PHARMACOLOGICAL REVIEWS Vol. 23, No. 2

Printed in U.S.A.

PULMONARY OXYGEN TOXICITY: A REVIEW

J. M. CLARK AND C. J. LAMBERTSEN

Institute for Environmental Medicine, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania and Environmental Systems Division, USAF School of Aerospace Medicine, San Antonio, Texas

TABLE OF CONTENTS

Prolonged exposure to oxygen at partial pressures greater than that in normal ambient air is accompanied by toxic effects which become progressively more severe as inspired P_{O_2} and duration of exposure are increased (17, 24, 26, 31–33, 47, 125, 135, 137, 172, 173, 196, 225, 284, 286, 422, 464). Although there is wide variation in susceptibility, no living cell can be expected to be completely immune to the toxic effects of oxygen (284). The most generally recognized adverse effects of oxygen upon specific organ systems include: pulmonary damage terminating in hypoxemia, acidosis and death (47, 105, 117, 169, 245, 265, 385, 417, 455, 459); central convulsions, permanent paralysis and death (17, 19, 24, 47, 66, 131, 138, 219, 249, 252, 284, 319, 449, 464, 493, 496); ocular toxicity (53, 360) producing visual field contraction (55, 536, 537), retinal damage (54, 184, 329, 361) and blindness (10, 11, 384); and other effects such as testicular damage (173, 369, 487) and erythrocyte hemolysis (229, 264, 339, 422). The speed of onset and rate of progression of toxic effects in specific tissues and organs depend upon local variables such as blood (oxygen) supply, tissue metabolic rate and susceptibility of the involved cells to oxygen poisoning. However, continued exposure of any animal to a toxic inspired P_{O_2} will produce progressive cellular damage and death in one organ system after another until the process is stopped by pulmonary damage or death of the animal.

Because the lungs are exposed to oxygen tensions higher than those in any other vital organ, it is not surprising that pulmonary oxygen toxicity is one of the principal factors limiting the safe and effective use of oxygen at increased pressures (24, 131, 284, 464). During oxygen breathing within a range of partial pressures at least as wide as 0.75 to 2.0 atm, the lung is the first vital organ to be severely affected by oxygen poisoning (47, 100, 114, 116, 120, 134, 161, 367, 405). Although the central nervous system appears to be affected first when oxygen is breathed at partial pressures of 2.8 atm or higher (138, 533), pulmonary toxicity undoubtedly occurs concurrently with the development of central nervous system (CNS) intoxication and often contributes to the death of animals exposed at the higher pressures (37, 39, 44, 250, 252, 255, 258, 261, 377, 494, 526). Continued exposure to toxic oxygen tensions causes progressive impairment of pulmonary function until oxygen uptake is impaired so severely that the increased inspired P_{O_2} necessary to sustain life in itself produces further damage to the lung. The occurrence of such a severe degree of pulmonary damage thus initiates a vicious cycle which can only end in death by oxygen poisoning.

In contrast to those toxic effects of oxygen which are ultimately fatal, there are non-toxic *physiological* effects which also occur during exposure to oxygen at increased partial pressures. Physiological effects of oxygen may be distinguished from the toxic effects by several characteristics. The most important of these is that the physiological effects do not endanger life and do not impose serious limitations upon the use of oxygen at increased pressures. Physiological effects are also usually characterized by a rapid onset, which is essentially concurrent with rise in P_{O_2} of the area affected, as well as a prompt and complete reversal, which coincides with return to a normal P_{O_2}. On the other hand, toxic effects upon pulmonary function become evident only after passage of a period

of time, the duration of which is inversely proportional to the inspired P_{O_2} (114, 115, 175, 250, 480, 481), and complete recovery from the reversible effects of pulmonary oxygen poisoning may require as long as several weeks (47, 100). Physiological effects of oxygen upon pulmonary function and respiratory control have been discussed in several recent reviews (283, 284, 287) and will be mentioned in this review only to distinguish them from the effects of pulmonary oxygen toxicity.

The detailed information contained on the following pages was obtained from individual papers related directly or indirectly to the subject of pulmonary oxygen toxicity. Summaries at the end of the lengthy descriptions of pathology and the mechanisms of pulmonary oxygen toxicity indicate which of the many findings the authors regard as particularly well established or significant.

TOXIC EFFECTS OF OXYGEN UPON THE LUNG

Pulmonary oxygen toxicity, a progressive process which destroys cells in the lung, is ultimately fatal if exposure to increased oxygen pressure continues and can be stopped only by reduction of the inspired P_{O_2} to a non-toxic level. The absence of demonstrable pathological changes within any specific group of cells in lungs that are damaged by pulmonary oxygen poisoning should not be interpreted as evidence that these cells are immune to the toxic effects of oxygen. Adverse effects can be expected to appear eventually, and the order of their appearance in different types of cells depends upon the relative susceptibilities of the cells to oxygen poisoning. It is conceivable that the sequence of toxic effects in various cell types may also vary at different levels of P_{O_2} and under the influence of factors which can modify the rate of development of overall pulmonary oxygen poisoning.

The same general principles that pertain to morphological and structural changes in the oxygen-poisoned lung can similarly be applied to the consequences of these changes in terms of pulmonary function. Continued exposure to a toxic level of inspired P_{O_2} and the resulting derangement of cellular metabolism throughout the lung can be expected to cause progressive impairment of one aspect of pulmonary function after another until the lung is no longer able to sustain an adequate gas exchange with the blood.

Pulmonary pathology

Pathological effects of pulmonary oxygen toxicity summarized by Bean in an early review (24) include: atelectasis, consolidation, edema, fibrin formation, congestion, inflammation, arteriolar thickening and hyalinization, bronchitis and alveolar cell hypertrophy, hyperplasia, degeneration and desquamation.

Although these findings have been generally confirmed (108, 205, 230, 261, 263, 273, 357, 358, 367, 375, 376, 395, 397, 415–417, 455, 494, 521), there are many inconsistencies in the numerous descriptions of pulmonary pathology found in various animal species after prolonged exposure to increased oxygen partial pressures. Some of these inconsistencies can be explained by differences in species, strain and individual susceptibility of experimental animals to pul-

TABLE 1A

Pulmonary oxygen tolerance in animals exposed to 0.9–1.0 atm of oxygen

Species	Number	Age	Weight	Oxygen Partial Pressure	Survival Time		Reference
					Mean	Range	
		mo	*g*	*atm*	*hr*	*hr*	
Drosophila	—*	—	—	1.0	168	144–192	159
Frog	2	—	—	0.90–0.98	Survived	>1176, 1632	151
Frog	4	—	49	0.98–1.0	Survived	>1248	72
Turtle	2	Adult	—	0.90–1.0	Survived	>240, 552	151
Turtle	5	Young	—	0.97–0.99	Survived	>504	151
Chicken	36	0.5–1.75	—	0.98–1.0	—	>672	514
Chicken	19	8–24	—	0.96–1.0	247	120–384	512
Quail	30	1.5+	—	0.98–1.0	336†	—	513
Mouse	44	—	—	0.97–1.0	120†	96–384	531
Mouse	20	2–2.5	25	0.99–1.0	—	120–192	504
Mouse (ST/J‡)	10	4–6	—	0.90–0.95	77	9§	310
Mouse (A‡)	10	4–6	—	0.90–0.95	97	12§	310
Mouse (SJL/J‡)	10	4–6	—	0.90–0.95	82	6§	310
Mouse (P/J‡)	7	4–6	—	0.90–0.95	86	18§	310
Mouse (129/J‡)	9	4–6	—	0.90–0.95	94	12§	310
Mouse	20	—	24.2	0.97	91.5†	68–?	121
Mouse (germ-free)	14	Adult	—	0.98–1.0	97.7	91–115	530
Mouse (conventional)	44	Adult	—	0.98–1.0	146.2	96–384	530
Mouse	25	—	—	0.95–0.99	126†	72–201	511
Mouse	347	—	20	1.0	111.3	1.4‖	175
Mouse	8	Adult	—	0.96–1.0	120	96–192	512
Mouse	40	—	—	0.92	306†	137–>360	319
Mouse	45	1–2	—	1.0	—	96–>192	428
Rat	—	—	120	0.94–1.0	56	—	35
Rat	—	—	160–220	0.98	134.4	38.4§	155
Rat	—	—	120	0.95–1.0	63.8	1.3‖	454
Rat	—	—	120	0.95–1.0	57	0.5‖	454
Rat	10	—	200	0.93–1.0	—	48–120	171
Rat	10	—	150–250	0.90–0.91	>240	—	432
Rat	34	—	—	0.98–1.0	118	20.4§	191
Rat	7	—	250–350	0.90–0.95	64.4	59–70	126
Rat	50	—	—	0.96–0.98	72†	—	501
Rat (germ-free)	8	—	200	0.98–1.0	81.4	73–91	530
Rat (conventional)	23	—	—	0.98–1.0	—	70–>120	530
Rat	60	2–7	—	0.95–0.99	60†	45–>77	511
Rat	—	—	—	1.0	71	—	452
Rat	—	—	—	1.0	57	—	452
Rat	20	4–6	—	0.99–1.0	90	72–144	20
Rat	—	Young	—	1.0	>528	—	384
Rat	110	—	—	0.92	—	336–>360	319
Rat	—	5	—	0.90–0.95	—	45–76	208
Rat	10	—	110	0.90–0.98	—	40–>70	42
Rat	6	—	—	0.97	—	71–>110	47
Rat	44	—	255–576	0.96	—	59–>192	132

* —Information not given.

† Lethal time required for death of 50% of the animals.

‡ Mouse strains used.

§ Standard deviation.

‖ Standard error.

TABLE 1B

Pulmonary oxygen tolerance in animals exposed to 0.9–1.0 atm of oxygen

Species	Number	Age	Weight	Oxygen Partial Pressure	Survival Time		Reference
					Mean	Range	
		mo	*g*	*atm*	*hr*	*hr*	
Guinea pig	11	—*	300–800	0.95–1.0	66.7	7.5§	444
Guinea pig	10	—	—	0.95–0.98	49	35–56	90
Guinea pig	—	—	—	0.91–0.98	—	96–144	230
Guinea pig	5	—	200–250	0.98	75	—	3
Guinea pig	5	—	200–250	0.98	96	—	3
Guinea pig	40	—	250	1.0	94	44–218	12
Guinea pig	23	Newborn	76–131	0.96–1.0	108	32–149	364
Guinea pig	10	3	—	0.95–0.99	79†	62–100	511
Guinea pig	8	—	—	0.92	118†	109–230	319
Guinea pig	4	—	—	0.97	—	71–>133	47
Rabbit	30	—	1420	1.0	75.8	11.7§	211, 119
Rabbit	9	—	—	0.98–1.0	70.7	21.8§	191
Rabbit	—	—	—	1.0	—	45–50	227
Rabbit	4	6	—	0.99–1.0	84	72–94	7
Cat	9	—	—	0.98–1.0	83.3	22.3§	191
Dog	7	—	—	0.98	67	61–79	99
Dog	—	—	10,000–15,000	0.95–0.98	54.6	32–83	455
Dog	5	Young	—	0.95–0.99	74†	47–149	511
Dog	8	—	—	0.92	119†	78–264	319
Dog	10	—	6,800–13,600	0.95–1.0	39	6–94	375
Dog	—	—	—	0.99–1.0	60	—	374
Dog	3	—	—	0.98–1.0	87	62–116	20
Monkey	4	—	3,060–6,010	0.98–0.99	390	144–528	416
Monkey	5	—	2,700–6,600	0.96–0.98	—	64–>336	415
Monkey	18	—	3,480	0.98–0.99	—	48–>312	265
Monkey	6	—	1,810–2,380	0.94–0.95	—	96–>336	417
Monkey	12	—	400–620	0.94–0.95	—	192–>336	417
Monkey	10	—	—	0.90–0.95	—	144–>480	164
Monkey	2	Young adult	—	0.95–0.99	183	150–216	511
Monkey	4	—	—	0.92	—	336–>360	319
Baboon	7	—	2,410–4,000	0.94–0.95	—	144–>168	417

* —Information not given.

† Lethal time required for death of 50% of the animals.

§ Standard deviation.

monary oxygen poisoning (24, 47, 108, 118, 121, 165, 220, 234, 263, 310, 319, 368, 413, 414, 417, 538). The magnitude of this variation in susceptibility is illustrated by the extreme range of average survival times for animals exposed to about 1.0 atm of O_2, ranging from 39 to more than 1600 hr (table 1). Variations in the susceptibility and in the pathological responses of different animals to pulmonary oxygen toxicity are particularly obvious when pulmonary lesions are compared after uniform durations of exposure to oxygen instead of after production of equivalent degrees of poisoning. The pathological changes of pulmonary oxygen intoxication are also dependent upon the age of the experimental animal. Immature animals are more resistant than older animals to

oxygen toxicity, and this appears to be due to a delayed onset of toxic effects rather than an increased tolerance to them (24, 86, 151, 177, 188, 280, 384, 399, 413, 456, 457, 463, 483, 514, 519).

Post-mortem changes in animals that have died during prolonged exposure to oxygen are also an important potential cause of the apparently diverse effects reported concerning the pathology of pulmonary oxygen poisoning (144, 145). Mice that were killed and autopsied immediately after a 48-hr exposure to about 1.0 atm of O_2 had no significant pulmonary changes. However, autopsy of similarly exposed mice after a 3-hr post-mortem delay revealed gross atelectasis and consolidation, decreased lung volume and histological evidence of edema, congestion and prominent intra-alveolar hemorrhage. Such post-mortem changes are explained in part by the observation that respiratory failure precedes cardiac arrest in the terminal stages of oxygen poisoning (251, 252, 377, 494). The absence of inert gas in the lungs then allows alveolar collapse to occur as oxygen, water vapor and carbon dioxide are absorbed.

Another possible cause of variability in the pathological effects of pulmonary oxygen toxicity is that the changes produced are partially dependent upon the oxygen partial pressure to which the animals are exposed. Prolonged oxygen breathing at an ambient pressure of 1.0 atm is accompanied by progressive pulmonary damage that terminates in acidosis and fatal hypoxemia which prevents continued exposure of the brain to high P_{O_2} (47, 265, 374, 375, 417, 455, 476). However, during exposure to several atmospheres of oxygen, central nervous system oxygen toxicity may induce lethal effects before lung damage becomes severe enough to produce fatal hypoxemia (247a, 449). Thus the degree of pulmonary pathology is much worse in animals dying in 5.0 atm of O_2 than in those dying in 8.0 atm of O_2 (78) and, even during oxygen breathing at 5.0 atm, tissue oxygen tensions in rabbits remain above normal until death occurs (47, 397).

Pathological changes produced by exposure of animals to toxic oxygen partial pressures below 1.0 atm may also be varied (132, 278, 456, 457). In these exposures, fatal hypoxemia may not occur or survival time may be sufficiently prolonged to permit the development of changes which secondarily increase tolerance to pulmonary oxygen poisoning (see Acquired Resistance to Pulmonary Oxygen Toxicity, page 73).

Atelectasis. The presence of alveolar atelectasis is a common finding in animals that have been fatally poisoned by oxygen (24, 47, 108, 132, 266, 267, 358, 387, 459, 464, 494, 521). Penrod (387) obtained evidence which suggests that the gross pathological changes induced in pulmonary oxygen toxicity are due in large part to atelectasis. The atelectasis that normally occurred during exposure of guinea pigs to 4.0 atm of O_2 was largely prevented by brief applications of positive intratracheal pressure at 30-min intervals. In addition, the pathological appearance of oxygen-poisoned lungs appeared to be extensively reversed by inflation with air. In rats exposed to 5.0 atm of O_2, however, post-mortem inflation did not refill some congested areas even when inflating pressures were great enough to rupture the lung, and edema fluid was not expelled (494). Further-

more, radiological studies indicated that significant atelectasis is not a primary event, but appears only when the lungs are severely damaged.

Dickerson (132) observed that pulmonary edema and pleural effusion preceded atelectasis during the development of pulmonary oxygen poisoning in rats and concluded that the atelectasis was primarily due to alveolar compression by the effused fluid. Other investigators who have studied the sequence of pathological changes in pulmonary oxygen poisoning have also found that edema and other manifestations of pulmonary damage appear before the onset of a significant degree of atelectasis (263, 265, 272, 273). However, interpretation of these results is complicated by the fact that preparation of the lungs included perfusion under positive pressure (+20 cm H_2O) with glutaraldehyde.

When the inert gas is washed out of the lungs during oxygen breathing, any source of airway obstruction will result in alveolar collapse because pulmonary capillary blood will completely absorb the oxygen, carbon dioxide and water vapor contained in alveoli distal to the obstruction (123, 130, 406, 412). The rate of collapse of obstructed alveoli is inversely proportional to the ambient pressure (412) since fewer oxygen molecules are contained in the alveoli at lower ambient pressure while metabolic consumption of oxygen is not altered under these conditions. Thus, aviators breathing pure oxygen at reduced ambient pressure are particularly susceptible to absorptional atelectasis and often experience it when airway obstruction occurs during exposure to sustained acceleration and increased gravity forces (4, 21, 201, 296, 305, 535). Regional hypoventilation, emphysema and other pulmonary conditions which cause air trapping also predispose the individual to absorptional atelectasis during oxygen breathing (143, 486).

The increased susceptibility to alveolar atelectasis during oxygen breathing can explain many of the inconsistencies regarding the role of atelectasis in the development of pulmonary oxygen intoxication. The occurrence of atelectasis in oxygen-poisoned lungs may be a primary effect related to chemical action of oxygen upon alveolar surfactant (see Role of Pulmonary Surfactant, page 93), a secondary effect of airway obstruction caused by pulmonary edema and pleural effusions (132), or it may originate from a combination of both effects. When pulmonary oxygen poisoning is produced by exposure to pure oxygen, the observed occurrence of atelectasis in conjunction with other manifestations of pulmonary damage does not permit differentiation between the two potential mechanisms. However, the interpretation that atelectasis is predominantly caused by physical rather than chemical effects of oxygen is favored by the observation that atelectasis is much less extensive after a fatal exposure to a mixture of oxygen and inert gas than it is after a similar exposure to the same partial pressure of pure oxygen (322, 521).

Pulmonary edema. One of the most common pathologic manifestations of pulmonary oxygen toxicity is the development of pulmonary edema, which first appears as a widening of interstitial spaces and progresses, in the most severe cases, to form massive pleural effusions (1a, 42, 132, 263, 265–267, 356a, 374, 375, 397, 454, 455, 459, 511, 521). In guinea pigs exposed to 0.9–1.0 atm

of O_2, a progressive increase in lung weight began after about 48 hr of exposure and continued until the ratio of lung weight to body weight was almost tripled in animals that survived for about 120 hr (167, 230). The increase in lung weight was attributed principally to an extravascular, interstitial accumulation of water, sodium and plasma proteins (3) since the cellular mass of pulmonary parenchyma, as estimated by total lung tissue content of potassium (3) or insoluble protein nitrogen (230), did not appear to be increased significantly. Monkeys breathing 96 to 98% O_2 at 1.0 atm also have a progressive increase in lung weight starting at about the 2nd day (415). During exposure of rats to 5.0 atm of O_2, lung weight began to increase after 30 to 60 min and almost doubled after 60 to 90 min of exposure (494).

Jamieson and van den Brenk (255) found that the fluid accumulated in the lungs of rats poisoned by exposure to 5.0 atm of O_2 was 42% whole blood, 20% cell-free plasma and 38% protein-free fluid. Other studies have shown intra-alveolar hemorrhage after exposure to several atmospheres of oxygen (37, 494), but lung hemoglobin content was not increased after fatal exposure to 0.9–1.0 atm of O_2 (230). These results suggest that the pulmonary capillaries are more severely damaged by exposure to oxygen at increased ambient pressures than they are by much longer periods of oxygen breathing at 1.0 atm.

The chemical composition of fluid from pleural effusions has been studied in rats (132, 418) and guinea pigs (9) after prolonged exposure to 0.86–1.0 atm of O_2. Comparison of the concentrations of organic and inorganic components in pleural fluid and serum suggest that the pleural effusions caused by pulmonary oxygen toxicity consist largely of dilute serum with variable contributions from cellular destruction and autolysis.

The mechanism of edema formation in pulmonary oxygen poisoning is most generally conceived to be due to an increase in the permeability of pulmonary capillaries, and histological evidence of capillary damage in oxygen-poisoned lungs supports this proposed mechanism (1a, 79, 94, 108, 263, 272, 273, 275, 321, 328, 356a, 357, 367, 376, 395, 419, 432, 494, 501, 532, 534). In addition, other workers (291, 522–524) found that the development of pulmonary edema in rats and dogs exposed to 3.0–4.0 atm of O_2 was accompanied by a sustained increase in systemic blood pressure. On the basis of this observation, they concluded that systemic hypertension was the principal mechanism of pulmonary edema in oxygen poisoning. However, hyperoxia does not consistently cause systemic hypertension (24, 55, 56, 448). Furthermore, sustained elevation of central venous pressure by intravenous infusion in dogs breathing O_2 or air at 1.0 atm caused pulmonary edema to develop more rapidly and after a smaller volume of infusion in the O_2-breathing dogs than in the air-breathing dogs (344). These results indicate that systemic hypertension, when present, may contribute to the development of edema in pulmonary oxygen poisoning, but that it is not the principal mechanism.

As an alternative mechanism, Maklári *et al.* (326) have suggested that hypercapnia is involved in the pathogenesis of pulmonary edema in oxygen intoxication. However, their own results in rats do not support this conclusion because

they show an increase in the ratio of lung weight to body weight before the carbon-dioxide concentrations of brain, liver and muscle tissues are significantly affected.

Pulmonary hyaline membranes. In the lungs of animals poisoned by exposure to 0.7–1.0 atm of O_2, many investigators have observed wide homogeneous strands of fibrinous material lining the walls of terminal bronchioles, alveolar ducts, atria and alveoli (1a, 6, 64, 90, 92, 108, 126, 310, 317, 356a, 397, 399, 421, 491). These strands of fibrinous material are called "hyaline membranes," and their morphology, localization and staining properties are very similar to those of membranes found in the lungs of premature infants who die from hyaline membrane disease (64, 90). Pulmonary hyaline membranes produced by exposure of small animals to oxygen have frequently been used as an experimental model of this disease (6, 64, 90, 92, 126, 317, 421). Formation of hyaline membranes during exposure to oxygen is enhanced by administration of ACTH, cortisone, atropine, heparin, pilocarpine and aerosols of hyaluronidase, trypsin or amniotic fluid (6, 90, 92, 166, 316). However, aerosols of fresh amniotic fluid or thromboplastin had no influence upon hyaline membrane formation in guinea pigs exposed to about 0.81 atm of O_2 (90). In the latter study, the effect of amniotic fluid may have been masked by a high susceptibility to oxygen alone as manifested by a 75% incidence of hyaline membranes. Membrane formation appears to be partially inhibited by administration of a thiol compound [S-(2-aminothyl)-isothiouronium bromide hydrobromide], an antifibrinolytic agent (*epsilon*-aminocaproic acid) and aerosols of "wetting agents" such as Alevaire and ethyl alcohol (6, 90, 166).

The tendency to form pulmonary hyaline membranes in response to oxygen poisoning is variable among different animal species and even among different strains of the same species (165, 310). Rats do not develop hyaline membranes as readily as do guinea pigs and rabbits. Fatal exposure to oxygen at 0.90 to 1.2 atm produced hyaline membranes in adult mice (1a, 165, 310, 399), but not in newborns (228, 366, 399). However, exposure to 3.0 atm of O_2 produced hyaline membranes in newborn mice who had a prolonged survival time (243), and newborn rats and guinea pigs developed membranes during toxic exposures to about 1.0 atm of O_2 (89, 126).

Although the incidence of development of hyaline membranes did not correlate with survival time among different strains of mice exposed to oxygen (165, 310), the incidence and severity of hyaline membrane development within a single strain of mice did increase with longer duration of exposure (310, 399). Conversely, in mice exposed to 0.90 atm of O_2, a marked reduction in the average survival time by elevation of ambient temperature from 23°C to 32°C was associated with an expected decrease in occurrence of hyaline membranes (310). The lower incidence of hyaline membrane formation with shorter exposure durations, even when fatal pulmonary oxygen poisoning is produced, may explain the infrequent observation of pulmonary hyaline membranes in animals exposed to oxygen pressures higher than 1.0 atm.

The pathogenesis of hyaline membrane formation in oxygen poisoning or in

any other condition is not accurately known, but proposed mechanisms or contributing factors include the following: increased capillary permeability and local cellular destruction in the lungs, leading to exudation and formation of a fibrin meshwork incorporating blood proteins and tissue debris (1a, 6, 64, 90, 92, 309, 491); and deficiency of fibrinolytic activity within the lungs (309, 396). Neither of these mechanisms has been established conclusively, but the histological observations of pulmonary capillary and parenchymal damage in oxygen poisoning (1a, 79, 94, 108, 263, 272, 273, 275, 321, 328, 356a, 357, 367, 376, 395, 419, 432, 494, 501, 532, 534) support the roles of increased capillary permeability and cellular exudation.

The observation that development of hyaline membranes in guinea pigs exposed to 0.98 atm of O_2 was preceded by significant decreases in total and free profibrinolysin and fibrinolytic inhibitor is consistent with deficient fibrinolysis as a mechanism of hyaline membrane formation (396). Significant decreases in blood clotting time and platelet count were also found in men who breathed oxygen at 1.0 atm for 1 hr (354). The tendency of guinea pigs and rabbits to develop hyaline membranes more readily than do rats has been ascribed to the presence of a higher level of plasminogen-activator activity in rat lungs (310). However, the plasminogen-activator content of lung tissue did not differ significantly in mouse strains who showed wide variation in the incidence of hyaline membranes produced by oxygen poisoning (310). Furthermore, the development of hyaline membranes in guinea pigs exposed to 1.0–1.2 atm of O_2 was enhanced by administration of heparin, an anticoagulant, and partially inhibited by administration of *epsilon*-aminocaproic acid, an antifibrinolytic agent (166). The inconsistency of these findings suggests that, although deficient fibrinolysis may contribute to the formation of hyaline membranes, it does not appear to be the dominant mechanism.

Mechanical factors may also contribute to the development of hyaline membranes in oxygen-poisoned lungs. Ciliary activity of rabbit tracheal epithelium, measured by an *in vitro* technique, was definitely reduced or absent after the rabbits were exposed to 0.70–0.80 atm of O_2 until the onset of symptoms (65). It was suggested that a similar depression of ciliary transport in bronchi and bronchioles would favor retention in the lung of material contributing to the formation of hyaline membranes. Measurements in intact, anesthetized animals have shown that the flow rate of tracheal mucus was reduced in cats (300), but not in dogs (320) after breathing O_2 at 1.0 atm for 10 to 20 min. Ciliary activity in tracheal mucosa from rabbits was normal after 60 min of exposure *in vitro* to 1.0 atm of O_2 (124). However, failure to observe decreased ciliary activity in some species after oxygen exposures which are too brief to produce detectable toxic changes in other areas of the lung is not inconsistent with a role of impaired ciliary transport in the genesis of hyaline membranes.

