situation. All anesthetized animals were sighed every two to three hours. Ambient oxygen concentrations were determined at regular intervals using a Beckman® * oxygen analyzer.

Arterial blood samples, obtained initially and at 12-hour intervals, were drawn into a heparinized glass syringe and analyzed immediately for P_{O_2} using a modified Clark electrode. The electrode was calibrated with gases of known P_{O_2} and correction factors for the difference between blood and gas calibration were determined by tonometry. Arterial *p*H was measured directly; HCO_3^- and P_{CO_2} were calculated by the Astrup method.[16] All gas values were corrected for the body temperatures of the animals.

All animals on respirators and two receiving oxygen alone were sedated continually with intra-arterial pentobarbital titrated to keep them inactive. Animals were turned and suctioned every two to three hours, and given procaine penicillin 300,000 units and kanamycin sulfate 10 mg, intramuscularly every 12 hours. Nutramigen® † was administered by gavage six times a day. Chest roentgenograms were obtained daily.

The duration of the experiment was determined by the spontaneous deaths of the animals in oxygen. Other lambs were sacrificed after an interval greater than the longest survival in oxygen by the intra-arterial instillation of saturated KCl. Immediately after death the tracheostomy tubes were removed and a cannula was inserted proximal to the tracheostomy site. *In situ* pressure–volume curves were determined with the thorax open, using an apparatus previously described.[17] Pressure was adjusted in increments of 5 cm H_2O and time allowed for volume equilibration, approximately two minutes at each pressure. Lungs were weighed and their volumes determined by displacement of water, to permit calculation of total gas volumes and to check for possible leaks during the previous inflation.

After excision the lungs were reinflated for inspection of the surfaces and photographed. Two- to three-gm specimens of lung from the most abnormal-looking areas of one or more lobes were minced, filtered through gauze and cycled for 12 to 18 hours on a modified Wilhelmy balance until a reproducible force–area relationship was established. Minimal surface tension on compression of the surface film to 15 per cent of the original area and maximal surface tension on re-expansion were recorded continually.

Specimens of lung from areas adjoining those used for surface-tension studies, as well as specimens from relatively normal-appearing areas, were immediately fixed in 10 per cent formalin, embedded in paraffin, stained with hematoxylin and eosin, and examined by light microscopy. Two pathologists reviewed the sections independently without prior knowledge of the treatment of the animals and assessed the degrees of edema, congestion and lymphatic dilatation on a 0–4+ scale. When they disagreed both opinions were recorded.

Results

Survival Time

Survival was shortest in animals which received high concentrations of oxygen without ventilatory assistance, longer in the high-oxygen–respirator group, and longest in the air–respirator animals (three of which were sacrificed). The fourth had an unexpected cardiac arrest at 72 hours and had pathologic evidence of pneumonitis at necropsy. The wide variation in duration of life in the high-oxygen groups did not correlate with amount of oxygen given or with Pa_{O_2} (table 1).

¶ V. Mueller and Co., Chicago, Ill.
* Model D2 Beckman Instruments, Inc., Fullerton, California.
† Protein hydrolysate formula, 20 cal/oz, Mead Johnson and Co., Evansville, Indiana.

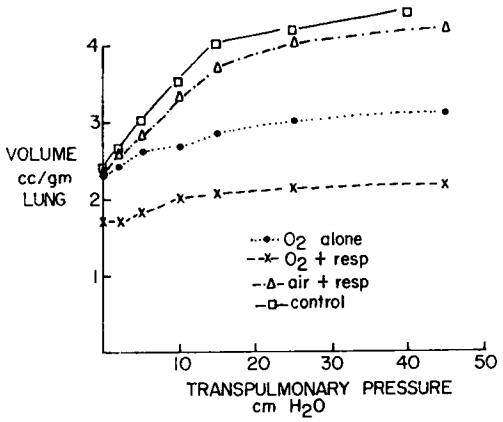

FIG. 1. Deflation pressure–volume curves. Volumes of air per gm lung tissue at any given transpulmonary pressure are substantially less in the O_2-treated lambs than in the air-breathing animals. The differences reflect in large part the greater lung weights of the O_2-treated animals.