It has also been suggested that extra-uterine respiration is an important factor in the formation of pulmonary hyaline membranes (90, 166, 438–440). This suggestion is based largely upon the observations that hyaline membranes have not been found in human stillborn infants (126, 166), or in stillborn guinea pigs whose

mothers die from pulmonary oxygen poisoning even when prominent hyaline membranes are found in the mothers (89, 126). In accord with these observations, Shanklin (438, 440) has proposed that a major element in the pathogenesis of hyaline membrane disease is the failure of postnatal adaptation to the significant elevation of oxygen tension which occurs in the pulmonary alveoli at birth.

Pulmonary vascular changes Adverse effects of increased oxygen pressures upon the pulmonary vasculature have been demonstrated repeatedly in experimental animals. Observations of interstitial and perivascular edema and intra-alveolar hemorrhage indicate that vascular permeability is increased in pulmonary oxygen poisoning (24, 59, 79, 84, 108, 132, 243, 265, 367, 456, 494, 511). Toxic effects upon the pulmonary capillary endothelium in the form of cytoplasmic changes, endothelial swelling and, in some cases, fragmentation of alveolar walls have been found in the lungs of mice (1a, 79, 108), rats (272, 273, 275, 357, 376, 395, 419, 432, 501, 532), rabbits (328), dogs (321, 534), goats (356a) and monkeys (263) after prolonged exposure to O_2 at 0.90 to 1.0 atm. In rats exposed for 72 hr to 0.99 atm of O_2, about half of the pulmonary capillaries were destroyed, and morphometric measurements showed that capillary volume and endothelial surface area were reduced to about half of the control values (272, 273, 275). Total endothelial cell volume in the pulmonary capillaries of monkeys was decreased to one-third of the normal volume after a 12-day exposure to 0.98–0.99 atm of O_2 (263). These results may be at least partly explained by the observation that the division rate of pulmonary capillary endothelial cells was profoundly decreased in mice after exposure to about 1.0 atm of O_2 for 1 to 4 days (148). The division rate of mammalian cells in tissue culture was also reduced by prolonged exposure to 0.40–1.0 atm of O_2 (88, 370, 426).

Other pulmonary vascular changes found in experimental animals after prolonged exposure to toxic oxygen pressures include: thickening and hyalinization of the walls of pulmonary arteries and arterioles with marked narrowing of vessel lumens and ultimate thrombosis of some arterioles (59, 278, 456, 511); formation and condensation of fibrous tissue outside the media of the arterial wall and thickening of the elastic tissue and smooth muscle layers (59); marked vasoconstriction of pulmonary arteries, arterioles and venules (521); erosion of the vessel media and merging of media with adventitia (278); and necrosis of the pulmonary veins (511). In order to explain the simultaneous existence of arterial wall erosion and hypertrophy in the lungs of rats exposed for 30 days to about 0.70 atm of O_2, Kydd (278) suggested that the hypertrophy represented a reaction of the vessel wall to an initial erosion produced by oxygen toxicity. Erosion appeared to be the dominant process at the time the rats were sacrificed.

In agreement with the histological results, pulmonary hypertension (59, 83, 84, 117), increased pulmonary vascular resistance (83, 84), right heart hypertrophy (83, 84) and dilatation (59, 266, 267) have been observed in rats, rabbits and dogs after prolonged exposure to 0.80–2.0 atm of O_2. By creating a surgical anastomosis between the left subclavian artery and the left upper lobe pulmonary artery in dogs, Liddle and Fyler (307, 308) demonstrated that perfusion of the pulmonary vasculature with normally oxygenated systemic blood for 3 months

caused moderate to severe pulmonary vascular disease manifested by advanced medial hypertrophy and intimal proliferation. The effects of increased blood flow and pressure on the pulmonary circulation were not responsible for the observed vascular disease, because the pathologic changes were not caused by a previous 3-month exposure of the same dogs to 10% oxygen (307).

Mitochondrial changes in the lung. In what appears to be the first application of electronmicroscopy to the study of pulmonary oxygen poisoning, Schulz (433) found swelling and vacuolization of alveolar epithelial mitochondria in rats that breathed oxygen at 1.0 atm for 8 hr. However, a similar study in rats that were exposed to oxygen at 1.0 atm for 38 hr or at 3.0 atm for 8 hr showed many large vacuolated inclusions in close proximity to completely intact mitochondria with no evidence of intermediate stages (484). On the basis of these results, Treciokas (484) concluded that both his findings and those of Schulz were normal and did not indicate mitochondrial damage. Alveolar cell mitochondria were not damaged in mice and only occasional swelling of mitochondria was found in severely poisoned rats after exposure to 0.95–1.0 atm of O_2 for as long as 3 to 6 days (108, 272, 273, 275). Mice that died during a 7-day exposure to 0.90 atm of O_2 had a similar absence of mitochondrial changes, but swelling and polymorphism were observed in the type II alveolar cell mitochondria of the survivors (1a).

In agreement with the studies cited above, little evidence of mitochondrial damage was found in the type II alveolar epithelial cells of rats after 48 hr of O_2 breathing at 1.0 atm (419). However, exposure to 0.85 atm of O_2, which the rats tolerated for 7 days with no obvious signs of distress or gross pulmonary pathology, produced definite pleomorphism, elongation and other mitochondrial changes. When these rats were subsequently exposed to 1.0 atm of O_2, initial signs of mitochondrial degeneration were followed within 2 or 3 days by exaggeration of the previous changes. Continued exposure to pure oxygen for 7 days produced a 5- to 6-fold increase in mitochondrial volume, while evidence of mitochondrial degeneration was found after 3 weeks of exposure (532). Swollen mitochondria with loss of matrix density were found in endothelial cells within 2 to 3 days and in type I alveolar epithelial cells after 10 to 14 days of oxygen breathing. Exposure of normal or "adapted" rats to 3.0 atm of O_2 for up to 6 hr produced clearly degenerative changes, such as loss of matrical density, swelling and rupture of the mitochondria (419). This observation was confirmed by other workers (357) who found mitochondrial swelling and vacuolization in the alveolar cells of rats exposed to 3.0 or 4.0 atm of O_2 for 2 to 6 hr.

The mitochondrial changes found in oxygen-poisoned lungs by many workers are non-specific and often rather subtle. Most of the inconsistencies in these observations probably can be attributed to technical difficulties encountered in the demonstration of such changes and the related problem of interpretation of the results. However, prolonged exposure of rats to a level of hyperoxia which did not produce acute oxygen poisoning appeared to cause definite mitochondrial alterations which could not be attributed to technical artifacts (419). Furthermore, these mitochondria were apparently conditioned to respond in an unusual way during a subsequent exposure to a more toxic level of hyperoxia. Explanation

of these interesting results may shed some light upon the mechanisms of pulmonary oxygen toxicity (see Acquired Resistance to Pulmonary Oxygen Toxicity, page 73).

Sequence of pathological changes. Studies of pulmonary oxygen poisoning in normal man have been necessarily limited to the early and reversible stages of this progressive and ultimately fatal toxicity. In contrast to this, the pathological manifestations of severe oxygen poisoning have usually been studied in animals who have died, or are near death, from the toxic effects of oxygen. In order to relate the effects of oxygen upon pulmonary function in man to the pathological changes found in experimental animals, it is necessary to identify the initial structural and morphological effects of oxygen poisoning in the animal lungs. Information relating to these early toxic effects in animals has been obtained by investigators who have studied lung structure and morphology at various stages throughout the development of oxygen poisoning (108, 263, 266, 272, 273, 275, 494).

Qualitative studies of the pathological changes found at progressive stages of pulmonary oxygen poisoning have been performed in rabbits (266) and mice (108) exposed to 0.80–1.0 atm of O_2. After 1 day in the oxygen environment, the lungs of the rabbits were essentially normal, but 2 days of exposure produced a variable degree of pulmonary pathology ranging from no involvement to early, fibrinous bronchopneumonia with marked congestion and edema. Fibrinous bronchopneumonia, which was characterized by degeneration and desquamation of alveolar epithelium, bronchial inflammation and fibrinous exudation into the alveoli, was an almost constant finding after 3 days and was little changed after 5 to 7 days of exposure. In the mice, 3 days of oxygen breathing produced mild capillary stasis and slight exudation into the alveoli. Perivascular and peribronchial edema appeared after 3 to 4 days of exposure. These changes were accentuated after 5 to 6 days at which point some of the mice died. Epithelial and endothelial swelling, alveolar cell destruction, collapse and dilatation of capillaries, intra-alveolar hemorrhage and hyaline membranes were also found in severely poisoned lungs. Both studies showed marked variability in different individuals and even in different areas of the same lung (108, 266).

A much more rapidly developing sequence of pathological changes is observed in rats exposed to 5.0 atm of O_2, with patchy congestion and dilatation of alveolar capillaries being detectable within 20 min (494). After 40 to 60 min, the alveoli contained fibrinous, hemorrhagic exudate and their walls were edematous and swollen. In the terminal stages of lung damage produced by 60 to 90 min of exposure, there was marked interstitial edema as well as perivascular and peribronchial edematous cuffing.

The stereologic and morphologic techniques employed by Weibel and his associates (263, 272, 273, 275, 506, 509) have provided excellent, quantitative descriptions of the time course of pathological changes during the development of pulmonary oxygen poisoning. Because of their importance to the understanding of the dynamic progression of pulmonary oxygen intoxication and the consequently increasing impairment of normal pulmonary function, these studies have

been reviewed in great detail. In rats exposed to 0.99 atm of O_2 for 6, 24, 48 and 72 hr, Kistler *et al.* (272, 273, 275) detected the first abnormalities after 48 hr of exposure. At this time the rats showed varying degrees of dyspnea upon return to room air. The lung surface was mottled and small quantities of pleural exudate were present. Electronmicroscopic findings included interstitial edema, occasional leucocytic infiltration and occasional early destruction of capillary endothelial cells.

When returned to room air after 72 hr of exposure, the rats were severely dyspneic, gasping and cyanotic. Some rats died after a few minutes of air breathing. Mottling of the lung surface was striking, and large quantities of partly hemorrhagic pleural exudate were found. Electronmicroscopy revealed that the interstitial edema was largely replaced by leucocytes, thrombocytes, other cells, cellular fragments and fibrin strands. Capillary endothelial cells were extensively destroyed and were completely absent in places. Capillary lumens contained distorted and fragmented erythrocytes. Alveolar epithelial cells were little changed morphologically, but there was an apparent hyperplasia during the period between 48 to 72 hr of exposure. Occasional swelling of alveolar cell mitochondria was noted in the terminal stages.

Results of stereologic measurements complemented the morphologic findings (fig. 1). Average thickness of the interstitial space was doubled after 48 hr and tripled after 72 hr of exposure. Average thicknesses of alveolar epithelium and capillary endothelium were normal up to 48 hr. After 72 hr, thickness of the epithelium was increased by 50% and that of the endothelium was decreased to 60% of the control value. The change in alveolar epithelium was attributed to cellular hyperplasia, and the endothelial change was due to capillary destruction. Total thickness of the air-blood tissue barrier and estimated resistance to diffusion were both increased slightly after 48 hr and doubled after 72 hr of exposure. Capillary volume and surface area were constant up to 48 hr and decreased to less than half their original values after 72 hr. Total alveolar surface area was not significantly changed but about 65% of the alveolar air space was obliterated by edema. Estimated diffusing capacity of the air-blood tissue barrier was decreased to about 80% of the control value after 48 hr and to about 25% after 72 hr of exposure. When corrected for obliteration of alveolar space by edema, estimated diffusing capacity after 72 hr was decreased to about 9% of the normal value.

Kapanci *et al.* (263) have used similar stereologic and morphologic techniques to study the rate of development of pulmonary oxygen poisoning in monkeys exposed to 0.98–0.99 atm of O_2 for 2, 4, 7 and 12 days (fig. 2). After 2 days of exposure, capillary endothelial cells often had clear cytoplasm and appeared to be slightly swollen, but total endothelial volume was not increased. Although there were a few foci of interstitial edema, total thickness of the interstitium was not changed.

After 4 days of oxygen breathing, the alveolar walls were severely damaged and at least 90% of the membranous (type I) pneumocytes were destroyed. The basement membrane was denuded and covered with fibrin strands. Total epithelial volume and mean epithelial thickness were reduced, respectively, to one-third

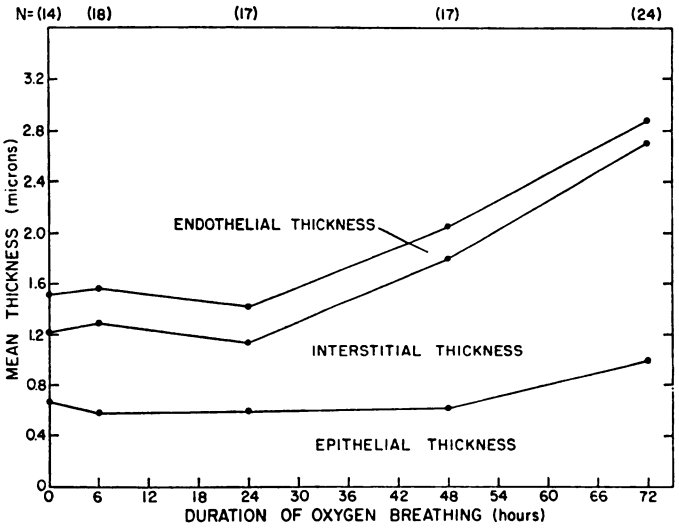

FIG. 1. Effect of pulmonary oxygen poisoning on the alveolar-capillary tissue barrier in the rat. Points on the graph represent average morphometric measurements of the mean thicknesses of the alveolar epithelium, interstitial space and pulmonary capillary endothelium in rats exposed to 0.99 atm of O_2 for 6, 24, 48 and 72 hr. N indicates the number of rats included in each average. Estimated resistance to diffusion was roughly proportional to the total thickness of the alveolar-capillary tissue barrier. [After Kistler *et al.* (272, 273, 275).]

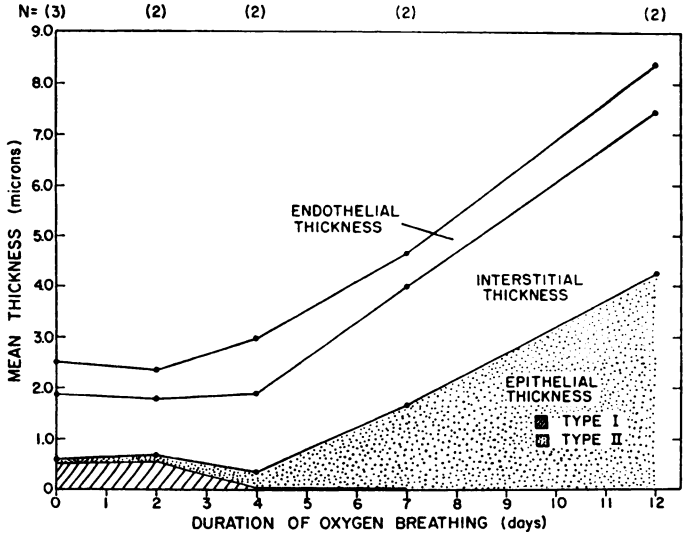

FIG. 2. Effect of pulmonary oxygen poisoning on the alveolar-capillary tissue barrier in the monkey. Points on the graph represent average morphometric measurements obtained in monkeys exposed to 0.98–0.99 atm of O_2 for 2, 4, 7 and 12 days. The stipled areas indicate the relative proportions of type I and II alveolar epithelial cells (membranous and granular pneumocytes, respectively). All other details are the same as those described for Figure 1. [After Kapanci *et al.* (263).]

and one-half of the control values. In contrast to the widespread destruction of membranous pneumocytes, the relative volume of granular (type II) pneumocytes was increased by a factor of 2.5. Endothelial cells were swollen and showed cytoplasmic changes. Total endothelial volume and mean endothelial thickness were increased. About 40% of the total interstitial volume was edematous tissue. The combination of epithelial destruction, interstitial edema and endothelial swelling produced a slight increase in total thickness of the air-blood tissue barrier.

In the lungs of monkeys exposed for 7 days, about 80% of the alveolar septa were lined by a continuous layer of granular pneumocytes which now constituted 95% of the alveolar epithelium as compared to 15% in the control animals. Total epithelial volume and average epithelial thickness were increased by 30% and almost 300%, respectively. Destruction of endothelial cells was indicated by the reduction of the total volume of endothelium per unit volume of tissue to one-half the control value. Total capillary volume and surface area were not changed because some of the remaining vessels were dilated. The mean thickness of the interstitium was increased by 80%, and it contained edema fluid, hemorrhagic foci, fibroblasts and leucocytes. Total thickness of the air-blood tissue barrier and the estimated resistance to diffusion were both approximately doubled.

The proliferative changes were even more accentuated after 12 days of oxygen breathing. All alveolar septa were lined by a continuous layer of granular pneumocytes which now constituted 100% of the alveolar epithelium. The estimated increase in the volume of granular pneumocytes alone was approximately 22-fold, and there was almost a 7-fold increase in mean epithelial thickness. Massive destruction of endothelial cells reduced the relative volume of endothelium to one-third the control value, but capillary volume and surface area were still unchanged. Average thickness of the interstitium was increased by a factor of 2.5, and half of the total interstitial volume was occupied by cells. Compared to shorter exposure durations, the volume of collagen fibers in the interstitium was increased, while that of edema fluid appeared to be reduced. Average thickness of the total air-blood tissue barrier and the estimated diffusion resistance were three to four times their respective control values.

Although extensive destruction of pulmonary capillary endothelium was produced in both rats (272, 273, 275) and monkeys (263) by prolonged exposure to about 1.0 atm of O_2, total capillary volume and surface area were decreased in the rat, but not in the monkey. Another notable difference between the responses of these two species to pulmonary oxygen toxicity was the relative integrity of alveolar epithelium in the rat as compared to the destruction of type I and the proliferation of type II epithelial cells in the monkey. Kapanci *et al.* (263) have attributed the differences between their results and those of Kistler *et al.* (272, 273, 275) at least partially to the following:

1) The rat, as studied by Kistler *et al.*, was more susceptible to oxygen toxicity than the monkey. Most of the rats died or were in a terminal state after 72 hr of exposure, whereas many of the monkeys survived for almost 2 weeks.

2) The pulmonary pathology found in the rats after 6 to 72 hr of exposure was related to only the initial phases of lung reaction. This comment would be valid with reference to repair processes, but not necessarily with reference to destructive processes, because the rats did develop fatal pulmonary oxygen poisoning within the period of study.

3) Since the biologic time constants or rates of development of pulmonary oxygen intoxication were different in the intact rat and monkey, they may also be different for the individual tissues within the lungs of the two species.

The principles proposed by Kapanci *et al.* (263) offer a plausible explanation of the apparent contradictions in many studies of pulmonary oxygen poisoning. Studies in the monkey have shown that there are two distinct phases in the pathological effects of pulmonary oxygen toxicity (263, 265, 415, 417). One is an acute exudative phase which is characterized by edema, hemorrhage, swelling and destruction of capillary endothelial cells and destruction of type I alveolar epithelial cells. The other is a subacute proliferative phase which consists of interstitial fibrosis, proliferation of type II alveolar epithelial cells and at least partial resolution of previously formed alveolar exudate. Although the time course and intensity of these responses varied among different species of monkeys (417), the proliferative phase was prominent only when the animals could survive the acute exudative phase either because of an inherent resistance to pulmonary oxygen toxicity (121, 164, 417, 511) or a reduced severity of the acute phase related to exposure to a lower oxygen partial pressure (415). Proliferative changes were minimal in rats that died or were near death after a 3-day exposure to 0.99 atm of O_2 (272, 273, 275), but they were more obvious in rats that survived a 10-day exposure to 0.92 atm of O_2 (432). Typical manifestations of the acute exudative phase of pathology were present in rats that died on the 4th day of exposure to 0.84 atm of O_2, while proliferation of alveolar epithelium and resolution of alveolar exudate were found in the animals that survived the acute illness and remained in the oxygen atmosphere (456, 457). Fatal exposure to 1.0 atm of O_2 caused thickening of the alveolar septa and altered the structure of alveolar epithelium in "preconditioned" rats whose survival times were prolonged by previous, intermittent exposures to oxygen, but not in normally susceptible rats (501). However, the observation that proliferative changes were minimal or absent in mice after exposure to 0.9–1.0 atm of O_2 for as long as 14 days (1a, 79, 108, 148) suggests that the subacute proliferative phase of pulmonary reaction to oxygen toxicity is not prominent in some animal species.

Reversibility of pathological changes during recovery from pulmonary oxygen poisoning. When monkeys that developed pulmonary oxygen poisoning during exposure to 0.78–1.0 atm of O_2 were removed from the toxic environment and allowed to recover, changes typical of the acute exudative phase of pathology resolved completely, but proliferative changes left residual scarring (263, 265, 415). Kapanci *et al.* (263) employed quantitative stereologic and morphologic techniques to study the lungs of two monkeys that were exposed to 0.98–0.99 atm of O_2 for 8 and 13 days, and then allowed to recover in room air for 56 and 84 days, respectively. After the recovery period, both monkeys were clinically normal, and lung structure was remarkably restored to an almost normal appear-

ance. Arterial blood P_{O_2} and P_{CO_2} were normal in the monkey who had an 84-day recovery preceded by a 13-day exposure (265). Nevertheless, structural and morphometric abnormalities were detectable in the lungs of both monkeys.

After 8 days of exposure and 56 days of recovery in the first monkey, the alveolar septa contained focal lesions which were characterized by increased numbers of fibroblasts and collagen fibers associated with some residual accumulations of edema fluid. The alveoli were again lined with normal membranous pneumocytes, but the proportion of granular pneumocytes was 30% greater than in the preexposure control lungs. Total interstitial volume was still increased, and 20% of the interstitial tissue appeared to be edematous. Although the endothelium was completely normal, capillary volume and surface area may have been slightly increased. Average thickness of the total air-blood tissue barrier was increased slightly, but estimated resistance to diffusion was normal.

In the monkey that was exposed for 13 days and allowed to recover for 84 days, the alveolar septa contained large scars which represented about 7% of the total alveolar tissue. Capillaries were found on both sides of the septal scar tissue. Average thickness of the interstitium was increased by about 50%, and collagen fibers constituted 66% of the total interstitial volume. Estimated resistance to diffusion was about 38% greater than the control value due to the increased thickness of the air-blood tissue barrier. Capillary volume was almost doubled, and capillary surface area was increased by about 25%. The calculated diffusing capacity of the air-blood barrier was almost normal which suggested that the increased capillary surface area and volume compensated for the decrease in diffusion conductance. The occurrence of these capillary changes during recovery from pulmonary oxygen poisoning in the monkey was particularly interesting because capillary proliferation has been observed in human patients who died after receiving prolonged oxygen therapy (401, 402).

A remarkable capacity for reversal of the pathological changes caused by pulmonary oxygen toxicity has also been observed in smaller animals (1a, 6, 90, 228, 419). These reversible effects included hyaline membranes (6, 90) and mitochondrial alterations (1a, 419), as well as acute exudative changes. However, hypertrophy and hyperplasia of alveolar cells (456) and reduced tolerance to acute hypoxia (2) persisted for 33 and 13 days, respectively, after multi-day exposures of rats to 0.84–0.89 atm of O_2. The latter results are consistent with observations in the monkey (263, 265, 415) that proliferative changes may require several weeks for resolution or may cause permanent scarring of the lung.

Pathology of pulmonary oxygen poisoning in man. Pathological changes caused by pulmonary oxygen toxicity as observed in experimental animals have also been found in the lungs of human patients who have died after prolonged oxygen therapy. In patients who were ventilated for several days with 90 to 100% O_2 at 1 atm, Nash *et al.* (356) observed two overlapping phases of pathology which they thought represented an early exudative phase followed by a later proliferative phase. The exudative phase consisted of congestion, alveolar edema, intra-alveolar hemorrhage, fibrinous exudate, prominent hyaline membranes and only a sparse chronic inflammatory component. The proliferative phase was characterized by marked thickening of alveolar and interlobular septa by a combina-

tion of edema and fibroblastic proliferation, early fibrosis, prominent alveolar cell hyperplasia and a variable component of exudative changes. Several of these alterations resembled features of the acute exudative and subacute proliferative phases of pathology that accompanied the development of pulmonary oxygen poisoning in the monkey (263, 265, 415, 417).

Many other investigators have observed similar pathological changes in human lungs after prolonged exposure to increased partial pressures of oxygen (22a, 82, 105–107, 169, 170, 202, 209, 245, 318, 341, 401–403, 461). In some cases these observations have been associated with marked increases in the alveolar-arterial P_{O_2} difference (82, 105, 106, 169, 209, 245, 318). Pulmonary function returned to normal in one patient within 15 weeks after toxic oxygen therapy exposures were stopped (245) and greatly improved in another patient when the inspired oxygen concentration was gradually reduced to normal over a period of 9 days (82). Continued exposure to toxic oxygen tensions, which was done in order to treat a terminal anaerobic infection in one individual (169) and to assist ventilation in another who had traumatic chest injuries (105), led to a progressive deterioration of pulmonary function and an ultimately fatal outcome. The lungs of these two patients had pathological changes that are commonly produced by pulmonary oxygen toxicity in experimental animals.

The pathology of pulmonary oxygen poisoning has also been observed in newborn infants after prolonged oxygen therapy for hyaline membrane disease (226, 362, 363, 424). In a comprehensive study of 32 infants with respiratory distress syndrome, Northway *et al.* (362, 363) found that exposure to 0.80–1.0 atm of O_2 for more than 150 hr caused chronic lung disease which appeared to consist of oxygen-induced damage to mucosal, alveolar and vascular tissues superimposed upon prolongation of the healing phase of the original syndrome. Continued epithelial necrosis, metaplasia, basement-membrane thickening, atelectasis and failure of alveoli to regenerate mature epithelia were detectable 1 to 2 days after the start of oxygen therapy and were thought to be precursors of chronic lung disease. Departure from the usual healing phase of respiratory distress syndrome was clearly apparent at 10 to 20 days of age, at which time alveolar epithelial injury persisted along with widespread metaplasia and hyperplasia of the bronchial and bronchiolar mucosa. There was marked mucous secretion, interstitial edema, focal thickening of the basement membrane, and coalescence of emphysematous alveoli with atelectasis of surrounding alveoli. In the five infants who died after receiving more than 150 hr of oxygen therapy, prominent pathological findings were interstitial thickening, pulmonary arteriolar lesions and marked cardiomegaly with right ventricular hypertrophy.

Westgate *et al.* (516) also suggested that the chronic pulmonary abnormalities seen in survivors of hyaline membrane disease were caused chiefly by prolonged exposure to increased partial pressures of oxygen. This suggestion was based upon the similarity of chest roentgenograms in survivors of hyaline membrane disease and in children who had received oxygen therapy for other reasons. In a series of 83 newborn infants who died from a variety of causes, pulmonary hemorrhage was associated with the use of oxygen therapy, particularly in premature infants (447). The incidence of pulmonary hemorrhage was highest in those in-

fants who received oxygen therapy continuously from birth to death, but the first 6 hr of life appeared to be the period in which the infants most readily developed this abnormality. Increased susceptibility to oxygen poisoning during the first few hours of life has also been observed in newborn mice (243), and possible causes of this phenomenon will be discussed later (see Inherent Resistance to Pulmonary Oxygen Toxicity, page 77).

Summary of pathological effects. The pathological response of the lung to oxygen toxicity can be differentiated into two overlapping phases of progressive deterioration. The first is an acute exudative phase which consists of interstitial and alveolar edema, intra-alveolar hemorrhage, fibrinous exudate, hyaline membranes, swelling and destruction of capillary endothelial cells and destruction of type I alveolar epithelial cells. The other is a subacute proliferative phase which is characterized by interstitial fibrosis, fibroblastic proliferation, hyperplasia of type II alveolar epithelial cells and at least partial resolution of earlier exudative changes. The individual components of each phase are not always found concurrently. Their presence and relative prominence are at least partially dependent upon variables such as the level of inspired P_{O_2}, exposure duration, species susceptibility to pulmonary oxygen toxicity and probably species differences in the reactivity of pulmonary tissues.

Swelling and destruction of pulmonary capillary endothelial cells along with interstitial and perivascular edema are the first toxic effects which are detectable during the development of pulmonary oxygen poisoning. The subsequent progression in severity of these acute changes is often accompanied by the formation of hyaline membranes consisting of a fibrinous meshwork of plasma proteins and cellular debris. Alveolar atelectasis is a variable component of pulmonary oxygen poisoning which appears to be caused predominantly by the physical consequences of inert gas removal from the lungs and may be enhanced by decreased surface activity of the alveolar lining material.

Pathological changes which are similar or identical to those caused by pulmonary oxygen toxicity in experimental animals are also found in the lungs of human patients who die after prolonged oxygen therapy. Although such alterations are not specific for pulmonary oxygen poisoning, the clinical course of these patients in conjunction with the known susceptibility of man to oxygen toxicity leave no reason to doubt that the observed pathological changes are in fact caused by pulmonary oxygen toxicity. In experimental animals and presumably also in man, recovery from pulmonary oxygen intoxication is accompanied by complete resolution of changes typical of the acute exudative phase of pathology. When exposure to hyperoxia is sufficiently prolonged for the development of prominent proliferative changes, however, recovery from these pathological effects is greatly delayed and incomplete resolution may leave permanent residual scarring of the lung.

Effects upon pulmonary function

Pulmonary oxygen poisoning is characterized by an insidious onset followed by a progressive increase in severity that eventually leads to severe hypoxemia and death. Effects upon pulmonary function become more marked in parallel

with the increasing severity of oxygen poisoning. When studies are carried out in animals exposed continuously to a toxic inspired P_{O_2}, severe functional derangements should be expected as death approaches. Observations made in these terminal studies do not relate quantitatively to studies in man during the early, more reversible stages of pulmonary oxygen poisoning. Direct comparisons between functional effects in man and animals therefore require comparisons in the same degree of toxic exposure.

Pulmonary mechanics. Change in the elastic properties of the lung is an early manifestation of oxygen toxicity in man. Dynamic lung compliance was decreased by about 15% in subjects who breathed O_2 at 2.0 atm for 6 to 11 hr (161) and by about double this amount in others breathing O_2 at 0.98 atm for 30 to 48 hr (100). Decreased lung compliance has also been observed in dogs (247a, 385, 455), rabbits (421) and rats (52, 87) after prolonged exposure to 0.79–2.0 atm of O_2. In normal men, breathing oxygen at rest, particularly at a low lung volume, can be accompanied by a reduction in lung compliance which is caused by absorptional atelectasis, rather than chemical toxicity of oxygen, and is rapidly reversible upon deep inspiration (96–98).

Possible mechanisms for the reduction in lung compliance during oxygen poisoning include atelectasis, pulmonary edema and congestion, asymmetrical narrowing of the airways, decrease in alveolar surfactant and change in retractile properties of pulmonary tissue elastic elements. Atelectasis, pulmonary edema and vascular congestion have been ruled out as probable causes of decreased compliance in early pulmonary oxygen poisoning in man (116, 161, 405). No evidence for or against the other possible mechanisms was found. The reduction in lung compliance observed in rats after exposure to 0.98–1.0 atm of O_2 for 60 to 66 hr was considered to be caused by a decrease in surfactant with a small contribution from increase in tissue rigidity (52). Development of severe pulmonary intoxication in dogs breathing oxygen at either 1.0 or 2.0 atm was accompanied by marked decreases in both lung compliance and surfactant activity (247a). The pathological changes found in the later stages of pulmonary oxygen poisoning in animals (3, 167, 230, 255, 261, 266, 267, 273, 397, 459, 494) and man (105, 169, 356, 363) suggest that many or all of the changes in the lung may ultimately contribute to decreased compliance.

Early but prominent pulmonary oxygen intoxication in man exposed to oxygen at 2.0 atm is not associated with marked increases in airway resistance or total pulmonary resistance (161). These observations are consistent with the absence of significant changes in expiratory flow rate in the same subjects (115, 116) and in men exposed to 0.98 atm of O_2 (100). It is nevertheless probable that continued exposure to a toxic P_{O_2} would eventually produce prominent airway obstruction secondary to edema formation or other mechanisms.

Lung volumes. Decrease in vital capacity has been produced by exposure of normal men to oxygen partial pressures ranging from 0.75 to 2.0 atm (47, 100, 115, 116, 120, 134, 367). Reduction of vital capacity is usually progressive throughout the oxygen exposure and can be described accurately by the early part of a dose-response curve (100, 114, 116, 367). Moreover, after prolonged

exposure to 2.0 atm of O_2, vital capacity continued to decrease in several subjects for the first few hours after oxygen breathing was stopped (115, 116). This indicates that the consequences of oxygen poisoning progressed in severity beyond the time of the exposure to the direct toxic process. Recovery of vital capacity was not immediate. It usually occurred within 2 to 3 days after the oxygen exposure (100, 115, 116, 367), but occasionally required several weeks (47, 100). Vital capacity returned to normal even after reductions as great as 40% of the control volume (47, 100, 115, 116).

Measurements of other lung volumes after prolonged oxygen breathing at 2.0 atm (115, 116) showed that reduction of vital capacity in pulmonary oxygen poisoning is related to a decrease in the inspiratory capacity. Inspiratory capacity was restricted by decrease in total lung volume and probably also by an increase in the functional residual capacity. Impairment of inspiratory function in early pulmonary oxygen poisoning was also indicated by significant decreases in the 1-sec forced inspired volume, the percent of the total forced inspired volume which could be inspired in 1 sec and the maximum mid-inspiratory flow. The equivalent expiratory volumes in the same subjects were not significantly affected (115, 116), and percent of the total forced expired volume which could be expired in 1 sec was not changed after a toxic exposure to 0.98 atm of O_2 (100).

Possible mechanisms for reduction of vital capacity in pulmonary oxygen intoxication include chest pain, atelectasis, pulmonary edema, decreased lung compliance and decreased force of inspiration. Decreased compliance probably contributed to reduction of vital capacity in the initial stages of pulmonary oxygen poisoning, but lung compliance changes in most subjects after toxic exposures to 0.98 and 2.0 atm of O_2 were too small to entirely account for the observed decreases in vital capacity (100, 116, 161). A decreased force of inspiration may have been partly responsible for reduction of vital capacity at 2.0 atm of O_2 (161). Chest pain did not appear to contribute significantly to reduction of vital capacity or inspiratory force in well-motivated subjects (116, 161), and decrease in vital capacity has been observed repeatedly in the absence of symptoms (47, 100, 116, 120). Although atelectasis and pulmonary edema probably are not responsible for reduction of vital capacity in early pulmonary oxygen poisoning (116, 161, 405), they would be expected to become prominent and contribute to this alteration in the later stages of toxic progression.

Pulmonary gas exchange. Breathing oxygen at increased partial pressures can influence the carbon monoxide diffusing capacity of the lung by two different mechanisms. An initial physiological response, which is probably caused by competition between carbon monoxide and oxygen for binding sites on the hemoglobin molecule, results in a decrease in CO diffusing capacity that is progressive with increase in alveolar P_{O_2} from 100 mm Hg to at least 3200 mm Hg (355, 423). With continued exposure to toxic partial pressures of oxygen, a pathological response is superimposed upon the initial physiological response (100, 405). Exposures of normal men to 0.98 atm of O_2 for 30 to 74 hr and 2.0 atm of O_2 for 6 to 11 hr produced average decreases in CO diffusing capacity of 19 and 16%, respectively (100, 405). A significant decrease in diffusing capacity for CO has been

reported after O_2 breathing at about 1.0 atm for 3 hr (147), but this observation could not be confirmed after subsequent exposures to the same inspired P_{O_2} for 3 and 6 hr (95, 420). Exposure of normal subjects to 3.0 atm of O_2 for 2 hr also failed to produce a significant decrease in CO diffusing capacity (420). The available evidence therefore indicates that pulmonary diffusing capacity is adversely affected only after several hours of exposure to a toxic inspired P_{O_2}. The impression that considerable time is required for the development of this pathological effect is supported by the observation that the decrease in CO diffusing capacity was greater 11 to 20 hr after the end of a prolonged exposure to 2.0 atm of O_2 than it was within 6 hr after cessation of the exposures (405).

The reduction of diffusing capacity in pulmonary oxygen poisoning could be caused by atelectasis, lengthening of the diffusion path across the alveolar-capillary tissue barrier, uneven ventilation-diffusion relationships, decrease in pulmonary capillary blood flow and alterations of the pulmonary vasculature. There was no evidence that atelectasis or uneven ventilation contributed to the decrease in CO diffusing capacity observed after a toxic exposure to 2.0 atm of O_2 (405). The same subjects had no significant changes in pulmonary parenchymal tissue volume or capillary blood flow, but they did have a 30% decrease in pulmonary capillary blood volume which could have accounted for the change in diffusing capacity.

Measurements of pulmonary capillary blood volume and diffusing capacity of the pulmonary membrane revealed apparent contradictions between results obtained after prolonged exposures to 0.98 and 2.0 atm of O_2 (100, 405). After the 0.98 atm exposure, membrane diffusing capacity was decreased by 35% and capillary blood volume was not changed, while the 2.0 atm exposure resulted in a 30% decrease in the latter with no significant change in the former. Technical differences make the results of the two experiments not strictly comparable with each other (405). It is also entirely conceivable that the nature of the initial pathological changes responsible for reduction of diffusing capacity in early pulmonary oxygen poisoning may vary at different levels of inspired P_{O_2}. Certainly there are abundant indications of forms of structural damage by oxygen which should lead to gross disturbance in transpulmonary diffusion.

Morphologic and morphometric studies in oxygen-poisoned rats and monkeys have shown interstitial edema, increase in thickness of the alveolar epithelium and pulmonary capillary destruction (263, 272, 273, 275). Decreases in capillary volume and surface area occurred in the rat, but not in the monkey. These changes could contribute individually and collectively to decrease in pulmonary diffusing capacity. Most or all of these changes would be expected to appear eventually in man during the development of severe pulmonary oxygen poisoning, but it is possible that the order in which they occur may vary at different levels of P_{O_2}. Therefore, it is conceivable that interstitial edema and increase in thickness of the alveolar membrane could appear initially during prolonged exposures to a relatively low P_{O_2}, while severe vasoconstriction and capillary destruction could occur first during exposure to very high, more acutely toxic levels of P_{O_2}. Such variation in the order of appearance of pathological changes at different levels of

P_{O_2} could account for what appears to be lack of agreement in the measurements of membrane diffusing capacity and capillary blood volume obtained during the development of pulmonary oxygen poisoning at 0.98 and 2.0 atm. Valuable information relating to this possibility could be obtained by application of the quantitative techniques employed by Weibel *et al.* (263, 506, 509) to a study of the rate of development of structural changes in the lungs during exposure of monkeys to 2.0 atm of O_2.

Although fatal hypoxemia is the ultimate outcome of the limitation of gas exchange in severe pulmonary oxygen poisoning, there is much evidence that marked impairment of arterial oxygenation in the lungs at rest is not one of the earliest events to occur during exposure to a toxic inspired P_{O_2} (15, 117, 129, 385, 417, 455, 458, 499). The development of early pulmonary oxygen poisoning in man is not accompanied by a prominent increase in the alveolar-arterial oxygen difference at rest (100, 116), but the pulmonary diffusing capacity may be sufficiently limited to cause a small reduction in arterial P_{O_2} during exercise (100). Some animal studies have indicated that a progressive impairment of arterial oxygenation starts relatively early during the development of pulmonary oxygen poisoning (47, 302, 328, 356a, 374, 375, 476). However, these results could be explained on the basis of unusual susceptibility of the animal species involved (table 1 and fig. 3) or the occurrence of absorptional atelectasis during oxygen breathing, particularly in anesthetized animals (96, 98, 116, 130, 385). The occurrence of marked impairment of arterial oxygenation in severe stages of pulmonary oxygen poisoning has been well established in animals (47, 117, 265, 356a, 385, 417, 455, 459) and in man (82, 105, 106, 169, 209, 245, 318).

Control of respiration. Direct toxic effects of oxygen upon the respiratory control mechanisms have not been studied. The physiological and rapidly reversible effects of hyperoxia upon control of ventilation include respiratory stimulation (283, 291, 295) and a simultaneous, but less prominent, respiratory depression (128, 139, 283, 284, 290, 311). Since these effects are concurrent and continuous, they tend to mask each other (283, 284, 290). The respiratory stimulation appears to be caused by the rise in brain P_{CO_2} and acidity (291, 292) that results from diminished reduction of hemoglobin in the brain capillaries when increased amounts of oxygen are supplied in physical solution (24, 190). The depressant influences upon respiration are manifested by an abrupt decrease in ventilation after the sudden administration of oxygen (128, 129, 283, 284) and by a decreased ventilatory response to inspired carbon dioxide (284, 290, 311). These depressant effects are related partly to removal of chemoreceptor activity (128, 218, 311) but appear to involve other, unidentified mechanisms as well (283, 284, 290).

The prolonged administration of oxygen at increased pressures appears to have little influence upon control of respiration over and above the initial, physiological effects (56, 120, 367). Increased respiratory rate and decreased tidal volume have been observed in normal subjects during toxic exposures to 0.95 and 2.0 atm of O_2 (96, 98, 116, 134). These changes caused a progressive increase in respiratory minute volume with an associated respiratory alkalosis

during exposure to 0.95 atm of O_2 for 42 to 110 hr (134). In all cases, the ventilatory alterations were preceded and accompanied by severe symptoms of tracheobronchial irritation which were exaggerated by inspiration and were probably responsible for the observed respiratory stimulation.

Decrease in respiratory frequency occurs in small animals during prolonged exposure to oxygen partial pressures of 1.0 atm or less (71, 132, 512, 514). Associated with labored breathing, frequency of respiration in guinea pigs (71) and rats (132) was reduced progressively from a normal value of about 100 to as low as 27 breaths per minute during oxygen exposure. Jamieson and Cass (251, 252) have found increased work of breathing in oxygen-poisoned rats, as evidenced by a prominent increase of diaphragmatic activity in conjunction with a progressive reduction in tracheal gas flow in the presence of lung damage. Decrease in respiratory frequency also occurs in chicks in the absence of detectable signs of severe pulmonary pathology (514). The anatomical uniqueness of the avian lung and the lack of information describing the physiological effects of oxygen upon respiratory control in birds prevent interpretation of this finding.

Symptoms and signs of pulmonary oxygen poisoning

The signs of pulmonary oxygen poisoning observed in animals are those of progressive respiratory insufficiency culminating in severe asphyxia and death (64, 73, 108, 167, 191, 347, 375, 397, 459, 464). The signs are similar in different species, but times of onset and rates of development are variable. In animals breathing about 1.0 atm of O_2, the first observed abnormality is usually restlessness, followed by lethargy, anorexia and sometimes vomiting. Dyspnea becomes apparent and progressively more intense. Terminal stages are characterized by cyanosis, labored or gasping respiration and frothy or bloody sputum.

When animals are exposed to oxygen at partial pressures above 3.0 atm, development of the sequence of signs described above is interrupted by the occurrence of convulsions or other manifestations of CNS oxygen toxicity (24, 47, 397, 464). Total apnea of several minutes duration may occur, after which respiration may become very irregular (24). Central nervous system oxygen intoxication may kill the animal before lung damage becomes severe enough to produce fatal hypoxemia (47, 78, 117, 397, 449). Jamieson and Cass have shown that the cause of respiratory failure in animals breathing oxygen at high pressure may be either peripheral or central (251, 252). Which predominates will depend upon the total oxygen pressure.

The overt effects of pulmonary oxygen toxicity that occur in man during the early stages of pulmonary involvement resemble those seen in animals. Human studies have the obvious advantage that sensations can be described and the observations of the investigator can be confirmed and considerably amplified by the observations of the subject. Symptoms of pulmonary oxygen poisoning have been produced in men breathing oxygen at partial pressures ranging from about 0.75 to 2.0 atm (47, 100, 115, 116, 120, 134, 367). Studies of oxygen toxicity in normal man at partial pressures above 2.0 atm have not been continued long

enough to permit description of the development of pulmonary symptoms (56, 78, 138, 533).

The symptoms of pulmonary oxygen poisoning which are observed in man appear to be those of a tracheobronchitis which originates in the area of the carina and spreads throughout the tracheobronchial tree (47, 100, 115, 116, 120, 134, 367). Beginning as a mild irritation which is accentuated by inspiration and occasionally induces a cough, the tracheal symptoms progressively become more intense and continuous until each inspiration is painful and coughing is uncontrollable. Pulmonary symptoms have first appeared after 6, 4 and 3 hr of oxygen breathing at partial pressures of 0.83, 1.0 and 2.0 atm, respectively (56, 116, 120, 367). Severity of symptoms in most subjects rapidly diminishes within the first few hours of the post-exposure period and the sensations of pulmonary irritation completely disappear over the following 1 to 3 days. Dyspnea at rest is produced by severe exposures (47, 115, 116, 134, 136) and dyspnea on exertion continues for the first few days of the post-exposure period (100, 116, 367).

Physical findings. After the production of early pulmonary oxygen poisoning in otherwise normal subjects, physical examination of the chest has shown significant abnormalities in only a few isolated instances (100, 120, 367). These, all following prolonged exposures at oxygen pressures of 0.83 to 0.95 atm, include bubbling rales, hyperemia and swelling of the nasal mucous membranes and fever (47, 48, 100, 134, 136).

The inadvertent production of a severe degree of pulmonary oxygen poisoning in a group of five patients who received prolonged oxygen therapy for respiratory insufficiency was associated with definitely abnormal physical findings (245). Evidence of alveolar atelectasis was found in four patients and all five had tenacious tracheal secretions which required frequent aspiration. Auscultatory findings, which were bilateral and more prominent over the lower lung fields, included coarse rales, rhonchi and bronchial breath sounds. Rectal temperatures usually ranged from 37.8°C to 38.9°C, but lower values were obtained during the course of oxygen therapy. The copious tracheal secretions gradually decreased in quantity within 5 to 10 days after the inspired P_{O_2} was lowered to 0.35–0.45 atm. Definite association of these abnormalities with pulmonary oxygen intoxication was complicated in three patients by the presence of bacterial pneumonia which was superimposed upon pulmonary emphysema in one patient and was followed by development of a lung abscess in another. However, the clinical signs of pneumonia had resolved in two of the patients at the time that oxygen poisoning was suspected.

Radiological changes. Radiological abnormalities have been demonstrated in human patients who developed subjective and objective manifestations of progressive pulmonary insufficiency during prolonged oxygen therapy or who later died and showed the pathological changes of pulmonary oxygen poisoning (20a, 82, 105, 245, 259, 341). The lesions appeared as diffuse, bilateral pulmonary densities which were irregular in shape and varied from 0.2 to 2 cm in width. Continued exposure to oxygen was accompanied by extension and coalescence

of the infiltrates until, in the most severe cases, almost the entire lung was densely opacified bilaterally. When the inspired P_{O_2} was lowered below 0.85 atm, clearing of the infiltrates could be detected within 5 to 9 days and was complete within 23 to 46 days (245). Time of onset of the radiological changes varied with the inspired P_{O_2} and exposure conditions. In one group of patients abnormalities were not detected before at least 60 to 70 hr of continuous administration of 90 to 100% O_2 at 1.0 atm (259), while roentgenographic changes were found after as little as 20 hr of pure oxygen breathing in patients with irreversible brain damage (20a). In normal subjects, however, chest roentgenograms were unchanged after exposure to 0.90–1.0 atm of O_2 for as long as 110 hr, with the possible exception of a small pleural effusion in one subject after 90 hr of oxygen breathing (48, 100, 120, 136). This discrepancy probably can be accounted for by pre-existent lung disease, inadequate ventilation and other factors present in patients who must receive oxygen therapy.

A characteristic evolution of radiological changes during prolonged exposure to increased oxygen partial pressures has also been observed in newborn infants with respiratory distress syndrome (362, 363, 424, 516), as well as in rats and guinea pigs (16, 364). In the human infants the reticulogranular densities normally seen on the chest roentgenogram in this disease did not disappear within the usual 10 days and sometimes persisted for several weeks. Early progression of the densities to nearly total opacification of both lungs was usually accompanied by death of the infant or was a precursor of chronic lung disease in the survivors. The appearance of scattered, small, radiolucent areas after 10 days of age correlated well with the circumscribed groups of emphysematous alveoli found in the infants that died at this time.

TOLERANCE TO PULMONARY OXYGEN TOXICITY

Determination of pulmonary oxygen tolerance in an animal or a man requires information describing the rate of development of pulmonary oxygen poisoning throughout the toxic range of inspired P_{O_2}. This relationship between inspired P_{O_2} and the duration of exposure necessary to produce toxic effects has been studied by many investigators. Although many of these experiments are not directly concerned with tolerance to pulmonary oxygen toxicity, they demonstrate general principles which can be applied to all forms of oxygen tolerance. Indices of toxicity used in the various studies have included: 50% inactivation of respiration of rat brain slices (131); conduction block in isolated cat nerve (131, 393); development of convulsions in mice (334, 398, 404), rats (378), rabbits (227, 404) and cats (404); hemolysis in mice (195); death in protozoa (519), Drosophila (156, 157, 159, 519), mice (131, 175, 334, 480), rats (250, 481) and rabbits (227); and the onset of pulmonary and CNS symptoms in men (131, 515). All workers have found that the oxygen pressure-exposure duration relationship for a particular toxic effect has the general form of a rectangular hyperbola, with a progressive increase in the rate of development of oxygen intoxication as inspired P_{O_2} is elevated. Actually, it is not surprising that similar relationships are

found for such a variety of effects, because oxygen toxicity affects individual cells and enzymes (125, 131, 225), regardless of species and animal form.

Pulmonary Oxygen Tolerance in Animals

Pulmonary tolerance to the toxic effects of oxygen varies greatly among different animal species and among different individuals of the same species. The magnitude of variation in susceptibility to pulmonary oxygen toxicity is illustrated by survival data obtained from several different studies of the rate of development of pulmonary oxygen poisoning in animals exposed to 0.9–1.0 atm of O_2 (table 1 and fig. 3). At this level of inspired P_{O_2}, the appearance of severe pulmonary pathology and obvious symptoms of respiratory insufficiency prior to death indicates that survival times are determined primarily by the development of pulmonary oxygen intoxication before other vital organs are fatally affected. Environmental variables such as inspired P_{CO_2}, ambient temperature, humidity and variation of inspired P_{O_2} within the specified narrow range are potential influencing factors, but these variables have been generally well controlled and their combined influence upon survival time has probably been very small in most of the studies. Age of the exposed animals is an important variable which has undoubtedly contributed to the experimental results in a few cases (151, 384, 514). In spite of these limitations, comparison of the data from the several studies provides an approximation of the magnitude of variation in individual and species susceptibility to pulmonary oxygen toxicity.

Although most of the average survival times for all of the mammalian species except the primates fall between 50 and 100 hr of exposure to 0.9–1.0 atm of O_2, individual guinea pigs, dogs and mice have survived for as long as 230, 264, and 384 hr, respectively, while young rats have lived for longer than 528 hr (319, 384, 530).

Complete survival data have not been obtained for many of the primate species because individual animals were still alive at the maximum durations of exposure in most of the studies. Average survival time for a group of four monkeys exposed to 0.98–0.99 atm of O_2 was 390 hr with a range of 144 to 528 hr (416). The primate species were relatively resistant to pulmonary oxygen toxicity more consistently than all of the other mammalian species that were studied.

Many non-mammalian species were also quite resistant to the toxic effects of oxygen. Quail had a 50% mortality after 336 hr of oxygen breathing (513), and chicks were alive and well after 672 hr of exposure to 0.98–1.0 atm of O_2 (514). Frogs were able to tolerate oxygen breathing for durations ranging from 1176 to 1632 hr with no apparent ill effects other than minor histological changes in the lungs (72, 151), and turtles did not appear to be harmed by oxygen exposures ranging from 240 to 552 hr (151).

Comparison of the survival data summarized in figure 3 and table 1 reveals important potential sources of inconsistency among studies of pulmonary oxygen toxicity in different animal species or in different strains of the same species. The results of a 3-day exposure to 0.9–1.0 atm of O_2 in a strain of rats for which this was a lethal exposure (126) would obviously not be comparable to data obtained

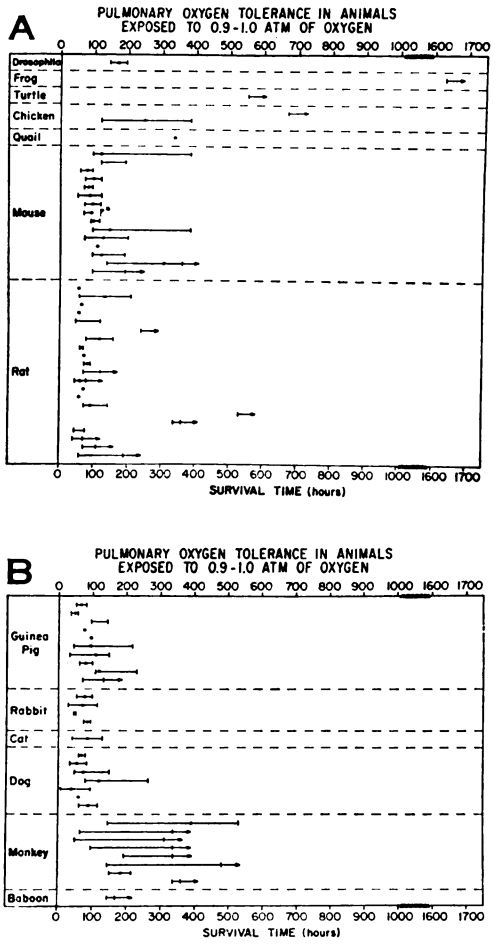

FIG. 3. Pulmonary oxygen tolerance in animals exposed to 0.9–1.0 atm of oxygen. Mean survival time of the animals is noted by a closed circle (●). The mean in this case is based only on the animals dying as a result of the exposure and does not take into account any animals who survived. The symbols used are: |—|, designates the range of survival times where known, or ± two standard deviations; |—|→, some animals survived the exposure; |⟶, all animals survived the exposure.