BLOOD GASES

In animals that died spontaneously on respirators the arterial blood gases remained relatively stable for the initial half of the experiment; rapid deterioration heralded death. Similar findings in dogs were noted by Smith *et al.*[8] Respiratory alkalosis was greater in animals ventilated with air than in those ventilated with oxygen, when the values throughout the experiment are considered, *p*H 7.52 compared with *p*H 7.41. Mean values calculated before the onset of clinical deterioration showed comparable degrees of respiratory alkalosis, *p*H 7.53 and *p*H 7.50 (table 1).

CLINICAL SIGNS

Foamy tracheal secretions and rales were observed concomitant with deterioration in blood gas values. Respiratory rate and effort, noted at regular intervals, were not helpful in judging the status of the spontaneously-breathing animals, and of course were not usable as clinical criteria in the animals on respirators. Cyanosis was present late in the course of the experiment in the few animals who had significant hypoxemia. Two lambs on respirators developed pneumonthoraxes; one breathing a high oxygen concentration died in spite of chest-tube aspiration of the gas; the other did well after needle aspiration.

RADIOGRAPHIC FINDINGS

Reticular densities were found in six of the seven oxygen-treated animals of which roentgenograms were made. These were generally located at the lung bases and were felt to represent interstitial edema. One air–respirator-treated lamb had a pneumomediastinum and subcutaneous emphysema 12 hours after onset of the experiment. This animal ultimately developed a pneumothorax, but survived.

PRESSURE–VOLUME STUDIES

The static–elastic behavior of the lungs and thorax is depicted in figures 1 and 2. The deflation limbs of the pressure–volume relationships are shown as composite curves obtained by calculating mean gas volume at a given pressure for animals in each group. In figure 1 gas volumes are divided by mean lung weight and expressed on the ordinate as cc/gm lung. This form of presentation suggests that the oxygen-treated lambs had less distensible lungs than those breathing room air.

Since there was some variation in size of the animals, and lung weight included edema as well as tissue weight, another form of presentation is shown in figure 2. The volume of air

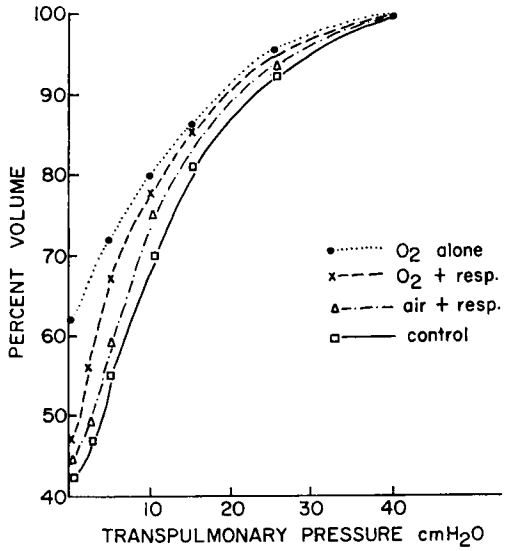

FIG. 2. Deflation pressure–volume curves. The oxygen-treated lungs showed no predisposition to premature closure, which would be expected if surface forces had been altered.

at any given transpulmonary pressure is expressed as a percentage of the total air volume at a pressure of 40 cm H_2O. Note that the inflated portions of the oxygen-treated lungs retained relatively more air throughout deflation and trapped larger volumes at zero transpulmonary pressure than the lungs not exposed to high oxygen concentrations.

Another method of depicting the volume events measured post-mortem is shown in figure 3. Since the edema could not be measured directly, the amount was calculated on the assumption that the lung tissue without edema would have borne the same relationship to body weight in treated animals as in controls. Thus, the expected tissue weight could be calculated knowing the body weight of each animal and the normal lung-weight–body-weight ratio. The difference between actual lung weight and expected lung weight was assumed to be the amount of edema. The gas volume at the peak distending pressure was added to the lung-tissue volume and edema volume to construct the columns in the figure. The ordinate is vol/gm of lung, to allow comparison of different sizes of animals. This comparison of lung volumes shows a marked increase in the amount of edema in the high-oxygen animals. This difference is also reflected in the lung-weight–body-weight ratios, where it can be seen that the air–respirator group had no significant edema, whereas mean lung weights in oxygen-treated animals were increased significantly (table 2). The total volumes of the lungs, including tissue, edema and air, after full inflation, were similar in all groups.