* Times of later deaths not specified.

from a similar experiment in a strain of rats that had less than a 1% mortality after 15 days of oxygen breathing (319). The extremely long survival times of young rats (384, 456, 457) and chicks (514) indicate that age is an important variable to be considered in different experiments. Wood (525) has shown that genetically inherited factors, even within the same strain of rats, influence susceptibility to oxygen toxicity. Identification and study of the factors responsible for individual and species variation in susceptibility could contribute much to the understanding of the mechanisms of pulmonary oxygen toxicity.

During exposure to oxygen pressures above 1.0 atm, average survival times are decreased progressively with the increase in inspired P_{O_2} (131, 156, 157, 159, 175, 227, 250, 334, 480, 481, 519). Analysis of survival data obtained from mice that were exposed to oxygen at pressures ranging from 4.0 to 11.0 atm (334) showed that the inspired P_{O_2}-exposure duration relationships for mortality of various percentages of the mice could be described by a family of rectangular hyperbolae which did not intersect throughout the range of P_{O_2} that was studied (114, 288a). This indicates that the hyperbolic inspired P_{O_2}-exposure duration relationship applies to individuals with varying susceptibility to oxygen toxicity as well as it does to average data. As inspired P_{O_2} is elevated, the decrease in survival times of resistant mice is greater than that of more susceptible individuals, such that the total range of survival times becomes progressively smaller at the higher levels of inspired P_{O_2} (334, 480, 481).

A complete description of pulmonary oxygen tolerance in any animal species requires determination of the lowest inspired P_{O_2} that will produce pulmonary damage during an indefinitely prolonged exposure. Many studies of tolerance to oxygen at slightly increased partial pressures have been performed in small animals to evaluate potential atmospheres for manned spacecraft. Inspired oxygen partial pressures and exposure durations of these studies are summarized in table 2. Indices of pulmonary oxygen toxicity employed included obvious

TABLE 2

Pulmonary oxygen tolerance studies in small animals exposed to less than 0.6 atm of oxygen

Species	Number of Animals	Ambient Pressure	Oxygen Partial Pressure	Exposure Duration	Reference
		atm	*atm*	*days*	
Mouse	40	0.34	0.23	246	150, 379, 380
Mouse	115*	0.26	0.24	51	320
Mouse	40	0.34	0.33	up to 235	14, 212, 220
Mouse	80	0.36	0.34	60	538
Mouse	16	0.44	0.40	60	538
Mouse	12	0.81	0.44	60	538
Mouse	116	0.52	0.48	60	538
Hamster	8	0.44	0.40	60	538
Hamster	6	0.81	0.44	60	538
Rat	50	0.34	0.23	246	150, 379, 380, 510
Rat	12	0.26	0.24	24	133
Rat	12*	0.28	0.26	334	389
Rat	65	0.34	0.33	up to 235	14, 212, 220, 274, 306
Rat	5	0.81	0.41	60	538
Rat	6	0.44	0.42	60	538
Rat	12	0.59	0.57	64	85
Dog	8	0.34	0.23	246	150, 379, 380, 510
Dog	8	0.34	0.33	up to 235	14, 212, 220, 306, 416
Monkey	4	0.34	0.23	246	150, 379, 380, 510
Monkey	19	0.34	0.33	up to 235	14, 212, 220, 306, 416

* Number does not include offspring born during exposure.

symptoms, mortality and lung pathology. No symptoms of respiratory distress were noted, and mortality of the animals exposed to hyperoxia was not significantly different from that of control animals breathing air. The few deaths that occurred were attributed to endemic disease. In some of the exposed animals, however, careful examination of pulmonary tissues with the light and electron microscope revealed the presence of significant changes which could conceivably have been caused by pulmonary oxygen toxicity (212, 274, 306, 510). Furthermore, the changes appeared to be reversible when the inspired P_{O_2} was returned to normal (212, 306).

The most quantitative descriptions of these alterations in pulmonary structure after prolonged exposure to mild hyperoxia were obtained by the use of morphometric techniques. Exposure of rats and dogs to 0.33 atm of O_2 for 14 and 240 days, respectively, was accompanied by a 27 to 30% reduction in the average ratio of alveolar surface area to body weight (274, 306). There was a concurrent decrease in capillary volume and surface area in the rat, but not in the dog. These changes were regarded as adaptations to the increased availability of oxygen in the rat rather than to toxicity because they were not associated with detectable tissue or cell damage. However, the much longer exposure of dogs to 0.33 atm of O_2 was also accompanied by a 54% increment in mean thickness of the alveolar-capillary tissue barrier and a similar increase in its estimated resistance to diffusion. The cause of the increased barrier thickness was an interstitial edema which was resolved almost completely after a recovery period of 30 to 40 days. Similar, but less marked, structural alterations due to interstitial edema were found in rats, dogs and monkeys after a 240-day exposure to only 0.23 atm of O_2 at an ambient pressure of 0.34 atm (510). Alveolar surface area was not reduced, but there was an increase in the average thickness of alveolar epithelium and some evidence of exudation into the alveolar lumina. Although these changes were not statistically significant in small groups of animals, they were consistent in all three species.

Interpretation of findings suggesting a production of toxic effects by prolonged exposure to an oxygen tension that is only 0.02 atm or about 15 mm Hg higher than the P_{O_2} of normal ambient air at sea level requires careful consideration of factors other than chemical toxicity that may have been responsible for the observed changes. Weibel *et al.* (510) suggested that their results could be attributed to other causes, such as the presence of some contaminant in the environmental chamber, exposure to reduced absolute pressure, return to ambient P_{O_2} and pressure before sacrifice of the animals, and variation in the duration of anesthesia preceding lung fixation. It is also possible that the morphometric techniques employed by Weibel and his associates are sufficiently sensitive to detect structural alterations that are functionally insignificant. If the observed changes were truly caused by pulmonary oxygen toxicity, the obvious implication is that any elevation of inspired P_{O_2}, however small, will eventually produce toxic effects in at least some animal species.

Evidence has been presented in several recent reviews (173, 193, 340, 438) in support of the related concepts that the ability of living organisms to survive in

a normal atmosphere at sea level required the evolutionary development of antioxidant defense mechanisms against an ambient oxygen tension of 0.21 atm and that even a normal life-span is determined at least partially by the interaction of antioxidant and oxidant influences. However, the intermittent exposure of mice to 1.08 atm of O_2 for a total duration of about 13% of their life-span produced no evidence of accelerated aging as evaluated by growth, mortality, hyaluronic acid and collagen contents of the skin and whole body nitrogen content (460)

Pulmonary oxygen tolerance in man

Information describing the tolerance of the human lung to oxygen toxicity is essential for the safe and effective use of oxygen at increased partial pressures in the fields of oxygen therapy, diving and aerospace medicine. The variability of pulmonary tolerance to oxygen in different animal species (fig. 3 and table 1) indicates that the quantitative data obtained in animals cannot be directly applied to man. Of all the animals that have been studied thus far, the subhuman primates appear to resemble man most closely in the rate of development and pathological effects of pulmonary oxygen poisoning (263, 265, 415, 417, 507). However, monkeys have frequently survived exposures to almost 1.0 atm of O_2 for more than 300 hr (fig. 3 and table 1), while the longest human exposure to the same P_{O_2} has been only 110 hr (134, 136). The occurrence of severe pulmonary oxygen poisoning in two subjects during exposure to 0.90 and 0.98 atm of O_2 for 65 and 74 hr, respectively, suggests that even a 110-hr exposure is dangerous for some individuals (47, 100). Uncertainty regarding the validity of extrapolation of animal data to man (even including that obtained from subhuman primates) and the serious consequences that could result from the inappropriate application of such data require that information describing pulmonary oxygen tolerance in man must be obtained directly from man.

Pulmonary tolerance to oxygen has been studied in normal men during exposures to oxygen partial pressures ranging up to 2.0 atm. The indices of pulmonary function and exposure durations employed in these studies are summarized in table 3. Significant changes were observed in the parameters which are marked by ‡. Most of the inconsistencies in the reported data are minor and can be explained adequately. The low absolute and progressively increasing values of arterial P_{O_2} obtained in normal men during prolonged exposure to 0.95 atm of O_2 (134) were almost certainly related to the inappropriate use of oxyhemoglobin measurements to calculate arterial P_{O_2} during oxygen breathing. The hyperventilation and respiratory alkalosis observed in the same study were probably responses to severe symptoms of tracheobronchitis. Similar ventilatory changes were found in subjects who experienced severe symptoms during oxygen breathing at 2.0 atm (96, 98, 116). The increase in arterial oxygen content and capacity and decrease in arterial pH that also occurred during prolonged exposure to 2.0 atm of O_2 were probably caused by factors unrelated to pulmonary oxygen poisoning, such as mild dehydration and metabolic acidosis (114). Failure to observe significant changes in the vital capacity and pressure-

volume curve of one subject who breathed oxygen at 2.0 atm for 11 hr (96, 98) was not surprising because some individual subjects of a much larger series (116) also had small changes during exposure to the same conditions.

When considered from a general viewpoint, the studies summarized in table 3 are quite consistent and provide much useful information relative to pulmonary oxygen tolerance in man. They show that multi-day exposures to oxygen partial pressures of 0.55 atm or less do not significantly impair pulmonary function. However, definite objective and subjective indications of pulmonary intoxication are produced by a 24-hr exposure to 0.75 atm of O_2, even with 15-min periods of air breathing every 3 hr (120). As inspired P_{O_2} is increased to 2.0 atm, there is a progressive increase in the rate of development of pulmonary oxygen poisoning. These data are consistent with the assumption of a hyperbolic relationship between the inspired P_{O_2} and exposure duration that will be tolerated before the production of a uniform degree of pulmonary oxygen poisoning in man.

In order to provide an objective basis for the definition of pulmonary oxygen tolerance in man, change in the vital capacity has been used as a quantitative index of the severity of oxygen intoxication (114, 115). Although this method of evaluation has some limitations (114), it proves to be more satisfactory than measurement of any of the other pulmonary function indices that are known to be altered by oxygen poisoning. Furthermore, the fact that vital capacity was measured in almost all of the studies of pulmonary oxygen tolerance in man (table 3) provides comparable data over a wide range of oxygen partial pressures.

A series of predictive curves has been derived based upon change in the vital capacity as an index of toxicity and upon the theoretical assumptions that pulmonary oxygen tolerance in man can be described by families of rectangular hyperbolae with asymptotes at zero time and at an inspired P_{O_2} of 0.5 atm (114, 288a). The family or group of curves shown in figure 4 defines the rate of development of pulmonary oxygen poisoning in 50% of the individuals exposed to increased partial pressures of oxygen. The curves in figure 5 show the variation in susceptibility to a uniform degree of pulmonary oxygen poisoning represented by a 4% decrease in vital capacity. Methods are described by which other families of pulmonary tolerance curves can be derived on the basis of different proportions of the exposed individuals or other degrees of intoxication (114).

The assumption that an inspired P_{O_2} of 0.5 atm is a practical horizontal asymptote for pulmonary oxygen tolerance curves implies that normal men can breathe oxygen at this P_{O_2} for a long period of time with the occurrence of only a minor degree of pulmonary oxygen poisoning. The validity of this assumption cannot be established conclusively even by the combined data from all available sources (table 3). Animal studies suggest that exposure to mild hyperoxia will cause adverse pulmonary effects if the exposure is sufficiently prolonged (212, 274, 306, 510, 538). However, the wide species variation in susceptibility to pulmonary oxygen toxicity (fig. 3 and table 1) indicates that these results may not be applicable to man even if they can be definitely confirmed in other animal species. Precise identification of the true inspired P_{O_2} asymptote for curves describing pulmonary oxygen tolerance in man will probably never be practical due to the

TABLE 3

Pulmonary oxygen tolerance studies in normal man

Oxygen Partial Pressure	Ambient Pressure	Exposure Duration	Number Subjects	Indices of Pulmonary Oxygen Toxicity*	Reference
atm	*atm*	*hr*			
0.23	0.25	408	8	VC, FEV, $C_{a_{O_2}}$, $Cap_{a_{O_2}}$, chest x-ray	348
0.23	0.25	408	2	VC, $FEV_{1.6}$, %FEV, MBC, V_T	349
0.24	0.26	120	2	VC	215
0.24	0.26	72	1	VC, FEV, ERV, IC, MBC, $\dot{V}_E$, V_T, chest x-ray	216, 422
0.25	0.26	336	6	VC, TLV, MBC, $D_{L_{CO}}$, $P_{a_{O_2}}$, chest x-ray	229
0.26	0.31	72	2	VC, $\dot{V}_E$, $P_{A_{CO_2}}$, $C_{a_{CO_2}}$, chest x-ray	47, 422
0.31	0.92	720	4	FEV, RV, MBC, $D_{L_{CO}}$, $P_{a_{O_2}}$	233, 411
0.32	0.34	336	3	VC, ERV, IC, FRC, RV, MBC, R_L, $D_{L_{CO}}$, C_L, R_{aw}, $\dot{V}_E$, $P_{a_{O_2}}$, $P_{a_{CO_2}}$, Single-breath distribution, chest x-ray	142, 232
0.32	0.34	336	4	VC, $P_{A_{O_2}}$, $P_{a_{O_2}}$, $P_{A_{CO_2}}$, $P_{a_{CO_2}}$, chext x-ray	346
0.33	0.34	336	6	VC, TLV, MBC, $D_{L_{CO}}$, $P_{a_{O_2}}$, chest x-ray	229
0.33	0.34	720	4	FEV, RV, MBC, $D_{L_{CO}}$, $P_{A_{O_2}}$, $P_{a_{O_2}}$	233, 411
0.45	1.0	168	2	$\dot{V}_E$, $P_{a_{CO_2}}$	408
0.49	0.50	336	6	VC, TLV, MBC, $D_{L_{CO}}$, $P_{a_{O_2}}$, chest x-ray	229
0.49	0.50	24	6	VC, f	120
0.51	1.0	24	10	VC, f	120
0.55	0.69	168	6	VC, f, chest x-ray	341a
0.75	1.0	24†	9	VC‡, f	120
0.83	1.0	53–57	6	VC‡, f, chest x-ray	367
0.90	1.0	65	2	VC‡, $P_{A_{CO_2}}$	47
0.95	1.0	42–110	12	VC‡, $\dot{V}_E$‡, V_T, f‡, pH_a‡, O_2 $sat._a$, $P_{a_{O_2}}$‡, $P_{a_{CO_2}}$ $C_{a_{CO_2}}$	134
0.98	1.0	24	34	VC‡, f, O_2 $sat._a$, $P_{a_{O_2}}$, $\dot{V}_E$, chest x-ray	120
0.98	1.0	30–74	4	VC‡, TLV‡, FEV, RV, $D_{L_{CO}}$‡, D_M‡, V_c, $P_{A_{O_2}}$, $P_{a_{O_2}}$, $P_{a_{CO_2}}$, pH_a, C_L‡, chest x-ray	100
1.99	2.0	6–12	13	VC‡, IC‡, ERV‡, RV, FRC, FEV, %FEV, MMEF, FIV‡, %FIV‡, MMIF‡, f‡, C_L‡, R_{aw}, R_L, V_t, $\dot{Q}_c$, $D_{L_{CO}}$‡, D_M, V_c‡, $P_{A_{O_2}}$, $P_{a_{O_2}}$, $P_{a_{CO_2}}$, pH_a‡, $C_{a_{O_2}}$‡, $C_{a_{CO_2}}$, $Cap_{a_{O_2}}$‡, chest x-ray	114, 116, 161, 405
2.0	2.0	11	1	VC, FRC‡, f‡, C_L, V_T‡	96, 98

* See "Symbols and Definitions" for explanation of symbols used in this column.

† Subjects breathed room air for 15 min every 3 hr. All other exposures were continuous

‡ Indicates a significant change during or after exposure.

SYMBOLS AND DEFINITIONS

$C_{a_{CO_2}}$	Arterial carbon dioxide content
$C_{a_{O_2}}$	Arterial oxygen content
$Cap_{a_{O_2}}$	Arterial oxygen capacity
C_L	Pulmonary lung compliance
$D_{L_{CO}}$	Carbon monoxide diffusing capacity of the lung
D_M	Diffusing capacity of the pulmonary alveolar membrane
ERV	Expiratory reserve volume

long duration of the required experiments and the inability to detect minimal impairment of pulmonary function. Furthermore, the exposure duration may be limited by hematologic or endocrine effects of mild hyperoxia before the occurrence of significant pulmonary intoxication (299, 315). Fortunately, however, the choice of 0.5 atm of O_2 can deviate from the true asymptote by only 0.3 atm at most, because 0.21 atm is the P_{O_2} of normal ambient air and 0.75 atm of O_2 is definitely toxic (120). Although an error of this magnitude could have serious consequences with reference to extremely long exposures to slightly increased oxygen partial pressures, it will have very little influence upon predicted tolerance of the lung to oxygen pressures of 1.0 atm or higher.

It should be emphasized that the information summarized by the curves in figures 4 and 5 specifically applies only to normal men who are continuously exposed to hyperoxia. Pulmonary tolerance to oxygen toxicity has also been studied in patients recovering from open-heart surgery (450a). Measurements of the effective intrapulmonary shunt, lung compliance and the ratio of dead space to tidal volume were not significantly different after ventilation for about 15 to 48 hr with either pure oxygen or the minimal inspired oxygen concentration required to maintain an arterial P_{O_2} of 80 to 120 mm Hg. A similar study in patients with irreversible brain damage showed that the alveolar-arterial P_{O_2} difference and effective intrapulmonary shunt were significantly increased after 40

---

f	Respiratory rate
FEV	Forced expired volume
$FEV_{1.0}$	One second forced expired volume
%FEV	Percent of forced expired volume expired in 1 sec
FIV	Forced inspired volume
$FIV_{1.0}$	One second forced inspired volume
%FIV	Percent of forced inspired volume inspired in 1 sec
FRC	Functional residual capacity
IC	Inspiratory capacity
MBC	Maximum breathing capacity
MMEF	Maximal flow rate during mid-expiration
MMIF	Maximal flow rate during mid-inspiration
O_2 sat.$_a$	Arterial oxygen saturation
$P_{a_{CO_2}}$	Arterial carbon dioxide tension
$P_{A_{CO_2}}$	Alveolar carbon dioxide tension
$P_{a_{O_2}}$	Arterial oxygen tension
$P_{A_{O_2}}$	Alveolar oxygen tension
pH_a	Arterial pH
$\dot{Q}_c$	Pulmonary capillary blood flow
R_{aw}	Airway resistance
R_L	Pulmonary resistance
RV	Residual volume
TLV	Total lung volume
V_c	Pulmonary capillary blood volume
VC	Vital capacity
$\dot{V}_E$	Expired minute volume
V_t	Pulmonary parenchymal tissue volume
V_T	Tidal volume

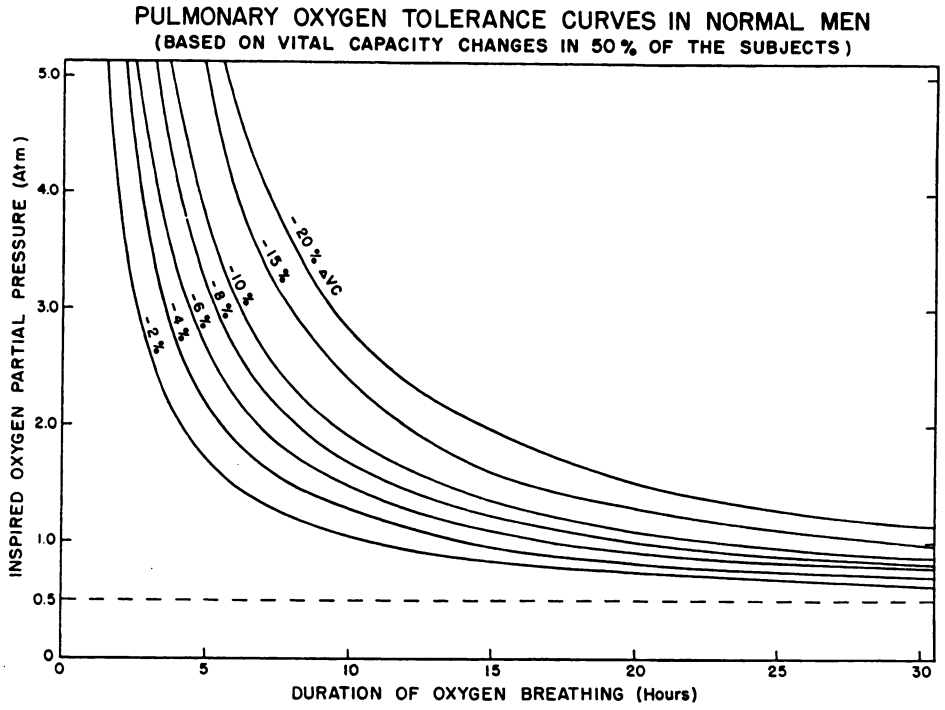

FIG. 4. Pulmonary oxygen tolerance curves for normal men based on vital capacity changes in 50% of the individuals exposed to increased partial pressures of oxygen. The curves describe rate of development of pulmonary oxygen poisoning in an individual with "average" susceptibility.

hr of ventilation with oxygen, while the ratio of dead space to tidal volume was increased after 30 hr (20a). Although these studies provide useful information with regard to pulmonary oxygen tolerance under the existing experimental conditions, which included abnormal pulmonary function at the outset, their results are not directly comparable to data obtained in normal men (table 3). The indices of pulmonary oxygen toxicity used in both experiments are not as sensitive as those which can be employed in alert, cooperative and well-trained volunteers (114, 116). Furthermore, the rate of development of pulmonary oxygen poisoning is very likely altered by hormonal influences, drugs and other variables found in patients with cardiopulmonary disease or brain damage (see Modification of Pulmonary Oxygen Tolerance, page 109). Until the effects of these variables can be identified and quantitatively evaluated, a prudent approach would seem to be utilization of the minimum oxygen partial pressure and exposure duration which are sufficient to correct the existing functional deficit. It is also important to supplement descriptions of pulmonary oxygen tolerance with studies of the rate of development of oxygen intoxication in other susceptible tissues, such as the brain, the eye, the gonads, the endocrine glands, the erythropoietic system and the kidney.

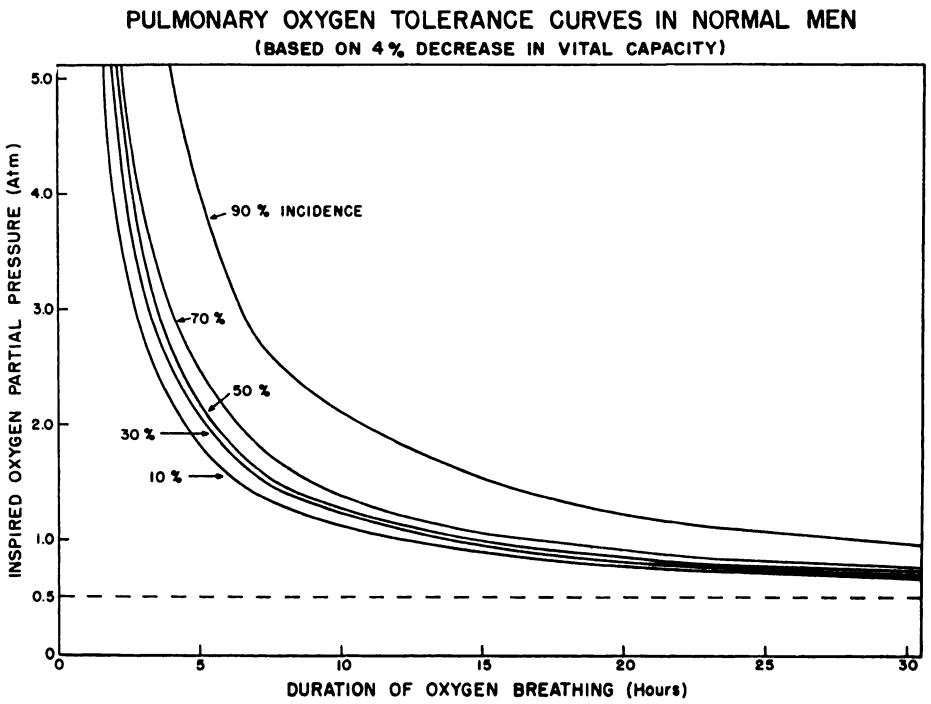

FIG. 5. Pulmonary oxygen tolerance curves for normal men based on a 4% decrease in vital capacity. The curves describe varying susceptibility to a uniform degree of pulmonary oxygen poisoning.

Resistance to pulmonary oxygen toxicity

Acquired resistance to pulmonary oxygen toxicity. In rats exposed continuously to 0.8–1.0 atm of O_2, many workers have observed that some of the animals are able to survive the acute onset of toxic effects and go on to develop a greatly increased tolerance to pulmonary oxygen poisoning (80, 132, 313, 314, 395, 407, 456, 457, 511). Typically, the rats showed obvious signs of severe pulmonary intoxication at 3 to 5 days of exposure when many of them died. The survivors of this acute "crisis" recovered significantly over the next few exposure days and were able to tolerate the hyperoxic atmosphere for as long as 72 days (456, 457). Although restoration of normal behavior and appearance were apparently complete in some rats (132), a sustained reduction in food intake, decreased activity and slow, labored breathing were observed in others (456, 457, 511). One group of rats that had become tolerant to 0.95 atm of O_2 began to deteriorate after 4 to 6 weeks of exposure, became anorexic and eventually died without significant pulmonary pathology or any other obvious cause of death (80).

Acquired resistance to pulmonary oxygen toxicity has also been induced in rats by intermittent exposure to a toxic P_{O_2} (20, 69–71, 501), gradual elevation of inspired P_{O_2} from 0.60 to 1.0 atm over a period of 8 to 10 days (20) and prolonged exposure to a level of hyperoxia that did not produce acute pulmonary intoxica-

tion (279, 419). In a strain of rats which normally had almost 100% mortality after exposure to 0.95–0.98 atm of O_2 for 3 to 5 days, Binet and Bochet (69–71) were able to induce acquired tolerance by feeding the rats a diet which elevated blood glutathione levels and enabled some of the animals to survive the acute "crisis" long enough to become more resistant to the hyperoxic atmosphere. Exposure of newborn lambs to 0.59–0.63 atm of O_2 killed about half of the animals within 15 days, but some lambs tolerated the environment for at least 40 days (448a). Serial lung biopsies showed an initial progression of oxygen poisoning followed by nearly complete reversal of the pulmonary edema and surfactant changes. The survival time of cats in 1.0 atm of O_2 was more than doubled by previous, intermittent exposure to the same atmosphere (476), but attempts to induce acquired tolerance in dogs, rabbits, guinea pigs and mice were not successful (20).

The conditions which promote the development of acquired tolerance to pulmonary oxygen toxicity in rats appear to involve exposure to a toxic level of hyperoxia which at least some of the animals are able to survive due to inherent resistance (80, 132, 313, 314, 395, 407, 456, 457, 511), intermittent exposure (20, 69–71, 501), chemical protection (69–71) or exposure to an inspired P_{O_2} which is low enough to minimize or avoid acute toxic effects of oxygen upon the lung (20, 279, 419). These conditions are very similar to those which have produced proliferative, sclerotic changes in the pulmonary structure of monkeys (121, 164, 263, 265, 415, 417, 511) and rats (432). Actually, the development of pulmonary resistance to hyperoxia in rats is frequently accompanied by a marked thickening of the alveolar walls due both to hypertrophy and hyperplasia of the alveolar cells (71, 313, 314, 395, 456, 457, 501). Additional evidence of an increased diffusion barrier in resistant rats was provided by the observation that many of them died when they were returned to normal air (71, 456, 457, 501). Furthermore, the pulmonary structure in resistant adult rats resembled that of normal young rats who also had an increased tolerance to pulmonary oxygen toxicity (71, 456, 457). When resistant animals were returned to normal air, the acquired tolerance to hyperoxia persisted for periods at least as long as 6 to 8 weeks (20, 456, 457, 476). Rats that had developed tolerance to about 1.0 atm of O_2 showed no evidence of increased resistance to oxygen pressures of 3.0 to 4.7 atm with reference to either mortality rates (20) or ultrastructural changes (419).

The results of other experiments suggest that pulmonary structural changes may contribute to the development of increased oxygen tolerance. During exposure to 0.99 atm of O_2, germ-free rats and mice had shorter and more uniform survival times than conventional rodents (530). The authors suggested that chronic pulmonary infection in the rodents commonly used for laboratory studies caused structural alterations in the lungs which resulted in greater oxygen tolerance. Ohlsson (367) found that pulmonary tolerance to 0.80–0.90 atm of O_2 was increased in rabbits with alveolar epithelial damage and marked symptoms of hypoxemia after non-lethal exposure to diphosgene. Responses of respiratory epithelium to changes in the ambient oxygen tension have also been observed in non-mammalian species. The gills of salamander "larvae" were modified in such

a way that their capacity for diffusion was reduced during exposure to hyperoxia and increased under hypoxic conditions (76, 140). However, acquired resistance to pulmonary oxygen toxicity cannot be attributed entirely to a widened diffusion barrier, because increased oxygen tolerance was not accompanied by the required structural changes in two studies (279, 419) and it preceded them in another (20).

In an attempt to explain the development of acquired tolerance to hyperoxia, Kydd (279) has proposed an interesting hypothesis based upon the remarkable capacity of rats to reabsorb fluid transudates from their lungs and pleural sacs during recovery from pulmonary oxygen poisoning. Kydd has suggested that one of the factors determining survival under these conditions is the capacity of the lymphatic system to remove fluid faster than it is formed by the toxic effects of oxygen. Presumably, sublethal exposures to hyperoxia would increase the rate of fluid clearance from the lungs and better equip the animal to withstand subsequent, more toxic exposures. As evidence in support of his hypothesis, Kydd cited the observation of an essentially direct relationship between fluid transudation and flow through the right lymphatic duct of the dog with no suggestion of a plateau (141). Beznak and Liljestrand (68), on the other hand, showed that oxygen breathing caused a 30% reduction of lymph flow through the right thoracic duct of anesthetized dogs and cats. However, this effect occurred after about 2 min of oxygen breathing and preceded the appearance of pulmonary edema. Direct information testing the validity of Kydd's hypothesis could be obtained by measuring the rate of lymph flow through the right thoracic duct of young rats and both normal and resistant adult rats when stressed with a standard fluid load in the thoracic cavity.

Another possible tolerance mechanism is suggested by the finding of Rosenbaum *et al.* (419) that the increased pulmonary oxygen tolerance acquired during a 7-day exposure of rats to 0.85 atm of O_2 was accompanied by ultrastructural changes in type II alveolar cells. These alterations included elongation of the mitochondria, an increase in free ribosomes and dilatation of the endoplasmic reticulum cisternae. The authors concluded that the mitochondrial changes in particular represented a compensatory response, rather than a degenerative one, because they did not occur during exposure to higher, more toxic levels of hyperoxia, and no gross or microscopic evidence of pulmonary oxygen poisoning was found in the rats that survived the 7-day exposure to 0.85 atm of O_2. However, no comment was made concerning the cause of death in about 15% of the rats that expired between the 2nd and 3rd day of this exposure. It is conceivable that these rats died from pulmonary oxygen poisoning, while the survivors either were less affected or were able to recover spontaneously. Rosenbaum *et al.* suggested that the mitochondrial changes could protect against oxygen toxicity by providing increased surface/volume ratios which compensated for the direct inhibition of enzymatic activity. It would be of great interest to determine whether similar alveolar cell ultrastructural changes accompany the induction of acquired pulmonary oxygen tolerance by intermittent exposure to a toxic P_{O_2} or the tolerance which can develop spontaneously during continuous exposure to

a lethal level of hyperoxia. However, it is doubtful that alterations in the mitochondria of type II alveolar cells can completely account for acquired resistance because such localized changes would offer no protection against the capillary endothelial damage which is a prominent feature of pulmonary oxygen poisoning (1a, 79, 108, 263, 272, 273, 275, 321, 328, 356a, 357, 376, 395, 432, 501, 532, 534).

Alterations in the adrenocortical response to hyperoxia may be another factor which contributes to the development of acquired pulmonary oxygen tolerance. Many studies, which will be considered later in this review, have shown that the adrenal cortex is stimulated during the development of intoxication at oxygen pressures of 1.0 atm or higher. Furthermore, the toxic effects of oxygen are enhanced by the presence of adrenocortical hormones (see Modification of Pulmonary Oxygen Tolerance, page 109). In rats exposed to about 0.48 to 0.61 atm of O_2 for 2 to 7 weeks, however, an initial increase in adrenocortical activity was followed by a return to essentially normal function while the animals were still in the hyperoxic environment (241, 335, 490). If normal adrenocortical activity had been maintained during subsequent exposure to a higher level of hyperoxia, pulmonary oxygen tolerance probably would have been increased. This possible mechanism could be studied by evaluation of hypophyseal-adrenocortical function in rats before, during and after the development of acquired resistance to pulmonary oxygen toxicity.

It is possible that complex metabolic factors are involved in the development of acquired resistance to oxygen toxicity. The profound anorexia and weight loss that commonly occur in acute oxygen poisoning have been found to a lesser degree in rats that have acquired increased oxygen tolerance (69–71, 456, 457). Many studies have shown that fasting provides partial protection against the toxic effects of oxygen (24, 103, 194, 369, 464). Pulmonary oxygen tolerance was also increased in rats fed a low protein diet (208). It is conceivable that the anorexia which is a relatively early effect of oxygen toxicity may result in metabolic changes that delay the subsequent appearance of more severe pathological effects. Decreased adrenocortical activity secondary to reduced ACTH secretion in protein-deficient animals may also contribute to the increased oxygen tolerance associated with prolonged fasting (208).

In agreement with a metabolic basis for acquired tolerance, marked decreases in the pulmonary elimination of CO_2 (69–71) and in the respiratory exchange ratio (277) have been observed in rats before or during the appearance of acute pulmonary oxygen intoxication. Although CO_2 elimination returned to normal when the rats were allowed to recover in air, it remained somewhat depressed during a second exposure to 0.95–0.98 atm of O_2, when the animals demonstrated greatly increased oxygen tolerance (69). It is possible that the acute decrease in CO_2 elimination was caused at least partially by pulmonary damage, but it is difficult to attribute the sustained reduction to the same cause, because accumulation of CO_2 in the tissues and blood would eventually restore CO_2 elimination to the level of CO_2 production. A sustained reduction in oxygen consumption also occurred during prolonged exposure of mice to 0.80–0.90 atm of O_2 (485). Furthermore, Kydd (277) found that rats that had been fasted in a normal atmosphere

had a decrease in respiratory exchange ratio which was similar to the change that accompanied the development of pulmonary oxygen poisoning. These results suggest that the reductions in CO_2 elimination, O_2 consumption and respiratory exchange ratio, which occurred during prolonged exposure to 0.80–1.0 atm of O_2, were mainfestations of metabolic changes caused by fasting, either alone or in combination with the direct inhibition of cellular enzymes.

A marked increase in the pulmonary oxygen tolerance of rats has also been observed after the animals were housed for 8 weeks at an ambient pressure equivalent to an altitude of 17,400 feet (ambient $P_{O_2} \sim 82$ mm Hg) (81). Average survival time during exposure to about 1.1 atm of O_2 increased from 51 hr to 188 hr after acclimatization to altitude. The greater oxygen tolerance of resistant rats was related to a delayed appearance of pathological changes in the lungs as well as to an increased tolerance of their ultimate effects upon pulmonary gas exchange. Even 30 days after the rats were returned to sea level, their survival time during exposure to hyperoxia was significantly prolonged. Brauer *et al.* (81) suggested that the increased pulmonary oxygen tolerance afforded by altitude acclimatization may be related to changes in the pulmonary circulation. Other potential mechanisms include both the possible enhancement of lymphatic drainage in response to the pulmonary edema of acute altitude sickness and the adrenocortical depletion caused by prolonged exposure to hypoxia (240). In contrast to the findings of Brauer *et al.* (81), the pulmonary tolerance of mice to 1.0 atm of O_2 was not increased after the animals lived at altitudes of 6,600 and 12,540 feet for 16 and 14 days, respectively (ambient $P_{O_2} \sim 125$ and 100 mm Hg) (13). The use of a different species, shorter exposures and higher ambient P_{O_2} levels may all have contributed to these conflicting results.

Inherent resistance to pulmonary oxygen toxicity. It may be possible to obtain additional clues relating to potential mechanisms of acquired pulmonary oxygen tolerance by studying the various animal species which are inherently resistant to oxygen toxicity (table 1). An extreme resistance is demonstrated by cold-blooded animals. At an ambient temperature of 23°C to 26°C, exposure of turtles to 0.90–1.0 atm of O_2 for 10 to 23 days did not cause detectable symptoms or pulmonary pathology (151). When exposed to the same atmosphere at an ambient temperature of 37°C to 38°C, the turtles became anorexic, developed progressive dyspnea and died within periods of time as short as 3 days. Post-mortem examination revealed pulmonary vascular congestion, hemorrhage and capillary dilatation. These results suggest that natural resistance to oxygen toxicity may be partially dependent upon the rate of biochemical activity and hence upon metabolism.

Avian species have also demonstrated a remarkable resistance to incapacitation by pulmonary oxygen toxicity (512–514). Although gasping respiration and intermittent apnea were observed in adult chickens before death, the lungs had an essentially normal appearance on gross examination (512). It was suggested that the semirigid avian lung with its continuous air capillaries and air sacs and a deficiency of surfactant may have contributed to the increased resistance to oxygen effects. It is equally probable that metabolic factors were also involved.

In a study designed to evaluate the influence of nutrition upon oxygen tolerance

in quail, Weiss and Wright (513) found that about 40% of the birds died after 5 to 10 days of exposure to 0.98–1.0 atm of O_2, while the remainder survived 12 to 24 days of exposure without signs of further deterioration. Although progressive reductions in body weight and food intake appeared to begin almost immediately in both groups of birds, these changes were significantly greater in the non-survivors by the 2nd day of exposure. Weight loss of the non-survivors was essentially linear throughout the exposure and little or no food was eaten after the 3rd to 4th day. In contrast to this, the survivors reached minima in body weight (85% of normal) and food intake (33–50% of normal) after 4 to 7 days of exposure and had a sustained, partial recovery thereafter. Quail that were force fed with about one-third of their normal daily intake appeared to have an increased mortality compared to the birds on an *ad lib* diet. An interesting observation was that force feeding somehow stimulated the appetite of the non-survivors to such a degree that their changes in total food intake and body weight were similar to those of the surviving birds. Gross post-mortem examination of the lungs and other organs failed to reveal a definite cause of death. An adequate explanation of these results may help to identify general principles which influence inherent resistance to oxygen toxicity.

Immaturity has been associated with increased oxygen tolerance in both mammalian and non-mammalian species (24, 151, 177, 188, 280, 384, 399, 456, 457, 463, 483, 514, 519). Tiisala (482, 483) has shown that increased resistance to hyperoxia in the immature rat can be partially attributed to the absence of a significant hypophyseal-adrenocortical response to stress. The uptake of radioactive phosphorus by the adrenals, thymus and spleen was measured in rats of varying ages after a 48-hr exposure to 0.92–0.96 atm of O_2. Significant responses to the hyperoxic stress were observed in adults, but not in 2-day-old rats. At the age of 10 days, the stress reaction was still insignificant; at 21 days, it was similar to the adult response, though less severe. The origin of the immature stress reaction was localized at the level of the hypophysis or hypothalamus, because the adrenals of newborn rats responded significantly to the administration of exogenous adrenocorticotrophic hormone (483).

In agreement with Tiisala's results, the tolerance of young rats (177) and mice (463) to 4.4–6.0 atm of O_2 greatly decreased between the ages of 12 and 21 days, and adrenocorticotrophic hormone could not be detected in the pituitary glands of rats until they were 18 days old (248). The observation that newborn mice were more susceptible to pulmonary oxygen toxicity during the first hours of extra-uterine life than they were at the age of 1 to 2 days (243, 399) could also be explained by an immature stress response in the presence of maternal corticosteroids which cross the placenta and remain active in the fetal circulation for several hours (483).

The finding that the pulmonary oxygen tolerance of 3-week-old puppies was similar to that of adult dogs (375) may have been related to activation of a significant hypophyseal-adrenocortical response to hyperoxia at about this age (482, 483). However, immature endocrine responses cannot be the only basis for the increased oxygen tolerance of young animals because the same phenomenon

has been demonstrated in young Drosophila (159, 519). The increased cellularity and thickness of the alveolar walls found in normal young rats may also contribute to their resistance to oxygen toxicity (71, 456, 457).

Nutritional factors may provide an additional mechanism for increased tolerance to hyperoxia in young animals. Polgar *et al.* (399) found that newborn mice, whose oxygen tolerance under conditions of continuous nursing greatly exceeded that of adults, became more susceptible than the adults when they were nursed intermittently at a slightly lower ambient temperature. Presumably, intermittent nursing was responsible for the increased susceptibility because environmental hypothermia had no detectable influence upon mortality or pulmonary pathology in newborn mice exposed to 0.90–1.0 atm of O_2 for 15 days (228).

MECHANISMS OF PULMONARY OXYGEN TOXICITY

Although the specific biochemical target sites in the lung have not yet been identified as well as they have in organs such as the brain, the direct toxic effects of oxygen in lung tissue must also originate from an inactivation of essential enzymes and the resulting disruption of cellular metabolism. These initial biochemical effects start a complex series of events that terminate in the overall pathological changes of pulmonary oxygen poisoning. Pathological studies reviewed previously show that the entire lung, from the epithelium of the upper respiratory tract down to the pulmonary capillary endothelium, can be damaged by prolonged exposure to oxygen at increased partial pressures. Other studies that will be reviewed below show that the mechanisms responsible for the total syndrome of pulmonary oxygen poisoning include multiple interacting factors, some of which are related to toxic effects of oxygen at extrapulmonary sites. The rate of development of the lethal effects of oxygen toxicity is extremely variable among different species and individuals (table 1 and fig. 3). Variability can similarly be expected in the relative importance of factors which influence pulmonary intoxication and is a possible explanation of contradictory results in different animal species or even in different individuals of the same species.

Bean (26, 31–33, 46) has repeatedly emphasized that oxygen at high pressure can affect the lungs by indirect mechanisms acting through hypophyseal-adrenocortical and sympatho-adrenomedullary pathways. Although such indirect effects are important in the development of pulmonary oxygen poisoning, the direct toxic effects of oxygen play a primary and prominent role. Studies *in vitro* (125, 131, 223, 225) have shown that many enzymes and metabolic pathways are susceptible to the toxic effects of oxygen in the absence of hormonal and neurogenic factors.

Direct toxic effect of oxygen

Experiments designed to expose only one lung of an intact animal to increased oxygen pressures have demonstrated that oxygen poisoning can cause pulmonary damage in the absence of extrapulmonary factors. Penrod (388) differentially catheterized the two main bronchi of anesthetized cats and ventilated one lung

with oxygen and the other with nitrogen or helium at an ambient pressure of 5.0 atm. The lung ventilated with inert gas was unchanged after 7 hr of exposure, but the lung ventilated with oxygen had extensive gross and microscopic damage. In a group of lightly tranquilized dogs, each lung was ventilated separately with air or with O_2 at 1.0 atm (534). Although similar degrees of patchy atelectasis and pneumonia were found in both lungs after 72 hr of exposure, only the oxygen-ventilated lung had pathological changes such as epithelial and endothelial cell damage, capillary thromobsis, interstitial edema and hyaline membranes. An equivalent reduction of surfactant activity was observed in the oxygen-exposed lungs of anesthetized dogs when either one or both lungs were independently ventilated for 12 hr with 1.0 atm of O_2 (351). A smaller reduction in surfactant activity occurred in air-exposed lungs when the opposite lung was ventilated with oxygen, but surfactant activity was normal when both lungs were spontaneously or mechanically ventilated with air. After 7 days of continuous ventilation of a dog's left lung with 1.0 atm of O_2 and right lung with air, the left lung had a liver-like consolidation while the right lung was relatively normal (110).

Winter *et al.* (520) demonstrated the occurrence of both direct and indirect components of pulmonary oxygen poisoning in a study designed to determine the effect of a healed large veno-arterial shunt upon survival time in dogs breathing O_2 at 2.0 to 2.5 atm. The shunt was created by anastomosis of the inferior vena cava to the right inferior pulmonary vein. Average arterial P_{O_2} in 10 such dogs breathing air was 40.7 mm Hg. Ten normal dogs were exposed to 2.5 atm of O_2 until convulsions occurred and were then exposed to 2.0 atm of O_2 until they died. Average time for onset of convulsions was 5.1 hr and average survival time was 12.3 hr. In contrast to this, 10 shunted dogs had no convulsions during 5.1 hr of O_2 breathing at 2.5 atm. They were then exposed to 2.0 atm of O_2 and lived for an average total time of 21.1 hr. Average arterial P_{O_2} of four shunted dogs during O_2 breathing at 2.5 atm was only 127 mm Hg. Because this small elevation of arterial P_{O_2} could not have produced fatal extrapulmonary pathology, death of the dogs must have been due to direct oxygen poisoning of the lungs. Although the shunted dogs had a longer average survival time, histological studies showed that the intensity of pathological changes in their lungs was equal to or somewhat greater than that found in the normal dogs. However, the lungs of shunted dogs which were sacrificed after an exposure duration equal to the average survival time of normal dogs were essentially normal except for slight hyperemia. It was suggested that shunted dogs lived significantly longer than normal dogs whose lungs were exposed to the same P_{O_2} because veno-arterial shunting reduced or eliminated the influence of neuroendocrine interaction in pulmonary oxygen poisoning. Since lungs of normal oxygen-breathing individuals and animals receive oxygen at high partial pressure by way of the bronchial circulation as well as the airways, it is likely that part of the tolerance of shunted animals is due to the lower "oxygen dose" experienced by lung tissue when bronchial arteries deliver essentially normoxic rather than hyperoxemic blood (502). It is also possible that the prolonged and severe hypoxia which the shunted dogs experienced may have indirectly protected against oxygen toxicity by inducing a depletion of

adrenal cortical hormones. A similar degree of hypoxia reduced the plasma corticosterone level in rats (240).

The results of a study designed to evaluate the influence of veno-arterial shunting upon pulmonory tolerance to about 1.0 atm of O_2 suggested that there was no indirect component of pulmonary oxygen poisioning at this level of hyperoxia (343). One to two months after the production of a large intracardiac shunt, arterial P_{O_2} in eight dogs breathing air or oxygen ranged from 29 to 58 mm Hg. All of the shunted dogs and 10 normal dogs were sacrificed after exposure to 0.98–1.0 atm of O_2 for 48 to 50 hr. Both groups of animals had similar responses with respect to symptoms of respiratory distress, pulmonary pathology and abnormal surface tension of lung extracts. With the exception of the surface tension measurements, however, there were no quantitative indices of toxicity. Confirmation of these results is important because they imply that arterial hypoxemia does not retard the rate of development of pulmonary oxygen poisoning in patients breathing oxygen at 1.0 atm.

The probability that elevation of the bronchial arterial P_{O_2} influences the severity of pulmonary oxygen poisoning is indicated by the results of a recent study in which dogs were intermittently exposed to 3.0 atm of O_2 after modification of the pulmonary circulation (478a, 540). In one group of dogs development of a bronchial collateral circulation was induced by ligation of the right pulmonary artery. In a second group of dogs the pulmonary artery to the right middle lobe was ligated after the dogs were made cyanotic by anastomosis of the left pulmonary artery to the left atrium. All dogs breathed O_2 at 3.0 atm during four 1-hr periods each day. After each exposure air was breathed for 1 hr before the next exposure. None of the dogs exhibited clinical evidence of respiratory distress, even after 120 exposures, but histological examination showed fibrosis, increased vascularity, interstitial thickening and increased cellularity of the alveolar membranes. These changes were most severe in the lungs of noncyantoic dogs on the side perfused by arterial blood *via* the bronchial collateral circulation. The normally perfused opposite lungs of the same dogs had less severe changes. In the cyanotic dogs proliferative changes were minimal in the abnormally perfused middle lobe and absent in the opposite lung. Marked increases in the minimum surface tensions of minced lung extracts from all four types of lung preparation were found to correlate with corresponding elevations of pulmonary venous P_{O_2} (478a). The authors concluded that the severity of chronic pulmonary oxygen poisoning at a constant inspired P_{O_2} is related predominantly to the degree of hyperoxemia in blood perfusing the lungs. Since the elevation of arterial P_{O_2} during oxygen breathing is much greater than that found in mixed venous blood (516a), the results of this study can probably be attributed primarily to augmentation of the bronchial circulation, with a minor contribution from hyperoxemic blood in the venous side of the pulmonary circulation. The delayed onset of acute (520) and chronic (478a, 540) pulmonary oxygen intoxication in cyanotic dogs with large veno-arterial shunts is probably partly related to reduction of the bronchial arterial P_{O_2} in addition to the decreased influence of neuroendocrine factors.

Interaction of pulmonary and central nervous system effects

A definite correlation between the degree of pulmonary damage and the severity of convulsive neuromuscular reactions produced in rats by exposure to 5.0–6.4 atm of O_2 was first reported by Bean and Johnson (37, 261) and later observed by other investigators (221, 377, 526). Severe convulsions appeared to precede the development of extensive pulmonary changes when they occurred, but gross pulmonary pathology was not always found in rats that had convulsed, particularly if the convulsions were mild or of short duration (43, 46, 261, 526).

Bean *et al.* (45) further found that drug-induced convulsions were associated with pulmonary changes similar to those seen in oxygen-poisoned lungs. In rats breathing O_2-enriched air at 1.0 atm, prominent lung changes occurred after convulsions were induced by administration of pentylenetetrazol, picrotoxin, W181 (1-N-butylamino-3-P-toluidino-2-propanol) or PTAP (1-P-toluidine-3-propylamino-2-propanol). Pretreatment with pentobarbital prevented both the convulsions and the pulmonary effects. Dibenamine, chlorpromazine and SKF 501 (N-9-fluorenyl-N-ethylene-β-chlorethylamine) had no effect upon convulsions but afforded definite protection against alterations in the lung. In contrast to this, *d*-tubocurarine eliminated the somatic component of the drug convulsions but did not prevent the associated pulmonary pathology. Other investigators have also observed pulmonary edema in rats after convulsions induced by pentylenetetrazol (221, 409) and thiosemicarbazide (478).

In studies designed to determine the effect of mechanical head injury upon the lung, Bean and Beckman (36, 49) found in rats that a sharp impact to the skull frequently produced congestion, hemorrhage, atelectasis and edema similar to that caused by severe pulmonary oxygen poisoning or drug-induced convulsions. Prominent lung changes were found in all of the rats that died within a few minutes after the cerebral trauma and in half of the survivors that were about to regain consciousness. The pathological changes were accompanied by a marked decrease in pulmonary compliance which appeared to be related to alterations in surface forces rather than to changes in tissue elastic or myogenic forces (50). The pulmonary pathology was prevented or greatly reduced by pretreatment with sympatholytic, antiepinephrine or anesthetic agents (36, 49). Pretreatment with dibenzyline also prevented the reduction in pulmonary compliance which followed head injury (50). Preliminary experiments showed that monkeys and rabbits were less susceptible than rats to the gross pulmonary effects of cerebral traumatization (36). In spite of the absence of gross pathological changes, however, head injury in the monkeys was followed by a prominent decrease in lung compliance which appeared to be related to changes in alveolar surfactant and was prevented by pretreatment with dibenzyline (51). Electrical stimulation of the stellate ganglion caused a similar decrease in pulmonary compliance along with an elevation of the minimum surface tension of lung washings.

It has been well established that many general anesthetics protect against the central nervous system manifestations of oxygen toxicity (23, 24, 57, 66, 188, 210, 219, 227, 250, 394, 449, 494) and that this protection is also extended to the lungs (43, 44, 93, 94, 251, 253, 254). Bean and Zee (43) showed that the protective

influence of general anesthesia is not due simply to depression of general metabolism. By administration of dinitrophenol or L-thyronine or by direct tetanic stimulation of striated muscles, the metabolism of rats anesthetized with pentobarbital was increased to a level equal to or above that measured before anesthesia. The manifestations of CNS and pulmonary oxygen toxicity were not observed in the anesthetized rats after an exposure to about 6.0 atm of O_2 for a duration sufficient to cause severe convulsions and extensive lung damage in unanesthetized rats.