Two animals were omitted from the pressure–volume measurements; one control animal because of technical error and one oxygen-treated lamb because of multiple leaks.

Surface-tension Studies

The results of measurement of surface tension are shown in table 2. All but one specimen achieved minimal surface tension on compression of the surface film to below 15 dynes /cm, which is normal in our laboratory. In two instances (animals 13 and 15) specimens from abnormal looking parts of the lungs had higher minimal surface tensions than sections

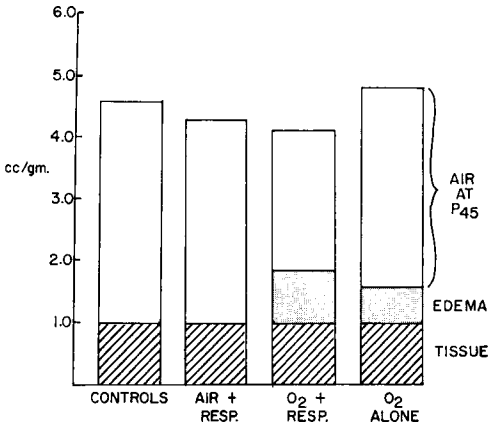

Fig. 3. Distribution of lung volume at maximal inflation. In the treated groups tissue weight is assumed to be that which would be expected knowing body weight and lung-weight–body-weight ratios in the controls. Edema represents the difference between actual and calculated lung weight. The air volume is that held by the lung at peak inflation at 45 cm H_2O pressure.

from areas which grossly looked more normal. On the average, minimal surface tensions of the lungs of oxygen-treated animals were slightly higher than those of controls and those of air-ventilated animals, but these differences are thought not to be of biologic significance.

Pathologic Studies

The lungs of animals which breathed high oxygen concentrations with or without respirators were strikingly different in gross appearance from lungs from air-respirator and control animals. First, all of the lungs were heavy and boggy. The pleural surfaces showed bleb formation on inflation (fig. 4). On deflation, segments of lung became atelectating, others remained inflated, and a white foamy tracheal effluent was noted. On the whole, the more dependent portions of the lung were most abnormal, although sometimes the abnormalities appeared randomly distributed.

Microscopically, the oxygen-treated lambs had changes of much greater magnitude than the air-breathing animals (table 1). Edema, alveolar thickening, congestion and lymphatic dilatation were the principal abnormalities found (fig. 5). There were marked differences in the degrees of histologic change among the oxygen-treated animals which did

not correlate with duration of exposure. On the whole, degrees of edema and lymphatic dilatation correlated better with differences in lung weight. Congestion and alveolar septal thickening were more variable. Hyaline membranes were found in only one lamb treated with oxygen and respirator (animal 2), and none showed hemorrhage or fibrosis. Squamous metaplasia was minimal and was distributed equally among the tracheostomized and non-tracheostomized lambs. Only one animal (10) had significant mononuclear infiltration. Since this was so exceptional, it was assumed it coud have existed before the experiments.

Discussion

The results of this study show clearly that oxygen, with or without artificial ventilation, causes fatal pulmonary damage in young lambs. We were able to demonstrate no adverse effects from the use of the ventilator without added oxygen.

The evidence in support of these conclusions is that only the high-oxygen-treated animals died; use of the respirator had no definite effect on survival; significant edema, as measured by changes in lung weight, abnormalities of pressure–volume relationships and histologic examination, was present only in animals breathing high oxygen concentrations; the