Some investigators have found that the severity of pulmonary oxygen poisoning could not be correlated with whether convulsions did or did not occur (251, 252, 325, 449, 463, 480). Although convulsions and lung damage usually occur coincidently, each of these toxic effects has been observed in the absence of the other (43, 46, 261, 449, 463, 480, 526). Prolonged exposure to convulsive levels of hyperoxia causes severe pulmonary pathology even when seizures are prevented by anesthesia (251, 252, 325, 480), and mild or brief convulsions are not always associated with significant lung damage (43, 46, 261, 526). It should be noted that acclimatization of rats to altitude greatly increases their pulmonary tolerance to 1.1 atm of O_2, but decreases their CNS tolerance to 7.0 atm of O_2 (81). These results do not imply that the pulmonary and CNS manifestations of oxygen poisoning are completely independent events, as has been suggested (81, 325, 449). Direct toxic effects of oxygen upon the lung and indirect effects originating in the central nervous system have both been conclusively established as mechanisms contributing to the total syndrome of pulmonary oxygen poisoning. The relative importance of direct and indirect factors should be expected to vary with species (221), at different levels of hyperoxia and under the influence of agents which modify the rate of development of oxygen poisoning itself.

Hypophyseal-adrenocortical interaction

Hypophysectomy of rats before repeated short exposures to 5.8–7.1 atm of O_2 provided marked protection against the pulmonary effects of oxygen toxicity (25, 37, 104). Pulmonary damage in hypophysectomized rats was distinctly less severe and mortality was lower than that found in normal rats after equal or shorter durations of exposure. Protected rats had delayed onset, lower incidence and decreased severity of convulsions. The protective action of hypophysectomy appears to be partially counteracted by administration of adrenocorticotrophic hormone (25), and posterior pituitary extract also enhances the toxic effects of a 30-min exposure to 6.0 atm of O_2 in normal rats (102). The observation that lung damage and mortality are greatly reduced in hypophysectomized rats exposed to 0.90–0.98 atm of O_2 for 70 hr (42) indicates that a retarding influence upon convulsions is not essential for the protection afforded by hypophysectomy. The harmful effects of exogenous adrenocorticotrophic hormone at subconvulsive levels of hyperoxia are manifested by increased hyaline membrane formation in guinea pigs (90) and aggravation of the pulmonary lesions in rabbits (328) exposed to 0.80–1.0 atm of O_2.

Significant changes in pituitary histological structure could not be detected

with the light microscope after brief, single exposures of rats to 5.0 atm of O_2 (34) or repeated exposures to 6.0 atm of O_2 which produced a low incidence of convulsions and pulmonary symptoms (146). In rats exposed to 0.5 atm of O_2 for 7 weeks, however, examination of the anterior pituitary with the electron microscope showed no changes at 1 and 5 weeks but ultrastructural evidence of secretory release from an increased number of adrenocorticotrophic cells at 7 weeks (335, 490). Interpretation of the findings on the longest exposure is complicated by the fact that the rats were housed in a noisy metal chamber and those exposed to oxygen for the full 7 weeks were subjected to a severe noise stress about 15 to 20 min prior to sacrifice. Other variables considered as conceivably influencing endrocrine function during the long exposure to a low level of hyperoxia included seasonal variations, age, temperature and humidity (490).

A major part of the protective influence of hypophysectomy against pulmonary oxygen effects can be attributed to the reduction of adrenocortical activity. Adrenalectomy lengthened survival time and decreased lung changes in rats breathing about 1.0 atm of O_2 (452). Rats (39, 180, 183, 470, 473) and mice (181, 182) that were adrenalectomized before exposure to 6.0–6.4 atm of O_2 had delayed onset and decreased severity of convulsions, reduced or delayed pulmonary damage and increased survival times. Isolation of the adrenal circulation *in situ* with circular ligatures decreased the degree of lung pathology and prolonged the survival of dogs breathing oxygen at 6.0 atm (205). Conversely, administration of cortisone enhanced the development of pulmonary oxygen poisoning in mice (92, 504), rats (42, 452) and rabbits (328) exposed to 0.80–1.0 atm of O_2 and counteracted in large degree the protective effect of hypophysectomy (42). Low doses of cortisone (180), hydrocortisone (473) or adrenal cortical extract (180, 470, 473) reversed most of the increased pulmonary and CNS oxygen tolerance afforded by adrenalectomy in rats exposed to 6.0 atm of O_2. Administration of deoxycorticosterone decreased tolerance to 6.0 atm of O_2 in normal rats, but had equivocal effects in adrenalectomized rats (470, 473). Oxygen tolerance was increased to a similar degree in adrenalectomized rats maintained on either water or saline (473). On the basis of these results, Taylor (473) concluded that alterations in water and electrolyte metabolism were not responsible for the protective influence of adrenalectomy. He suggested that reduced cerebral blood flow and cellular oxygen consumption may contribute to the increased oxygen tolerance of adrenalectomized animals.

In contrast to reversal of the "protective" effects of adrenalectomy by administration of low doses of cortisone and adrenal cortical extract, the use of high and unphysiological doses of the same substances either had no significant effect or appeared to further delay the development of oxygen intoxication in adrenalectomized rats (180, 470, 473). In adrenalectomized mice exposed to 6.0 atm of O_2, however, survival time was progressively decreased by increasing doses of cortisone and adrenal cortical extract (181, 182). Gerschman *et al.* (180) have discussed several possible mechanisms for the non-uniform action of adrenocortical hormones.

Histological and biochemical studies have provided additional evidence for

hypophyseal-adrenocortical interaction in the development of the overall pulmonary effects of oxygen poisoning. Single and repeated exposures of rats to O_2 partial pressures ranging from about 2.8 to 7.1 atm caused adrenal changes which were roughly proportional to the duration and number of exposures (38, 146). The adrenals were larger and heavier after exposure to oxygen, particularly in the rats that had had numerous seizures. The zona fasciculata was thickened with cellular hypertrophy and reduction of lipid content. The same changes were present to a lesser degree in the zona reticularis, while the zona glomerulosa was not changed. Rats exposed to 2.0–3.0 atm of O_2 for 3 to 4 hr had a decrease in adrenal ascorbic acid content (174). However, exposure to 6.0–7.0 atm of air for 30 min produced a similar decrease in ascorbic acid which was attributed to excitement of the rats with insufficient time for stabilization. Repeated exposures of mice to 3.4 atm of O_2 for 30 min caused no overt signs of toxicity and no significant change in the ratio of adrenal weight to body weight (450).

Ultrastructural changes in adrenal cortical cells and severe depletion of adrenocortical lipid content were produced in rats by either a 1-hr exposure to 2.0 atm of O_2 or infusion of hydrogen peroxide into the adrenal circulation (405a). Mitochondria were increased in number and enlarged with a ballooning degeneration and frequent rupture of their membranes. Similar, but much less severe, alterations were found when intact adrenals were incubated in oxygen at 4.0 atm for 1 hr. After the oxygen exposure at 2.0 atm, reversal and repair of the mitochondrial changes were initiated within 2 hr, becoming essentially complete within 18 hr.

The production of severe pulmonary oxygen poisoning in rats (174) and guinea pigs (428, 444) by prolonged exposure to 0.95–1.0 atm of O_2 was also associated with a decrease in adrenal ascorbic acid. The rats appeared to have an initial fall in ascorbic acid at 3 to 12 hr of exposure due to an alarm reaction. This was followed by a regenerative rise above normal at about 21 hr and a terminal fall as poisoning became severe after 48 to 72 hr of exposure (174). Accordingly, the decrease in adrenal ascorbic acid observed in rats after only 2 hr of O_2 breathing at 1.0 atm (8) may have been caused by an alarm reaction.

Monkeys exposed to about 0.5 atm of O_2 for 22 days had a progressive increase in adrenal weight to a level about 76 % above the control value on the 22nd day (488). Data obtained from rats exposed to about 0.48–0.61 atm of O_2 for up to 64 days were equivocal, but suggested that a mild pituitary-adrenocortical response to hyperoxia was followed by adaptation and return to the control level of function (22, 85, 241, 335, 490). In rats (390) and monkeys (488) exposed to 0.26–0.33 atm of O_2 for 30 to 32 days, there was no evidence of a stress response except for an initial, transient elevation of plasma corticosterone in the rats.

Direct measurements of adrenocortical hormones or their metabolites in the blood and urine of intact animals during exposure to about 1.0 atm of O_2 have yielded contradictory results. Hale *et al.* (214) found in normal, resting men that 4 hr of oxygen breathing was associated with a slight decrease in plasma cortisol, and no significant change in the excretion of urinary 17-hydroxycorticosteroids.

In contrast to this, the concentration of 17-hydroxycorticosteroids in adrenal vein blood of anesthetized dogs was increased by 69 to 95% after 2 hr of oxygen breathing (333). Serum corticosterone levels in rats exposed to 0.92–0.99 atm of O_2 were progressively and significantly elevated at 2 and 3 days of exposure (240, 241). Incubates of adrenal glands obtained from the rats exposed for 3 days produced corticosterone at almost twice the normal rate (241). Serum or adrenal gland samples were not collected after 4 days of exposure when most of the rats were dying.

Most of the findings obtained from small animals (174, 240, 241, 428, 444) and men (214) during oxygen breathing at about 1.0 atm suggest that the adrenocortical response to this level of hyperoxia is not significant until after at least 24 hr of exposure and then increases progressively in parallel with the severity of pulmonary oxygen poisoning. Of the two studies which showed an earlier adrenocortical response to 1.0 atm of O_2, Marotta *et al.* (333) suggested that their use of pentobarbital anesthesia in dogs could have resulted in hypercapnia and acidosis which affected adrenocortical function, while the results of the second study, in rats, may have been influenced by an alarm reaction during the first 2 hr of exposure (8). The existing discrepancies should be resolved by additional experiments carefully designed to study the rate of development of adrenocortical response to oxygen breathing at 1.0 atm in the absence of other influencing factors.

The influence of exposure to oxygen upon adrenocortical activity is more definite at greater than atmospheric pressures. Igarashi *et al.* (246) found that the content of corticosterone was significantly increased in both venous blood and adrenal gland homogenates obtained from normal rats after 30 min of O_2 breathing at 3.0 atm. In hypophysectomized rats exposed to the same conditions, however, the corticosterone content of blood and adrenal homogenates was slightly decreased. The apparent inhibitory effect of oxygen on formation of corticosterone was confirmed with exposures *in vitro* of adrenal gland slices from rats and rabbits. These data, along with the known protective influence of hypophysectomy against oxygen toxicity (25, 37, 42, 104), and evidence obtained from studies of adrenal cell ultrastructure (405a), suggest that adrenocortical stimulation during exposure to hyperoxia is predominantly indirect, as by central carbon dioxide accumulation or an action upon the hypothalamus or pituitary. The observation that the adrenal cortex of immature rats, which was not affected by 48 hr of exposure to 0.95 atm of O_2, could be stimulated by exogenous adrenocorticotrophic hormone is consistent with such a mechanism (483).

Sympatho-adrenomedullary interaction

Many of the studies that were reviewed in the foregoing discussion of central nervous system influences upon pulmonary oxygen poisoning indicate that sympatho-adrenomedullary pathways are involved in the transmission of central effects of oxygen to the lungs. Additional evidence for such involvement has been provided by the observation that bilateral adrenal medullectomy decreases the pulmonary damage and mortality of rats (365, 371, 425) and mice (181, 182)

exposed to 3.0–6.0 atm of O_2. In dogs breathing O_2 at 6.0 atm, the protection against pulmonary oxygen poisoning afforded by isolation of the adrenal circulation is enhanced by section of the splanchnic nerves (205). Studied as an indication of increased sympathetic activity, the size of nucleoli was found to be increased in the stellate ganglion and adrenal medulla of rats after 4 to 8 weeks of daily exposures to 6.0 atm of O_2 for durations adjusted to give a low incidence of convulsions and pulmonary symptoms (146). Administration of epinephrine enhances the development of pulmonary oxygen poisoning in rats breathing O_2 at 1.0 atm (452) and augments both pulmonary and CNS effects of oxygen toxicity in rats (39, 40, 102, 337, 473) and mice (178, 181) exposed to higher oxygen pressures. Epinephrine also partially or completely reverses the protection against oxygen effects afforded by adrenal medullectomy (425) or total adrenalectomy in rats (39, 180, 473) and mice (181) exposed to 3.0–6.4 atm of O_2. Exogenous norepinephrine shortens the survival time of mice breathing oxygen at 6.0 atm (178, 181) and appears to enhance slightly the overall pulmonary effects of oxygen poisoning in rats exposed to 4.0 atm of O_2 (332), but its effects are not as consistent as those of epinephrine.

The interaction of indirect sympatho-adrenomedullary factors with the direct toxic effects of oxygen upon the lung has been further substantiated by the demonstration that many adrenergic blocking drugs have a protective influence against effects of pulmonary oxygen poisoning. Although they had no effect on the incidence and severity of convulsions, both dibenamine and SKF 501 decreased pulmonary pathology and mortality in rats breathing O_2 at about 6.4 atm (262) and prevented the lung damage that accompanied drug-induced seizures (45). The pulmonary edema, hemorrhage, congestion and atelectasis, as well as the concurrent decrease in pulmonary compliance, which occurred after head trauma in rats was prevented or decreased by prior administration of dibenzyline or SKF 501 (36, 50). Dibenzyline also provided significant protection against the composite effects of pulmonary oxygen poisoning in rats exposed to O_2 pressures ranging from 3.0 to 6.4 atm (261, 327, 365, 372). The influences on the lungs were accompanied by protection against CNS oxygen poisoning in one group of rats (365, 372), but not in another (261). Survival times of normal, adrenalectomized and demedullated mice exposed to 6.0 atm of O_2, which were increased by dibenzyline when given alone (178, 181, 182), were not affected when the same drug was administered with epinephrine or norepinephrine (178, 181). Dehydrobenzoperidol (Droperidol) provided considerable pulmonary and less effective CNS protection in rats exposed to 5.0 atm of O_2 for 30 min (365). Both hydergine and phentolamine appeared to decrease pulmonary edema with little or no effect upon the survival times of rats breathing O_2 at 4.0 atm (332). In another study, the onset of convulsions in hyperoxic rats was delayed by phenotolamine and by propranolol (337).

The ganglionic blocking drugs, hexamethonium and tetraethylammonium, have also been found to provide significant protection against the toxic effects of oxygen. Hexamethonium decreased lung damage, mortality and the incidence of convulsions in rats exposed to 6.4 atm of O_2 (261), but it had no detectable

effect upon the onset of seizures in mice breathing O_2 at about 4.4 atm (378). Administration of tetraethylammonium decreased the pulmonary pathology in guinea pigs (203) and rats (261) exposed to 1.0 and 6.4 atm of O_2, respectively. Although the same drug also protected the rats against convulsions, it had no effect upon mortality (261). The lung damage associated with head trauma in rats was prevented or ameliorated by prior administration of hexamethonium, but not by tetraethylammonium (36).

Chlorpromazine decreased the evidence of pulmonary pathology caused by exposure of rats (171), rabbits (328) and guinea pigs (203) to 0.8–1.0 atm of O_2, with the exception of one study in rats (338) where it apparently had no effect. Chlorpromazine also reduced the toxic effects of O_2 pressures ranging from 4.4 to 6.8 atm upon the lungs (28, 178, 365, 495) as well as the central nervous system (28, 365, 378, 495) of rats and mice. Reserpine provided similar protection in rats exposed to 5.0–6.8 atm of O_2 (27, 28, 365, 373). The lung changes associated with drug-induced convulsions (45) and head trauma (36) in rats were also blocked by chlorpromazine. Bean (28) attributed the protective influence of both reserpine and chlorpromazine to hypothalamic suppression with diminution of the influence of the adrenal cortex and the sympathetic nervous system upon the toxic process. Additional potential mechanisms included the depletion of catecholamine stores by reserpine (365, 373) and the adrenolytic action of chlorpromazine (28).

The effects of other autonomic drugs upon oxygen poisoning are generally consistent with exaggeration of indirect influences by the sympathetic nervous system and antagonism of such action by the parasympathetic nervous system. Thus, survival time of rats exposed to 3.7 atm of O_2 was decreased by administration of dextroamphetamine and dihydroxyphenylalanine (391, 522). In rats breathing O_2 at about 5.4 atm, the time for onset of convulsions was hastened by methamphetamine and delayed by carbachol (60). Both carbachol and methacholine diminished pulmonary changes, delayed convulsions and increased the survival time of mice exposed to 6.0 atm of O_2 (178, 181, 185). The protective influence of methacholine was reversed by prior injection of atropine (181, 185). Administration of atropine alone markedly enhanced hyaline membrane formation in mice breathing O_2 at 1.0 atm (92). It also decreased survival time in mice (181, 185) and increased the severity of convulsions in cats (394) exposed to 6.0–7.1 atm of O_2, but it had no apparent effect upon pulmonary pathology in guinea pigs exposed to 5.5 atm of O_2 (205). The observation that the sympathomimetic drugs tryptamine and oxytyramine increased survival time in mice exposed to 6.0 atm of O_2 (178, 179, 181, 185) was not consistent with sympathetic enhancement of oxygen toxicity. Furthermore, the protective actions of tryptamine and methacholine were additive (178), and tryptamine had no significant effect upon hyaline membrane formation in mice breathing O_2 at 1.0 atm (92). In rats exposed to 5.4 atm of O_2, scopolamine increased the time for onset of convulsions and physostigmine had no apparent effect (60). These latter results indicate that the effects of some autonomic drugs upon oxygen poisoning do not fall into a simple pattern of sympathetic enhancement and parasympathetic retardation of direct oxygen toxicity.

Studies of the effects of vagotomy on the development of oxygen toxicity have also provided a complex pattern of results. Unilateral cervical vagotomy in guinea pigs before a 6- to 8-hr exposure to almost 1.0 atm of O_2 reduced the pulmonary pathology in both lungs, with the operated side receiving the greater protection (198). In dogs breathing O_2 at 6.0 atm, pulmonary changes were decreased by vagotomy before exposure and were increased when the same procedure was performed during the development of convulsions (205). An apparent protective influence of vagotomy is not consistent with parasympathetic antagonism of the toxic effects of oxygen upon the lungs. Critical evaluation of the evidence is difficult because the work in guinea pigs was described in a preliminary communication (198) and only two dogs were vagotomized prior to oxygen exposure (205). Furthermore, Groshikov and Sorokin (205) cited an older, generally unavailable Russian report which indicated that bilateral block or section of the vagus nerve exaggerated the pathological effects of pulmonary oxygen poisoning. In addition to their function as an efferent parasympathetic pathway, the afferent vagal pathways evoke respiratory reflexes (517). Influences of such reflexes upon pulmonary oxygen poisoning in different animal species are not known (517).

In contrast to the observations reviewed above, bilateral cervical vagotomy in newborn rabbits greatly increased the lung damage caused by a 3-hr exposure to 6.0 atm of O_2 (441). Exposure of the same experimental model to O_2-enriched atmospheres at 1.0 atm showed that the potentiating interaction between hyperoxia and vagotomy became progressively worse with increasing percentages of oxygen (436, 443). In such studies of the effects of various oxygen mixtures at total pressures ranging up to 3.0 atm, the degree of lung damage in vagotomized newborn rabbits was proportional to the fractional composition of oxygen and not to the inspired P_{O_2} (437, 440). Air at 3.0 atm (P_{O_2} = 0.63 atm) had about half the influence upon the lungs of animals subjected to vagotomy and exposed to air at 1.0 atm (P_{O_2} = 0.21 atm) and about one-seventh the effect of 60% O_2 at 1.0 atm (P_{O_2} = 0.60 atm). When the nitrogen in the inspired mixture was replaced by other inert gases, the composite effects of vagotomy and oxygen upon the lungs were greatly enhanced by a helium-oxygen mixture and retarded by sulfur hexafluoride and oxygen (445). These results suggest that the interaction between bilateral vagotomy and hyperoxia was due, not to an influence upon toxicity, but to an increased rate of alveolar atelectasis, possibly related to bronchiolar tone and secretions, paralysis of laryngeal muscles and the ventilatory abnormalities which follow vagotomy.

The occurrence of stimulation of the sympathetic nervous system by hyperoxia is suggested by the observation that the norepinephrine content of brainstem, adrenal gland and myocardium, as well as adrenal epinephrine content, are all decreased in rats exposed to 6.1 atm of O_2 for 15 to 30 min (94). Pretreatment with barbiturates prevents the catecholamine losses and markedly decreases lung damage, particularly the vascular changes. In mice breathing O_2 at pressures ranging from 1.0 to 6.0 atm, brain norepinephrine content decreased progressively with duration of exposure, and the rate of depletion was proportional to the inspired P_{O_2} (149). Brain norepinephrine levels were significantly

decreased in one strain of rats after a 1- to 2-hr exposure to 6.0 atm of O_2 (213), but not in another strain exposed to 4.95 atm of O_2 for 1 hr (74). Rabbits breathing O_2 at 6.0 atm appeared to have a slight decrease in the norepinephrine contents of brain and adrenals before and during convulsions, with a return to normal in the terminal stages of exposure (189). Adrenal epinephrine content increases before convulsions and then decreases during and after the seizures.

The sympatho-adrenomedullary response to hyperoxia has been studied in rats exposed to O_2 pressures ranging from 0.5 to 5.9 atm for durations of 49 days to 16 min, respectively (122, 241, 242, 490). Severe exposures to the highest oxygen pressures, especially when accompanied by toxic reactions, are associated with marked sympathetic stimulation characterized by decreased hypothalamic norepinephrine, decreased adrenal epinephrine and increased serum concentrations of both catecholamines. Prior to the onset of symptoms at inspired P_{O_2} levels higher than 2.0 atm, the degree of sympathetic stimulation is moderate. Exposure to 0.91 atm of O_2 is associated with a progressive decrease in urinary norepinephrine excretion starting within the 1st day and a significant increase in epinephrine excretion on the 3rd day. Multi-day exposures to O_2 pressures of 0.50–0.61 atm produces a sustained decrease in norepinephrine excretion and either no change in epinephrine excretion (122, 242) or a marked increase followed by a return to normal (490). In men breathing O_2 at 1.0 atm for 4 hr, urinary excretion of both norepinephrine and epinephrine was significantly decreased (214). Reduced norepinephrine excretion during prolonged exposure to hyperoxia may be related to inactivity in response to the early stages of oxygen poisoning, while a subsequent increase in epinephrine excretion could be attributed to the development of a more severe toxic reaction.

Novelli *et al.* (365) have proposed the hypothesis that both the pulmonary and CNS lesions of oxygen toxicity are the direct result of adrenal and sympathetic hyperactivity. Although adrenal and sympathetic factors are undoubtedly involved in the pathogenesis of the syndrome of pulmonary oxygen poisoning, the existence of a direct toxic effect of oxygen upon the lungs has been well established (110, 343, 388, 520, 540). It therefore cannot be ignored as the primary toxic event. With this clearly in mind, Houlihan and his associates (236–239, 242) have suggested that the oxidative cyclization of epinephrine to highly reactive indoles such as adrenochrome and adrenolutin may contribute to the development ot the direct toxic effects of oxygen upon the lungs and brain. Spectrophotometric and spectrofluorometric analysis of plasma and lung extracts from rats exposed to 5.0 atm of O_2 for 30 min showed an increased conversion of epinephrine to adrenochrome, adrenolutin, soluble melanin and their intermediates. Sulfhydryl donors blocked this conversion and delayed the symptoms of oxygen toxicity. In support of the proposed mechanism, a 3- to 4-fold increase in the adrenochrome content of brain and adrenals was found in rabbits that were severely poisoned by prolonged exposure to 3.5 or 6.0 atm of O_2 (189). Administration of adrenochrome monosemicarbazone hastened the onset of convulsions in mice exposed to about 3.5 atm of O_2 (281). Aminochromes were found in the blood of patients with a variety of psychiatric disorders (5a). In a

summary of his findings, many of which are still unpublished, Houlihan (236) stated that an increase in the percentage of epinephrine undergoing oxidative cyclization could be attributed to the action of an enzyme which responds to severe stress and is absent in the immature animal. He further suggested that an enhanced production of highly reactive indoles could have manifestations such as convulsions, coma, red blood cell hemolysis and pulmonary damage. Confirmation of this interesting hypothesis would provide a mechanism for the observed toxic interaction between epinephrine and oxygen poisoning.

Influence of thyroid activity

Involvement of the thyroid gland in modifying the development of oxygen intoxication was first reported by Campbell (102, 104) when he found in rats that the toxic effects of a 30-min exposure to 6.0 atm of O_2 were enhanced by pretreatment with thyroxin and delayed by thyroidectomy. These early observations have been generally confirmed and extended by more recent work. In both intact and adrenalectomized rats exposed to similar conditions, thyroid extract hastens convulsions and increases lung damage (470, 473). Administration of thyroid extract has the same effect in rats (468), rabbits (468) and cats (188) breathing O_2 at pressures ranging from 4.0 to 8.1 atm, but thyroidectomy provides significant protection only for the cats. In three groups of rats given no drug, desiccated thyroid or propylthiouracil prior to a 1-hr exposure to 5.5 atm of O_2, mortality was directly correlated with oxygen consumption (207). The survival rates of hyperthyroid, euthyroid and hypothyroid rats were 29%, 56% and 80%, respectively. Administration of desiccated thyroid or thyroxin to both normal and hypophysectomized rats before and during exposure to 0.95–1.0 atm of O_2 showed that the protection afforded against pulmonary oxygen poisoning by hypophysectomy was due in part to elimination of thyrotropin as well as to elimination of ACTH (35, 454). Experimental groups ranked in order of increasing survival times were: normal rats given thyroid, normal rats given no thyroid, hypophysectomized rats given thyroid and hypophysectomized rats given no thyroid.

Many investigators have suggested that susceptibility to oxygen poisoning can be influenced by the rate of cellular metabolism (179, 180, 184, 206, 400, 464). In hypothermic rats (206) and hibernating ground squirrels (400) exposed, respectively, to 5.2 and 6.0 atm of O_2, mortality was closely correlated with oxygen consumption. The observation of similar correlations between oxygen tolerance and changes in oxygen consumption produced by alteration of thyroid function in rats (207) and cats (188) suggests that thyroid influences in oxygen poisoning may also be due to changes in cellular metabolism.

An alternate, central mechanism of thyroid action was proposed by Bean and Zee (43). These investigators found that administration of pentobarbital along with L-thyronine or L-thyroxine to rats before exposure to 4.8–5.1 atm of O_2 blocked the potentiating effect of the thyroid hormones on pulmonary and CNS oxygen poisoning, but retained the protective influence of pentobarbital. This occurred in spite of the fact that the metabolic depression normally caused by

anesthesia was reversed by the thyroid hormones. On the basis of these results, the authors concluded that both pentobarbital and thyroid hormones have a central mechanism of action, probably at the hypothalamic and sympathetic levels. This conclusion does not appear to be justified in the case of thyroid hormone because both its potentiating influence on oxygen toxicity and its stimulating effect on cellular metabolism were blocked by pentobarbital anesthesia.

The results of experiments designed to measure thyroid activity in hyperoxic animals are generally consistent with the conclusion that thyroid function is stimulated by increased oxygen pressures. Thyroid hypertrophy is commonly observed in cats repeatedly exposed to 6.0–8.0 atm of O_2 (187). Thyroid weight is also significantly increased in rats after 4 to 8 weeks of daily exposure to 6.0 atm of O_2 for durations long enough to give a low incidence of convulsions and respiratory symptoms (146). After similar exposures for only 4 to 5 days, thyroid weight was found to be decreased, but uptake of radioactive iodine by the thyroid was increased (451). The discordant results of the two studies were attributed to a dual action of hyperoxia on thyroid function consisting of an early thyroid involution induced by nonspecific stress followed by a dominant, specific stimulating effect of oxygen. It was also pointed out that uptake of iodine should be expected to respond to thyroid stimulation more quickly than changes in weight could occur.

Other indications of an influence of hyperoxia upon thyroid function are an increase in the thyroid uptake of radioactive phosphorus and histological evidence of thyroid hyperactivity in rats exposed to 0.95 atm of O_2 for 48 hr (482, 483). On the other hand, serum protein-bound iodine decreased progressively throughout a 3-day exposure of rats to about 1.0 atm of O_2 (153, 154). Although this result suggested that thyroid activity was decreased by hyperoxia, it is possible that thyroid hyperactivity was present in conjunction with increased uncoupling of thyroxine from carrier proteins. Serum protein-bound iodine was not changed in rats exposed to 0.33 atm of O_2 for 14 days (152, 153).

Influence of sex hormones

Bruns and Shields (90) have shown that sex hormones may also play a role in the pathogenesis of pulmonary oxygen toxicity. Administration of chorionic gonadotropin with progesterone to male or female guinea pigs just before exposure to 0.98 atm of O_2 caused severe disruption of the pulmonary vasculature and a marked decrease in survival time. Administration of estrogen to female guinea pigs just before exposure had a similar effect, whereas the survival time and lung pathology of male guinea pigs given estrogen resembled those of animals that had received no hormones before prolonged oxygen breathing. Female guinea pigs also had no change in survival time when they were given either estrogen or chorionic gonadotropin with progesterone and exposed to oxygen after a 24-hr delay. The physiologic significance of these results is obscured because only large doses of exogenous hormones were administered.

Role of pulmonary surfactant

The role of surface active phenomena in the pathogenesis of pulmonary oxygen poisoning has received increasing attention within the past decade. The studies summarized in table 4 are limited to those in which pulmonary surface activity was determined directly, either by measuring the surface tension of pulmonary extracts or by observing the stability of bubbles squeezed from pulmonary tissues. Other workers have estimated surface activity indirectly by comparison of air and saline pressure-volume curves (52, 87), special analysis of the deflation portion of the air pressure-volume curve (421), measuring the lecithin content of a tracheal transudate obtained by saline perfusion of the pulmonary vasculature (52), staining the autofluorescent alveolar lining layer (119, 211, 521), and measuring the uptake of radioactive palmitate into lung phospholipids (323, 359). The majority of investigators have found that surface activity of material lining the alveoli is reduced by exposure to oxygen at increased partial pressures (table 4) (52, 421, 521). However, other workers have found no significant reduction of surface activity, even in the presence of severe pulmonary oxygen intoxication (table 4) (87).

Comparison of measurements of alveolar surfactant in different laboratories is complicated by failure to adequately describe procedural details and by the use of non-uniform methods for the extraction, preparation and analysis of surface active material and the actual measurement of surface tension (1a, 191). In addition, the many interacting factors which constitute the syndrome of pulmonary oxygen poisoning should be expected to have variable influences upon pulmonary surface activity in different species and individuals (1a). It is especially likely that animals breathing oxygen at greater than atmospheric pressures will die from CNS oxygen intoxication before pulmonary surfactant function is significantly affected (247a).

Pattle (382) has pointed out many of the potential sources of erroneous conclusions regarding oxygen effects upon the characteristics of the alveolar surface material. It has been shown that atelectasis (303, 304) and edema (427), both common findings in oxygen-poisoned lungs, decrease the surface activity of pulmonary extracts. Addition of large quantities of blood to the extract can produce similar results (211), but it is unlikely that the degree of hemorrhage caused by pulmonary oxygen toxicity significantly affects surface activity (191, 211, 258). McSherry *et al.* (324) have found that pulmonary surfactant in rabbits is significantly reduced by rapid decompression from 3.0 to 1.0 atm in less than 3 min after brief exposures to either 3.0 or 0.20 atm of O_2 at increased ambient pressure. However, decompression of rats (359), guinea pigs and dogs (247) from 3.0 to 1.0 atm was not accompanied by changes in pulmonary surface activity.

Potential mechanisms of actual reduction of surfactant concentration in pulmonary oxygen poisoning must be considered to include direct inactivation, the formation of inhibitory substances, decreased synthesis and physical disruption of the alveolar lining film by pulmonary edema (52, 99, 119, 191, 211, 258, 324, 347). Little evidence for or against the direct oxidation of pulmonary surfactant

TABLE 4

Effect of prolonged exposure to hyperoxia on pulmonary surface activity

Species	Number	Oxygen Partial Pressure	Exposure Duration	Method of Surfactant Extraction	Minimum Surface Tension	Reference
		atm	*hr*			
Mouse	—*	0.9	24–148	Endobronchial lavage	Increased	1a
				Minced lung	No change	1a
				Bubble stability†	No change	1a
Mouse	3	1.0	108–192	Bubble stability†	No change†	383
Rat	34	1.0	118 ± 20.4	Endobronchial lavage (saline foam-fractionation)	No change	191
				Minced lung	Increased	191
Rat	20	1.0–1.2	24–48	Saline perfusion	No change	77
Rat	24	2.0	5–18	Minced lung	Increased	269
Rat	—	3.0	1–6	Minced lung	Increased	505
Rat	8	3.0	3.5 ± 1.5	Bubble stability†	No change†	359
Rat	7	5.0	1.25	Endobronchial lavage plus minced lung	Increased	258
Rat	7	8.0	0.33–0.75	Saline perfusion	Increased	77
Guinea pig	24	0.9–1.0	3–96	Minced lung	No change	167
Guinea pig	6	3.0	1–4	Homogenized lung	No change	247
Guinea pig	—	3.0	1–6	Minced lung	Increased	505
Rabbit	9	1.0	70.7 ± 21.8	Endobronchial lavage (saline foam-fractionation)	Increased	191
				Minced lung	Increased	191
Rabbit	30	1.0	72–96	Minced lung	Increased	119, 211
Rabbit	3	1.0	72–96	Bubble stability†	Unstable†	119, 211
Rabbit	9	2.0	1–5	Minced lung	Increased	323
Rabbit	5	2.0	1.0 × 9	Minced lung	No change	323
Rabbit	5	2.0	2.0 × 9	Minced lung	Increase	323
Rabbit	10	2.0	3.0 × 9	Minced lung	No change	323
Rabbit	9	3.0	1–5	Minced lung	No change	323
Rabbit	10	3.0	1.5 × 9	Minced lung	Increased	324
Rabbit	11	4.0	2.7 ± 0.1	Minced lung	Increased	325
Rabbit	7	4.0	4	Minced lung	Increased	324
Cat	9	1.0	83.3 ± 22.3	Endobronchial lavage (saline foam-fractionation)	Increased	191
				Minced lung	Increased	191
Dog	8	0.7–1.0	44.5–52	Endobronchial lavage	Increased	347
Dog	16	1.0	12	Minced lung	Increased	351
Dog	16	1.0	6–30	Minced lung	Increased	301, 345
Dog	10	1.0	55.4	Homogenized lung	Increased	247a
Dog	8	1.0	61–79	Saline perfusion	Increased	99
Dog	5	1.0	63–79	Minced lung	Increased	99
Dog	10	2.0	23.4	Homogenized lung	Increased	247a
Dog	13	3.0	1–4	Homogenized lung	No change	247
Dog	10	3.0	5.7	Homogenized lung	No change	247a
Dog	10	4.0	2.8	Homogenized lung	No change	247a
Dog	17	3.0	1.0 × 120	Minced lung	Increased	478a
Lamb	9	0.8–1.0	9–96	Minced lung	No change	129

* Information not given.

† Refers to rate of collapse of bubbles squeezed from pulmonary tissues.

has been obtained. Measurements made after prolonged exposure to about 1.0 atm of O_2 suggest that an active inhibitory substance is present in rabbit lungs (211) and dog lungs (301) or blood (99). The type II alveolar epithelial cells have been associated with the production of pulmonary surfactant (91, 276), and degenerative changes in the lamellar bodies of these cells were found after exposure to hyperoxia (347, 351, 484, 532). These observations suggest that multiple factors influence the effects of oxygen toxicity upon the properties of the surface active lining film.

The effect of pulmonary oxygen poisoning upon the lipid composition of pulmonary extracts has also been studied with inconsistent results. The lipid composition of the supernatant from minced lung extracts of guinea pigs was not changed after 96 hr of exposure of the animals to 0.9–1.0 atm of O_2, even in the presence of severe pulmonary edema (167). On the other hand, significant changes were observed in the lipids of pulmonary extracts obtained from dogs by endobronchial lavage after 44.5 to 52 hr of exposure to 0.7–1.0 atm of O_2 (347). The total phospholipid content of the lung washings was relatively decreased. In the lecithin fraction, the proportion of palmitic acid was consistently reduced with a concomitant reduction of total saturated fatty acids. The appearance of pulmonary edema and the entry of plasma into the alveoli were accompanied by a further decrease in palmitic acid, an increase in arachidonic acid and increases in the total lipid and protein contents of the endobronchial wash. Similar changes in the lipid composition of pulmonary extracts were also found in anesthetized dogs after exposure to 3.0 atm of O_2 for 5 to 10 hr (381). Morgan *et al.* (347) attributed the differences between their results and those of Fujiwara *et al.* (167) to the probability that pulmonary extracts obtained by lung mincing reflected principally the lipid composition of whole lung, whereas those obtained by endobronchial lavage were more representative of changes in the alveolar lining material. In agreement with this proposal, the production of severe pulmonary oxygen poisoning in mice was associated with an increase in the minimum surface tension of extracts obtained by endobronchial lavage, while the surface activity of minced lung extracts was not significantly changed (1a). However, the opposite results were obtained in rats (191).

McSherry and Gilder (323) attempted to correlate reduction of pulmonary surfactant in rabbits with varying durations of exposure to 2.0 or 3.0 atm of O_2. Measurements of the surface activity of minced lung extracts were technically unsatisfactory and yielded inconsistent results. However, continuous exposure to either 2.0 or 3.0 atm of O_2 for 1 to 5 hr was accompanied by a progressive decrease in the uptake of radioactive palmitate into pulmonary phospholipids. Significant, objective evidence of pulmonary edema was found only after 5 hr of O_2 breathing at 3.0 atm. Rate of incorporation of labeled palmitate into pulmonary phospholipids was also markedly reduced in rabbits after a 72-hr exposure to 0.98 atm of O_2 (410). In contrast to these observations in rabbits, the uptake of radioactive palmitate into the phospholipids of rat lungs was increased after exposure to 3.0 atm of O_2 for a total of 5 hr (359). Pretreatment of rats with pentobarbital partially prevented the lung damage and reduction of surfactant caused by a 75-min exposure to 5.0 atm of O_2 (258).

As a summary of the many and diverse findings, it appears to be reasonably well established that the surface activity of the alveolar lining material is significantly decreased in the lungs of animals that are exposed to hyperoxia until death from pulmonary intoxication. Whether the reduction of pulmonary surfactant occurs as a direct effect of oxygen toxicity or only as a secondary consequence of the concomitant, adverse effects of pulmonary oxygen poisoning still remains to be determined. In either case, reduced surfactant function probably contributes to the pathological changes found in the lungs during the terminal stages of oxygen intoxication. It should be noted that pulmonary surfactant appears to be diminished or absent in animal species such as frogs, turtles and chickens, whose overall pulmonary oxygen tolerance exceeds that of mammals (342). The fluorescent layer lining the alveoli in frogs and chickens is also much less prominent than that in mammals (75).

Role of carbon dioxide

Addition of low, normally innocuous concentrations of carbon dioxide to the inspired gas potentiates the toxic effects of oxygen at partial pressures of 3.0 atm or more (24, 44, 190, 213, 227, 231, 235, 250–252, 260, 289, 326, 334, 336, 388, 394, 448, 464, 467, 477, 494, 496, 503, 522). Although most investigators have recognized an enhancement of CNS oxygen poisoning, the toxic effects of oxygen upon the lung also appear to be potentiated by increased carbon dioxide tensions (44, 250, 260, 326, 388, 467, 494, 522). The pulmonary damage produced in rats by exposure to about 3.0–7.0 atm of O_2 was increased by adding CO_2 at partial pressures ranging from 40 to 190 mm Hg to the inspired gas mixture (44, 250, 260, 326, 467, 494, 522), and a similar potentiating effect of carbon dioxide upon pulmonary oxygen intoxication has been observed in cats (388).

Bean and Zee (44) have attributed the detrimental effect of carbon dioxide upon pulmonary oxygen poisoning to the increased intensity of neurogenic factors associated with the concurrent potentiation of CNS oxygen intoxication by hypercapnia. In agreement with this concept, the lung damage in rats exposed to 4.0–7.0 atm of O_2 and 60 to 100 mm Hg of CO_2 was markedly decreased by pentobarbital anesthesia (44), urethane anesthesia (250) or by pretreatment with an adrenergic blocking drug (260). Stimulation of the adrenal cortex and medulla by prolonged exposure to low carbon dioxide tensions in atmospheric air has been reported (270, 271, 431, 489).

It has been proposed that the acceleration of CNS oxygen poisoning by increased partial pressures of carbon dioxide is due to cerebral vasodilatation and the resulting rise in brain oxygen tension (289). Average internal jugular P_{O_2} in four men increased from 76 mm Hg during O_2 breathing at 3.5 atm to 1000 mm Hg when CO_2 (about 53 mm Hg) was added to the inspired gas (289), and a rise in cerebral tissue P_{O_2} also occurred in rats when low concentrations of CO_2 were added to several atmospheres of inspired O_2 (29, 256). Since gross changes in carbon dioxide tension induce other central actions in addition to effects on cerebral blood flow, their composite influence upon pulmonary oxygen tolerance in extreme exposures is probably modified by the effect of carbon dioxide upon

intracellular pH and the progressive narcosis produced by increasing P_{CO_2} levels (334).

The narcotic influence of carbon dioxide has been cited by Bean and Zee (44) in order to explain the inhibition of oxygen convulsions by extreme tensions of inspired P_{CO_2} (334), and the concurrent protection against pulmonary damage was thought to stem from the resulting narcotic reduction of neurogenic factors which ordinarily would have been expected to exaggerate the effects of pulmonary oxygen poisoning. Thus, convulsions and lung damage in rats exposed to 3.0–7.0 atm of O_2 were enhanced by adding CO_2 at partial pressures of 40 to 190 mm Hg to the inspired gas (44, 250, 260, 326, 467, 494, 522), but they were prevented by further increasing the inspired P_{CO_2} to 300 mm Hg (44). Although they developed little or no obvious pulmonary damage, rats breathing the highest P_{CO_2} became comatose within the same duration of exposure that produced both convulsions and severe lung damage at the lower P_{CO_2} levels. In mice exposed to O_2 pressures ranging from 3.0 to 11.0 atm, the onset of convulsions was inhibited by inspired CO_2 tensions greater than 120 mm Hg (109, 334). However, elevation of inspired P_{CO_2} progressively decreased survival time at all partial pressures of oxygen (334). The interactions of hyperoxia and hypercapnia therefore hasten the development of fatal CNS oxygen intoxication even when convulsions are inhibited. These results are consistent with Bean's hypothesis that extreme levels of carbon dioxide suppress the sympathoadrenal stimulation induced by oxygen convulsions and limit the secondary pulmonary effects of oxygen poisoning.

The possible direct influences of carbon dioxide-induced changes in intracellular pH upon cellular oxygen toxicity have not been as extensively studied as the indirect effects. Stadie *et al.* (465) found that incubation of rat brain slices in about 8.0 atm of O_2 with CO_2 tensions exceeding 100 mm Hg produced toxic effects no more severe than those observed in 8.0 atm of O_2 alone. Perot and Stein (392) showed that onset of conduction block in isolated frog sciatic nerve exposed to about 12 atm of O_2 was hastened by simultaneous exposure to a P_{CO_2} of about 500 mm Hg, but this does not imply an effect upon oxygen poisoning itself. In contrast, exposure of cat ulnar nerve to similar conditions significantly delayed the onset of conduction block (393). It is probable that narcotic effects of such extremely high carbon dioxide tensions were superimposed upon the separate influences of change in intracellular pH and any toxic action of oxygen.

The influence of carbon dioxide in modifying the toxic effects of oxygen at atmospheric pressure is not as well established as its potentiating effect upon the toxicity of higher oxygen pressures. Ohlsson (367) found that pulmonary oxygen poisoning was enhanced in rabbits exposed to 0.8–0.9 atm of O_2 by the addition of 23 to 27 mm Hg of CO_2, but others have not confirmed this. Barach *et al.* (20) reported that 2 to 15 mm Hg of CO_2 did not alter survival time of rats exposed to about 1.0 atm of O_2. Carbon dioxide levels ranging from 30 to 90 mm Hg in O_2 at 1.0 atm slightly prolonged survival time and decreased lung damage in normal (127, 453) and hypophysectomized rats (453). Addition of 100 to 117 mm Hg of CO_2 to O_2 at 1.0 atm also protected against lung damage but significantly de-

creased survival time (127). The median survival time was only 82 min in mice breathing O_2 at 1.0 atm with an inspired P_{CO_2} of 200 to 229 mm Hg (334).

The available data do not permit definite conclusions regarding the interaction of hypercapnia and subconvulsive levels of hyperoxia. With the exception of the study by Ohlsson, the descriptions of experimental results have been limited to either preliminary reports or brief statements in papers not primarily concerned with the influence of hypercapnia on pulmonary oxygen intoxication. More detailed studies will be required in order to determine whether or not the potentiation of pulmonary oxygen poisoning by hypercapnia is related only to the augmentation of CNS oxygen toxicity or to other, more direct forms of interaction at the lung as well.

The role of endogenous carbon dioxide in the pathogenesis of oxygen poisoning has been the object of many studies (15, 23, 57, 101, 190, 292, 294, 435, 472, 475, 477). Gesell (190) pointed out that failure of hemoglobin reduction while breathing oxygen at high pressure impaired carbon dioxide transport and caused accumulation of carbon dioxide in the tissues. Gesell further proposed that this carbon dioxide retention sensitized the organism to exogenous carbon dioxide and contributed to the development of oxygen convulsions. Almost all subsequent investigators have confirmed that oxygen breathing does indeed result in accumulation of carbon dioxide in the metabolizing tissues. However, the magnitude of carbon dioxide retention is not great and its influence upon oxygen poisoning must be interpreted in the light of effects of small, rather than gross, degrees of hypercapnia (292). Moreover, the observation that carbon dioxide enhances oxygen toxicity in Drosophila, a species devoid of respiratory blood pigments, indicates that carbon dioxide retention is not necessary for interaction between oxygen toxicity and exogenous carbon dioxide (519).

The work of early investigators suggested that carbon dioxide retention during oxygen breathing was severe enough to cause very large, toxic increases in tissue P_{CO_2} (47, 101, 397, 435, 477). Analysis of the contents of subcutaneous and abdominal gas depots and intraperitoneal fluid depots suggested that average tissue P_{CO_2} was as high as 100 to 200 mm Hg in rabbits (101), cats (477) and guinea pigs (435) exposed to 3.5–5.0 atm of O_2. However, later analyses of subcutaneous gas depots in rabbits, cats, dogs and men sampled at the pressure of exposure during the first 3 hr of O_2 breathing at pressures of 3.0 to 4.0 atm (294) did not confirm the reported elevation of P_{CO_2}. In longer exposures of animals, a marked rise in depot P_{CO_2} occurred, but only after the appearance of convulsions and gross pulmonary damage. The extreme elevations of depot P_{CO_2} reported in earlier studies were therefore attributed to sources of technical error such as insufficient time for equilibration of depot P_{CO_2} with the tissues, decompression to 1 atm of ambient pressure before sampling from gas depots, incorrect calculation of fluid depot P_{CO_2}, and sampling from the depots after the occurrence of convulsions and lung damage (15, 294).

Direct measurements of the P_{CO_2} and pH of arterial and venous blood have shown conclusively that a relatively small degree of carbon dioxide accumulation occurs during oxygen breathing at high pressure (23, 57, 289, 291, 292, 472, 475).

Average P_{CO_2} and pH changes ranged from +2.0 to +6.5 mm Hg and −0.02 to −0.04 units in the mixed venous blood of anesthetized dogs (57) and in the cerebral venous blood of unanesthetized men (289, 291, 292) exposed to 3.0–4.0 atm of O_2. In rats (472) and cats (475) exposed to 6.0 atm of O_2, there were no significant changes in the acidity of arterial or mixed venous blood until after the onset of obvious toxicity. Continuous, electrometric measurements of arterial and venous blood pH showed decreases ranging from 0.05 to 0.19 units in anesthetized dogs exposed to 4.0–5.0 atm of O_2 (23). These blood pH changes were greater than those described above, but they were still much too small to be consistent with the large elevations of gas or fluid depot P_{CO_2} reported by earlier workers (47, 101, 397, 435, 477).

Although it has been shown that carbon dioxide retention during oxygen breathing does not play the prominent causative role in oxygen poisoning that was formerly ascribed to it, it is clear that acid-base factors in several ways contribute to development of the overt syndromes of CNS and pulmonary oxygen intoxication. There appears to be no clear evidence for a direct interaction between oxygen toxicity and either carbon dioxide narcosis or the disruptive effects of change in hydrogen ion concentration. There are established, additional influences of narcosis and acidosis, as well as influences of carbon dioxide tension and pH upon vascular tone, vagal activity and sympathetic activity. Together, these often concurrent effects of carbon dioxide produce alterations of oxygen poisoning.

Not all of the effects of carbon dioxide lead to exacerbation of oxygen effects. Adaptation to inspired P_{CO_2} levels of about 70 or 140 mm Hg has been found to significantly delay the onset of convulsions in mice that were subsequently exposed to 6.0 atm of O_2 (503). Even a 3-hr exposure to an inspired P_{CO_2} which gradually increased to about 43 mm Hg afforded similar protection to rats that later breathed O_2 at about 6.4 atm (231). These results suggest that adaptation to hypercapnia can rapidly induce changes which delay the manifestations of CNS oxygen toxicity and might be expected to have a similar influence upon the indirect factors in development of pulmonary oxygen poisoning at convulsive levels of hyperoxia. Consistent with this suggested mechanism of protection is the observation that acclimatization to altitude, which includes physiological changes that are opposite to those induced by chronic hypercapnia, significantly hastens the onset of convulsions in rats subsequently exposed to 7.0 atm of O_2 (81).

Involvement of acid-base factors in modifying the pathogenesis of oxygen poisoning is also suggested by the influence of alkalinizing agents upon the toxic effects of oxygen. Administration of the intracellular buffer, tris(hydroxymethyl) aminomethane (THAM) before exposure of mice (197, 353, 430), rats (30 331, 367a, 496) and rabbits (325, 331) to 3.0–6.4 atm of O_2 provided protection against both the CNS and pulmonary effects of oxygen toxicity. In one group of rats (367a), these protective influences were associated with reduction of P_{O_2} and elevation of P_{CO_2} in subcutaneous gas pockets. The gas tension changes were attributed to hypoventilation induced by THAM and were apparently counter-

acted to some degree by a concurrent decrease in oxygen consumption. The observation that THAM did not decrease the mortality rate of rats exposed to 0.95–1.0 atm of O_2 (155, 338, 353) suggests that direct oxygen poisoning had continued and that the reduction of lung damage by THAM at higher oxygen pressures may result indirectly from the delayed onset of convulsions. The protective influence of THAM has been attributed to its buffering action which can decrease P_{CO_2} and increase pH in the tissues and blood (225, 353) but there is no evidence that such changes affect enzymatic poisoning by oxygen. Other proposed mechanisms include decrease in oxygen consumption (353), hypoventilation (367a), chelate formation with trace metals such as copper and zinc (353), interference with cation function (197) and suppression of sympathoadrenal stimulation (352). The ability of THAM to counteract the vasodilatation of retinal vessels induced by carbon dioxide breathing (353) suggests that its protective influence against oxygen toxicity may be at least partially related to a decrease in brain oxygenation caused by reduction of the response of cerebral vessels to an elevated, or perhaps even a normal, arterial P_{CO_2} .

The effect of sodium bicarbonate administration upon oxygen poisoning varies with dose and timing of administration. Pretreatment of mice (353, 430), rats (496) and cats (394) with bicarbonate before exposure to 3.0–8.0 atm of O_2 was found in different experiments to hasten convulsions (353, 394, 430), delay convulsions (353, 430) or have no effect on brain damage (496). The variation probably relates to the length of time allowed for absorption and distribution of bicarbonate (430), as across the cell and blood-brain barrier. The depressant influence of bicarbonate (decrease in hydrogen ion concentration) upon respiration (268, 288, 293) and the associated increase in arterial P_{CO_2} and brain blood flow suggest a mechanism for the potentiation of CNS oxygen toxicity under appropriate acute experimental conditions (353, 394, 430). The effects might be expected to be different in acclimatization to chronic alkalosis. In rats exposed to 0.95–1.0 atm of O_2 daily administration of bicarbonate markedly decreased mortality in one study (338) and had no effect in another (155). These studies were not completely comparable in that one group of rats (155) was exposed continuously, while the others (338) were apparently removed to room air along with control rats for daily injections of bicarbonate or saline. This intermittent exposure to air may have facilitated the observed protective influence of exogenous bicarbonate.

Chronic administration of sodium lactate also delayed the onset of convulsions in cats breathing O_2 at about 8.0 atm (394) and doubled the survival time of rats exposed to 0.98 atm of O_2 (155). In contrast to the marked effect of lactate, the development of pulmonary oxygen poisoning in the rats was not significantly altered by daily intraperitoneal injections of THAM, bicarbonate, acetate or pyruvate. Since the buffering capacities of these ineffective agents were equivalent to that of lactate, Felig and Lee (155) suggested that the protective influence of lactate may be due to some other mechanism, such as the reduction of diphosphopyridine nucleotide, which is a by-product of lactate metabolism.