TABLE 2. Lung Weight, Static Elastic Properties and Surface Tension

Animals	Body Weight (kg)	Lung Weight (kg)	Lung Wt./ Body Wt.	C-R cm	Lung volume (cc) at a given pressure (cm H_2O)				Surface Tension* (dynes/cm)	
					V_{45}	V_{15}	V_5	V_0	Max.	Min.
Controls										
3	4.5	0.103	0.023	52	—	—	—	—	36, 33	7, 2
4	4.5	0.135	0.030	48	334	271	182	118	36	7
C_1	6.8	0.147	0.022	59	635	560	382	280	38	8
C_2	5.2	0.119	0.023	55	529	446	314	227	36	6
C_3	5.4	0.140	0.026	52	459	388	250	172	35	5
MEAN	5.3	0.128	0.024	53					36	6
Air and respirator										
5	4.7	0.110	0.023	48	253	233	198	148	33	2
6	4.4	0.108	0.025	45	349	298	205	142	40	1
10	4.6	0.126	0.027	52	407	328	202	147	36	3
11	4.9	0.109	0.022	54	426	357	226	174	42	3
MEAN	4.6	0.113	0.025	50					38	2.3
O_2 and respirator										
1	3.0	0.113	0.038	51	132**	127	99	67	44	3
2	4.7	0.150	0.032	52	180	161	137	105	35, 40	2, 7
12	5.2	0.121	0.023	46	419	363	282	229	36	5
13	4.8	0.268	0.056	54	85	65	46	36	32, 43	13, 20
MEAN	4.4	0.163	0.037	51					38	8
O_2 alone										
7	4.3	0.248	0.058	52	235	212	186	172	—	—
8	3.4	0.150	0.044	50	—	—	—	—	33	10
9	4.6	0.150	0.033	52	274	241	194	150	33, 35	0, 7
14	4.8	0.172	0.036	52	410	375	286	278	—	—
15	6.2	0.161	0.026	56	614	536	420	317	32, 35	4, 12
MEAN	4.6	0.176	0.038	52					33	6.6

* Where two values are given, the first represents a specimen from a cephalad lobe; the second from a caudad lobe.

** V_{35}—lung leaking at V_{45}.

lungs of lambs ventilated in room air were nearly normal.

The mechanical derangements observed were quantified by analysis of the pressure–volume relationships. It was immediately evident that the lungs of oxygen-treated lambs held less gas at a given transpulmonary pressure than air–respirator or control lungs. One possible interpretation of this observation is that the lungs were either fibrotic or in some other way less distensible after oxygen poisoning. Alternately, it is possible that the edema was space-occupying and that the elastic properties of the lung available for inflation were normal. The evidence strongly supports the latter possibility. When the deflation limbs of the pressure–volume curves were compared on the basis of the percentage of maximal volume at a transpulmonary pressure of 40 cm H_2O, the oxygen-treated lungs actually had relatively greater gas volumes at low transpulmonary pressure than the controls. Since foam was often visible in the airways it seems probable that it contributed to gas-trapping. Further support for the hypothesis that the distensible portions of the lungs were not abnormal comes from the analysis depicted in figure 3. The oxygen-treated animals had total volumes similar to those of the controls when lung–tissue volume, edema volume, and gas volume were calculataed. Alterations in surface forces or the presence of significant fibrosis should have reduced both gas and total volumes at the peak distending pressure.

The results of surface-tension measurements coupled with the absence of premature closure in the deflation limbs of the pressure–volume curves support the thesis that oxygen is not primarily injurious to pulmonary surfactant in lambs. Some studies in other species have shown alterations in surface tension with exposure to high oxygen concentrations [15, 19-24]; others have not.[20, 25] Morgan detected a reduction in phospholipid content in lung washings of dogs exposed to high oxygen concentrations for 48 hours, suggesting an impairment in surfactant synthesis.[23]

The problem of interaction of high oxygen concentration and pulmonary surfactant is complicated by the concurrence of edema, which may of itself displace the surfactant.[26]

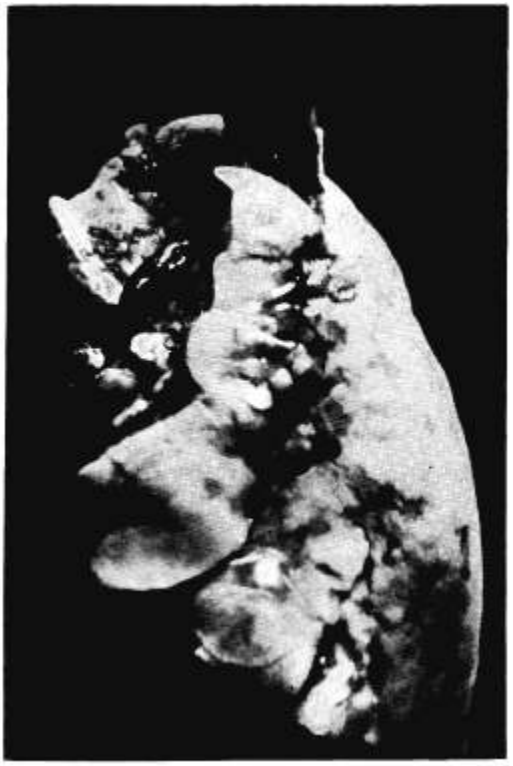

FIG. 4. Inflated excised lung from the oxygen-treated lamb. Note the somewhat uneven inflation and the subpleural bleb.

The possibility that edema comes first and the alterations in surface tension are secondary is supported by the findings in this study and by the morphologic findings of others. Electron microscopic examinations of rats show the earliest lesion to be an accumulation of liquid in the interstitial spaces, with destruction of the capillary endothelial lining.[27, 28] Abnormalities in the alveolar lining cells, thought to be a site of synthesis of the surfactant, are not regularly present.[15, 27, 29]

Necropsy findings in these animals were compatible with the events that have been measured during life in animals and man with either pulmonary oxygen toxicity or pulmonary edema from other causes.[6, 29-31] A reduction in dynamic lung compliance is regularly present and is reversible after forced inflation. The volume of trapped gas in the lungs during life is not significantly increased, but when the lungs are fully distended, as in post-mortem volume–pressure studies, previously-

FIG. 5. Photomicrographs of representative lung specimens from the four test groups (hematoxylin and eosin ×135). *A*, lung from a control animal, showing normal-looking alveoli with delicate septal walls. *B*, the air-respirator lung shows only minimal congestion and no other abnormalities. *C*, the O_2-respirator lung shows severe congestion, edema, and thickened alveolar septae. *D*, the lungs from lambs which spontaneously breathed high oxygen concentrations are indistinguishable from the O_2-respirator lungs.

collapsed alveoli are opened and foam formation occurs.[32]

The problem of the etiology of the pulmonary lesion seen in adults and infants after prolonged use of respirators and high oxygen concentrations cannot be resolved by this short-term study. However, we do confirm the findings of Lee *et al.*[22] that when a high oxygen concentration is administered via a respirator the acute lesion seen is the lesion of oxygen toxicity alone, and that the respirator does not appear either to produce or to aggravate the injury. Others have shown that chronic exposure of monkeys and rats [14, 33] to increased levels of oxygen has produced proliferative pulmonary lesions similar in many respects to those found in humans. This suggests that oxygen, not the fact of assisted ventilation, underlies the chronic pulmonary changes seen after assisted ventilation with high oxygen concentrations.

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Drugs

PENTAZOCINE COMPARISON Analgesic potency of oral and intramuscular pentazocine was evaluated in a double-blind crossover of graded single doses in patients with chronic pain due to cancer. Oral pentazocine was one third to one fourth as potent as intramuscular pentazocine. Single oral doses of 240 mg caused psychotomimetic reactions four out of 23 times. These reactions were transient; otherwise, adverse effects were not significantly different for equianalgesic doses of oral and intramuscular pentazocine. The oral form of the drug may be useful in treating moderately severe or severe pain which is not being treated with potent narcotics. (*Beaver, W. T., and others: A Clinical Comparison of the Effects of Oral and Intramuscular Administration of Analgesics: Pentazocine and Phenazocine, Clin. Pharmacol. and Ther. 9: 582 (Sept.) 1968.*)

HALOTHANE AND HEPATIC FAILURE Of the first 150 cases reported to the Fulminant Hepatic Failure Surveillance Study, 80 patients presumably had had viral hepatitis, and 62 of these patients had died. Of 41 patients who had had recent surgery, 36 died. Thirty-five of these patients exhibited massive hepatic necrosis less than three weeks after halothane anesthesia. Of these, 77 per cent had multiple exposures to halothane. Although the danger of hepatic failure from halothane is small, this complication was present in about 25 per cent of the patients presented in the study. This observation supports the authors' conclusion that when the use of halothane is desired, multiple exposures should be avoided. In addition, the authors point out that "unexplained" fever after exposure to halothane is an important warning sign, which should be thoroughly investigated prior to further exposure to this anesthetic. (*Trey, C., and others: Fulminant Hepatic Failure, Presumable Contribution of Halothane, N. Eng. J. Med. 279: 798 (Oct.) 1968.*)