Role of respired inert gas

The possible consequences of replacing the inert gas in the lungs with oxygen were discussed in a previous section. These consequences, which may include atelectasis with hypoxemia, result from physical factors such as airway obstruction or regional hypoventilation. If the precipitating condition is of a transient nature, pulmonary physiology may be quickly restored to normal by deep inspiration or by addition of inert gas to the inspired mixture. On the other hand, airway obstruction caused by a progressive, toxic process can result in atelectasis and hypoxemia which are more difficult to reverse. Apart from these physical effects of inert gas removal is the question concerning possible influences of inert gas or its absence upon the rate of development of pulmonary oxygen poisoning. Studies which provide information relating to this question are reviewed below.

Exposures of men and several animal species to oxygen environments at reduced ambient pressures have shown that almost total removal of inert gas from the atmosphere has no apparent detrimental effect, even during multi-week exposures. An atmosphere almost devoid of inert gas has been well tolerated by men for 30 days (233, 411) and by small animals for 11 months (389). During some of the animal exposures, litters were born and developed normally in the absence of inert gas (320, 389).

The early work of Bert (66) indicated that the rate of development of oxygen poisoning was solely a function of the inspired P_{O_2}. In agreement with Bert's early observations were the results of recent studies in which rats were exposed to 1.0 atm of O_2 with 0 to 4.0 atm of N_2 (521) or to 3.0 atm of O_2 with 0 to 3.0 atm of N_2 or He (322). Variation of the inert gas partial pressure had no significant effect upon average survival time (322, 521) or the onset of convulsions (322). Rats fatally exposed to the mixture of 1.0 atm of O_2 and 4.0 atm of N_2 had pink, air-filled lungs with minimal atelectasis, but marked pulmonary edema and pleural effusion were present. The degree of atelectasis and consolidation increased progressively with reduction of the inspired P_{N_2} and was almost total in the rats exposed to pure oxygen at 1.0 atm. The authors concluded that the total atelectasis often seen in oxygen-poisoned lungs appeared to result from resorption of oxygen as respiration failed (521).

The results of other studies, however, have indicated that elevated inert gas partial pressures can themselves modify the rate of development of oxygen intoxication in various ways. These include not only direct effects of inert gas such as narcotic influences, but interference with elimination of carbon dioxide as alveolar ventilation is handicapped by the greater gas density at higher total ambient pressure. Lanphier (297) found that the onset of CNS oxygen poisoning in exercising divers exposed to about 2.0 atm of O_2 was enhanced by concurrent exposure to an additional 2.0 atm of N_2. Under such conditions arterial carbon dioxide tension is increased (298). Bennett (63) showed that 48 atm of He markedly hastened the appearance of convulsions in rats exposed to 5.3 atm of O_2. Addition of 13.3 atm of helium, nitrogen or argon to the same inspired P_{O_2} progressively

shortened the preconvulsive time in proportion to the increase in density of the respired gas (62, 63). In contrast to these observations, the onset of convulsions and loss of consciousness in mice exposed to 4.0 atm of O_2 appeared to be delayed by addition of 2.2 or 4.8 atm of N_2 to the inspired gas mixture (5), and dogs breathing 66% O_2 and 33% N_2 at 3.0 atm survived for at least 24 hr, while those breathing pure O_2 at 2.0 atm died within 17 to 21 hr (458). The influence of these exposures upon alveolar ventilation and carbon dioxide retention is not known. In their abstract (458), Smith *et al.* concluded that the dogs died from myocardial or central effects of oxygen toxicity, but they did not describe the histological appearance of the lungs in either group of animals.

Fenn *et al.* (156, 160) demonstrated an unequivocal synergism between the effects of hyperoxia and inert gases in Drosophila. Mean survival times of fruit flies exposed to O_2 partial pressures ranging from 1.0 to 6.0 atm were markedly decreased by addition of 24 to 34 atm of N_2. Synergism was greatest at 1.0 atm of O_2 and was almost absent at 6.0 atm of O_2. However, survival time in 6.8 atm of O_2 was slightly but significantly decreased by addition of as little as 6.8 atm of N_2. Similar synergistic effects between oxygen and inert gases were obtained with 13.6 to 24 atm of argon, 1.7 atm of xenon and 1.2 to 1.7 atm of nitrous oxide, but not with 24 to 34 atm of helium. These findings relate not only to the influence of inert gases upon oxygen toxicity, but to the influence of oxygen toxicity upon the separate phenomenon of inert gas narcosis. As such these may be additive.

In an important series of experiments, Thompson *et al.* (481) demonstrated an influence of inert gases upon the rate of development of pulmonary oxygen poisoning in rats exposed to 2.0–10.0 atm of O_2. Concurrent exposure to high oxygen pressure and either 13 or 26 atm of N_2 produced a nearly identical decrease in average survival time with both nitrogen pressures at 2.0 atm of O_2, a progressive decrease at 3.0 and 5.0 atm of O_2, and little or no decrease at 8.0 and 10.0 atm of O_2 where survival time in O_2 alone was less than 40 min. During exposure to 3.0 atm of O_2 and 26 atm of a N_2-He mixture, the decrease in survival time and increase in lung water content were progressive and approximately linear as the relative proportion of N_2 was increased from 25 to 100%. The interactions of hyperoxia and high helium pressures were particularly interesting. When 13 atm of He were added to the O_2, average survival time was increased at 2.0 atm of O_2, not significantly changed at 3.0 atm of O_2, decreased at 5.0 and 8.0 atm of O_2, and almost unaltered at 10.0 atm of O_2. With 26 atm of He, survival time was slightly, but not significantly, prolonged at 2.0 atm of O_2, decreased at 3.0 atm of O_2 and almost identical to that found with 13 atm of He at the other O_2 pressures. Total water content of the lungs from rats exposed to oxygen and 13 atm of N_2 or He was often significantly greater than that from rats exposed to pure oxygen. In the animals that breathed oxygen and 26 atm of inert gas, total lung water was significantly increased, as compared to the pure oxygen series, only in the group exposed to 3.0 atm of O_2 and 26 atm of N_2.

The mechanisms of interaction between any form of oxygen toxicity and inert gas effects are poorly understood. Elevations of cerebral P_{CO_2} levels caused by inert gas narcosis and diminished alveolar ventilation due to increased gas density

are probably involved to some extent in man and other mammals (61–63, 282). The resulting increase in cerebral blood flow would effectively raise the P_{O_2} of central neurons and enhance the development of CNS oxygen poisoning with a related and similar indirect effect upon pulmonary intoxication (37, 221, 261, 377, 526). The use of breathing equipment which has a high dead space and resistance could also contribute to carbon dioxide retention in divers exposed to increased partial pressures of oxygen and inert gas (297, 298). Based upon his observations that an oxygen-inert gas synergism similar to that demonstrated in Drosophila also occurred in Paramecia and *Streptococcus faecalis*, Fenn *et al.* (160) suggested that an interaction may occur at the protoplasmic or cellular level. Studies in man (163) and non-mammalian organisms (156, 160) have shown that the synergism between the effects of oxygen and inert gases probably involves an augmentation of inert gas narcosis by increased oxygen tensions in addition to the influence of elevated inert gas pressures upon oxygen toxicity.

Biochemical changes in the lungs

Biochemical alterations have been observed in the lungs of rats exposed to 5.0 atm of O_2 (221, 253, 254, 365). Dehydrogenase activity and sulfhydryl content of the lung, which were reduced significantly after 15 to 30 min of oxygen breathing, continued to decrease progressively throughout a 45- to 90-min exposure (253, 254). At the time of the initial biochemical alterations, no macroscopic and only slight microscopic changes were present in the lungs. After 45 min of exposure, the lungs were damaged and disulfide content was significantly increased. Pretreatment of the rats with pentobarbital prevented the dehydrogenase, sulfhydryl and disulfide changes. Cysteamine afforded similar protection to dehydrogenase activity but was less effective than pentobarbital.

Novelli *et al.* (365) used histochemical techniques to show that the enzymatic activities of alkaline phosphatase, 5′-nucleotidase, adenosine triphosphatase and lipase were all markedly reduced in the lungs of rats after 30 min of O_2 breathing at 5.0 atm. Inactivation of the enzymes was partially or completely prevented by adrenal medullectomy or pretreatment with dibenzyline or reserpine. The authors concluded from these results that the enzymatic changes, as well as the pulmonary pathology and convulsions observed in the same animals, were all caused by adrenergic hyperactivity induced by hyperoxia.

Total lung non-protein sulfhydryl content is slightly reduced after the non-convulsive exposure of rats to 3.0 or 5.0 atm of O_2 for 60 or 30 min, respectively (221). The production of convulsions, however, by exposure to 5.0 atm of O_2 for 60 min or by administration of pentylenetetrazol is accompanied by much greater decreases in non-protein sulfhydryl content. Pretreatment of the rats with serotonin prevents the loss of sulfhydryl content associated with pentylenetetrazol convulsions.

Little is known about the biochemical changes that occur in the lungs of intact animals during exposure to subconvulsive levels of hyperoxia. Stadie *et al.* (466) found no significant changes in oxygen uptake and respiratory quotient of lung slices taken from dogs with severe pulmonary pathology after exposure to 1.0

atm of O_2 for 48 to 116 hours. Seelkopf (434) found only a slight reduction in dehydrogenase activity of pulmonary tissues taken from animals exposed to about 0.9 atm of O_2 for 72 hr.

The biochemical alterations described above and their relationship to the pathological changes of direct pulmonary oxygen poisoning cannot yet be correlated with deficits in lung function. Although the neuroadrenergic stimulation and pulmonary damage that accompany the occurence of convulsions appear to have a prominent influence upon the biochemical composition of the lung, detectable changes have also been observed before the onset of either seizures or significant pulmonary pathology. Furthermore, the sulfhydryl content of lung homogenates is rapidly oxidized in the absence of hormonal influences even during exposure to the P_{O_2} of room air (253). Failure to find similar biochemical changes in the lungs of animals poisoned by breathing O_2 at 1.0 atm suggests that susceptible enzymes are protected from oxidation, as by soluble reducing substances. Determination of the relationship of biochemical alterations to the development of pulmonary oxygen poisoning with both *in vivo* and *in vitro* experimental models is an important area for future investigation.

Other possible factors

The work of several investigators suggests that histamine may in some way be involved in the development of the syndrome of pulmonary oxygen poisoning. The content of histamine in the pulmonary tissues of guinea pigs was elevated nearly 3-fold after a 6-hr exposure to 0.95 atm of O_2 (162). Administration of exogenous histamine to rats and guinea pigs exaggerated the gross pulmonary pathology produced by a similar oxygen exposure (204). Pretreatment with promethazine, metyramine or thiazinanium partially protected the lungs of rats but not guinea pigs from the toxic effects of oxygen (171, 204). With sterile gelatin sponge fragments which were enclosed under the pleura of rats as an experimental simulation of an inflammatory process, Grandpierre *et al.* (199) found that the congestive and exudative reaction provoked by prolonged exposure to 0.90–0.98 atm of O_2 resembled that produced by repeated injections of histamine. However, Wittner and Rosenbaum (521) reported that the survival time of guinea pigs and rats exposed to 1.0 atm of O_2 was not affected by histamine depletion, administration of promethazine or both combined. In mice breathing O_2 at 5.0 atm, pretreatment with histamine significantly delayed the onset of convulsions and prolonged survival time (495). Additional experiments will be required to explain these contradictory results and further evaluate any role of histamine in the pathogenesis of pulmonary oxygen poisoning.

Buckingham *et al.* (93, 94) have suggested that serotonin may be a mediator of vasoconstriction and edema formation in pulmonary oxygen intoxication. The lung serotonin content in rats was reduced to about half of the normal value after a 30-min exposure to 6.0 atm of O_2 . Severe pulmonary injury was associated with platelet degeneration and degranulation of serotonin-containing perivascular mast cells. Administration of Trasylol, a proteinase inhibitor, prevented mast cell degranulation, discharge of serotonin and the occurrence of pulmonary edema.

Pentobarbital partially prevented release of serotonin, protected against the pulmonary vascular alterations and markedly inhibited lung damage. On the other hand, depletion of total body serotonin by repeated administration of reserpine did not alter the survival time of guinea pigs and rats breathing O_2 at 1.0 atm (521), and other investigators have found that administration of exogenous serotonin delayed the onset of convulsions (67, 281, 495) and prolonged survival time (495) in mice exposed to 3.0–5.0 atm of O_2. Serotonin also markedly reduces the severity of pulmonary edema produced in rats by 60 min of O_2 breathing at 5.0 atm (495). It is conceivable that a detrimental effect of serotonin upon the pulmonary vasculature could be masked at convulsive levels of hyperoxia by a central action which delays the onset of convulsions and the associated augmentation of pulmonary damage. Information regarding this possibility could be obtained by studying the effect of exogenous serotonin upon the rate of development of pulmonary oxygen poisoning at subconvulsive levels of hyperoxia.

There is much indirect evidence which suggests that the inactivation of enzymes and cofactors by molecular oxygen involves the intermediate formation of oxidizing free radicals. Possible mechanisms for the formation of these intermediates and the evidence for their role in oxygen toxicity have been discussed extensively in several recent reviews (125, 172, 173, 192, 193, 225, 340). In addition, many similarities have been observed between the toxic effects of oxygen and the biological effects of irradiation (158, 173, 176, 179, 192, 340). Irradiation of mice (179) and Drosophila (479) just before or during exposure to hyperoxia markedly hastens the rate of development of oxygen intoxication. Several drugs which effectively increase tolerance to irradiation also provide significant protection against oxygen poisoning in rats and mice exposed to 5.0–6.0 atm of O_2 (175, 179, 495). Furthermore, the radioprotective properties of many of these drugs are reduced or abolished by simultaneous exposure to increased oxygen pressures (495, 498).

The influence of hyperoxia upon the toxic effects of irradiation has also been studied with inconsistent results. Although increased oxygenation of normal and neoplastic tissues clearly enhances their radiosensitivity (112, 113, 200, 492, 497, 518, 539), the lethal effects of irradiation are variously reported to be increased (58, 111, 168, 312, 479, 492, 495), unaltered (312, 495) or decreased (492) by simultaneous exposure to hyperoxia. Interpretation of these contradictory results with respect to pulmonary effects is further complicated by the fact that death from whole body irradiation is usually caused by fatal damage to the gastrointestinal tract or hematopoietic system. In experiments specifically designed to study the influence of hyperoxia upon pulmonary radiation poisoning, the lungs of rats were irradiated either in air or during brief exposures of the animals to 3.7–4.0 atm of O_2 (350, 492). The combination of pulmonary irradiation and hyperoxygenation was associated with a smaller change in lung compliance (350) land a reduced mortality (492) within the first 6 weeks after irradiation, but similarly treated rats that survived this period had a higher incidence of pulmonary radiographic opacities (492).

Van den Brenk and Jamieson (495) have suggested that the analogy of oxygen poisoning to radiation damage is only superficial. Although several drugs afford similar protection against oxygen poisoning and irradiation, this correlation is not always present and some drugs are effective against only one of the two forms of toxicity. They have proposed that the reduction of extracellular or intracellular P_{O_2} by drug actions is a possible protective mechanism which offers an alternative to the removal of free radicals as a common basis for chemical protection against oxygen toxicity and radiation damage.

Summary of mechanisms

The total syndrome of pulmonary oxygen poisoning is caused by multiple interacting factors which include direct toxic effects upon the lung tissues themselves and additional, indirect effects related to toxic actions of oxygen at extrapulmonary sites. Experimental results have established conclusively that prolonged exposure to hyperoxia in the absence of indirect influences can severely damage the lung. Direct effects of oxygen toxicity, which appear to be related to increased oxygen tensions in the bronchial circulation as well as in the alveolar gas, should therefore be considered to play a primary and prominent role in the pathogenesis of pulmonary oxygen intoxication. In the lung, as in the brain or any other organ, the direct toxic effects of oxygen must originate from inactivation of essential enzymes and the concomitant disruption of cellular metabolism. The biochemical changes which have been demonstrated in the lungs of intact animals exposed to hyperoxia, and probably other still unknown metabolic derangements, represent the lethal effect of oxygen toxicity upon pulmonary cells.

Superimposed upon the direct, cellular pulmonary intoxication by oxygen are other adverse effects which are related to the development of central nervous system oxygen poisoning and are particularly obvious after the occurrence of convulsions. Drug-induced convulsions and mechanical injury to the head are also associated with pathological and functional changes in the lungs similar to those which accompany oxygen poisoning. The pulmonary effects associated with all three forms of cerebral injury are presumably mediated by way of hypophyseal-adrenocortical and sympatho-adrenomedullary pathways.

Many observations are indicative of an hypophyseal-adrenocortical involvement in the rate of development and severity of pulmonary oxygen poisoning. The lung damage and mortality of animals exposed to hyperoxia are decreased by either hypophysectomy or adrenalectomy, and these protective influences can be at least partially reversed by administration of adrenocorticotrophic hormone or cortisone. When the same drugs are given to normal oxygen-breathing animals, the development of pulmonary intoxication is greatly enhanced. Prolonged, acute exposure to hyperoxia produces a decrease in adrenal ascorbic acid content and chronic, intermittent exposures are accompanied by an increase in adrenal weight. The adrenocortical response to oxygen breathing at 1.0 atm appears to be insignificant for at least the first 24 hr and then increases progressively in parallel with the severity of oxygen poisoning. During oxygen breathing at higher ambient pressures, adrenocortical activity becomes evident more rapidly. Stimulation of

the adrenal cortex during exposure to hyperoxia appears to be predominantly indirect by way of the hypothalamus or pituitary.

The involvement of sympatho-adrenomedullary pathways in the transmission of central effects of oxygen toxicity to the lungs is also well documented. Many general anesthetics offer protection against both the central nervous system and the pulmonary manifestations of oxygen toxicity. Pretreatment with adrenergic blocking drugs reduces the severity of pulmonary pathology, even when oxygen convulsions are not affected. Lung damage and mortality during exposure to hyperoxia are decreased by bilateral adrenal medullectomy and enhanced by administration of epinephrine. The effects of many, but not all, autonomic drugs upon pulmonary oxygen intoxication are consistent with exaggeration of indirect influences by the sympathetic nervous system and antagonism of such action by the parasympathetic nervous system. Hyperoxic stimulation of the sympatho-adrenomedullary system, which is generally proportional to inspired P_{O_2} and exposure duration, is greatly enhanced by the occurrence of convulsions.

The protection afforded against pulmonary oxygen poisoning by hypophysectomy is due in part to cessation of thyrotropin secretion as well as to elimination of adrenocorticotrophic hormone. Experimental modification of thyroid activity in animals exposed to hyperoxia is accompanied by corresponding changes in the severity of pulmonary pathology. The observation of similar correlations between oxygen tolerance and changes in oxygen consumption in a variety of metabolic states suggests that thyroid influences upon oxygen poisoning may be at least partially related to changes in cellular metabolism. Studies of thyroid function in animals exposed to hyperoxia are generally consistent with the conclusion that thyroid activity is increased under these conditions, but contradictory results have been reported.

Although it is clear that oxygen convulsions are associated with prominent neural and hormonal influences upon the lungs, the relative contribution of these indirect effects to the development of pulmonary oxygen intoxication at subconvulsive levels of hyperoxia is still not known. Since no living mammalian cell is immune to the toxic effects of oxygen, every organ and tissue in the body must be gradually and progressively poisoned by exposure to toxic oxygen tensions. The practical significance of this general principle is obscured by wide variations in "oxygen dose," susceptibility, and capacity for compensation or recovery at the local sites of action. The direct effects of oxygen toxicity upon the cellular metabolism and function of the endocrine glands are not well understood. Evaluation of these direct effects and their potential influences upon pulmonary oxygen poisoning is an important area for future research.

In spite of extensive investigation within the past decade, the role of surface active phenomena in the pathogenesis of pulmonary oxygen intoxication is still disputed. Most workers have found that the surface activity of the alveolar lining material is decreased in oxygen-poisoned lungs, but it is uncertain whether this occurs as a direct effect of oxygen toxicity or only as a secondary consequence of the concomitant effects of pulmonary intoxication. Potential mechanisms for reduction of surfactant concentration in oxygen poisoning include direct

inactivation, the formation of inhibitory substances, decreased synthesis and physical disruption of the alveolar lining film by pulmonary edema. It is possible that more than one of these actions may occur simultaneously. In any case, reduced surfactant function probably contributes to the pathological changes found in the lungs during the terminal stages of oxygen intoxication.

Both the central nervous system and the pulmonary effects of oxygen toxicity are markedly potentiated in animals exposed to convulsive levels of hyperoxia by the addition of low, normally innocuous, partial pressures of carbon dioxide to the inspired gas. The enhancement of pulmonary oxygen poisoning under these conditions appears to be related to the increased intensity of neurogenic and endocrine factors associated with the concurrent potentiation of oxygen convulsions. When the inspired P_{CO_2} is elevated to extreme levels during oxygen breathing, convulsions are inhibited and lung damage is minimal or absent. These protective influences are probably related to the narcotic effects of carbon dioxide. However, the development of fatal central nervous system intoxication is hastened by the interactions of hyperoxia and hypercapnia, even when convulsions are inhibited. Studies of carbon dioxide influences upon the toxic effects of oxygen at atmospheric pressure are not conclusive. Additional experiments will be required in order to determine whether the potentiation of pulmonary oxygen poisoning by hypercapnia is related only to the augmentation of central nervous system oxygen toxicity or to other, more direct forms of interaction at the lung as well.

Although it is now known that endogenous carbon dioxide retention during exposure to hyperoxia does not play the prominent causative role that was formerly ascribed to it, it is clear that acid-base factors contribute to development of the syndromes of central nervous system and pulmonary oxygen intoxication. Failure of hemoglobin reduction while breathing oxygen at high pressure impairs carbon dioxide transport and causes accumulation of carbon dioxide in the tissues. The resulting, relatively modest degrees of hypercapnia and acidosis appear to modify the toxic effects of oxygen upon the lungs, but the mechanism by which this occurs is not known. There is no conclusive evidence for a direct interaction between oxygen toxicity and hypercapnia. In the absence of such evidence, it must be considered that oxygen poisoning can be influenced by other effects of hypercapnia and acidosis such as alterations in vascular tone, sympathetic activity and vagal activity.

Apart from an increased susceptibility to alveolar atelectasis and hypoxemia, total removal of inert gas from the lungs appears not to exaggerate the pulmonary manifestations of oxygen toxicity. Most investigators have found that the rate of development of pulmonary oxygen poisoning is solely a function of the inspired P_{O_2}, regardless of the presence or absence of small concentrations of inert gas. When oxygen is breathed along with narcotic levels of inert gas, however, both pulmonary and central effects of oxygen toxicity are definitely enhanced. This interaction is related not only to the influence of inert gas upon oxygen intoxication, but also to the separate and possibly additive influence of increased oxygen tensions upon inert gas narcosis. Under these conditions, the toxic effects of oxy-

gen are probably further potentiated by the elevation of cerebral P_{CO_2} associated with inert gas narcosis and the impairment of alveolar ventilation by increased gas density.

The existence of many potential mechanisms of pulmonary oxygen poisoning provides the means for marked variability in the interactions between these mechanisms. For example, the influence of neuroendocrine interaction is much more prominent at convulsive levels of hyperoxia than it is during oxygen breathing at 1.0 atm. The relative prominence of other influencing factors may also be altered at different oxygen tensions and durations of exposure. Since the rate of development of the lethal effects of pulmonary oxygen intoxication varies over a wide range in different animal species and individuals, similar variability should be expected with regard to the dominant mechanisms which are responsible for these lethal effects. It is conceivable that many apparently inconsistent results obtained in different experiments may be explained by changes in the interrelationships of the multiple direct and indirect influences which contribute to the total syndrome of pulmonary oxygen poisoning.

MODIFICATION OF PULMONARY OXYGEN TOLERANCE

The rate of development of pulmonary oxygen poisoning in intact animals can be influenced by a wide variety of conditions, procedures and drugs (table 5).

TABLE 5A

Factors influencing rate of development of pulmonary oxygen poisoning

Decrease Survival Time or Increase Severity of Pulmonary Pathology	
Influencing factor	Reference
Adrenocortical hormones	25, 42, 90, 92, 180–182, 328, 452, 473, 504
Adrenocorticotrophic hormone	25, 90, 328
Aspartic acid	528
Atropine	92, 181, 185
Carbon dioxide	44, 227, 250, 260, 326, 334, 367, 388, 467, 494, 522
Chorionic gonadotropin with progesterone	90
Epinephrine	39, 40, 102, 178, 180, 181, 425, 452
Estrogen	90
Glutamic acid	528
Dextroamphetamine	391, 522
Dihydroxyphenylalanine	391, 522
Histamine	204
Hyperthermia	104, 151, 244, 310
Inert gas (inspired at high ambient pressure)	481
Insulin	41, 179
Norepinephrine	178, 181
Thyroid hormones	35, 41, 43, 102, 104, 207, 454, 468, 473
Vitamin E deficiency	262, 469, 471, 474, 508
X-irradiation	179, 194

TABLE 5B

Factors influencing rate of development of pulmonary oxygen poisoning

Increase Survival Time or Decrease Severity of Pulmonary Pathology	
Influencing factor	**Reference**
Adrenal medullectomy	181, 182, 365, 371, 425
Adrenalectomy	39, 180–183, 452, 473
Adrenergic blocking drugs (dibenamine, SKF 501, dibenzyline, dehydrobenzoperidol)	178, 181, 182, 260, 261, 323, 327, 365, 372
Alanine	528
Altitude acclimatization	81
Anesthesia (barbiturates, alpha-chlorolose, propylene glycol, urethane)	43, 44, 93, 94, 227, 250, 253, 254, 258
Antihistamines (promethazine, metyramine, thiazinanium)	171, 204, 328
Antioxidants (*alpha*-tocopherol polyethylene glycol 1000 succinate, ascorbic acid, NN'diphenyl-*p*-phenylenediamine, hydroquinone, methylene blue, propyl gallate, trihydroxyphenone antioxidants, *beta*-aminoethylisothiuronium, nordihydroquiaretic acid)	175, 179, 185, 257, 398, 474
Arginine	528
Carbachol	178, 181, 185
Chlorpromazine	28, 171, 178, 203, 328, 365, 495
Cobalt (II)	175
Coenzyme A	179
Convulsions	37, 221, 261, 377, 526
Cystamine	175
Cysteamine	175, 179, 185, 186, 254
Cysteine	179, 185
Dimercaprol	500
Ethanol	179
gamma-Aminobutyric acid	526–529
Ganglionic blocking drugs (hexamethonium, tetraethylammonium)	203, 261
Glutathione	175, 179, 185, 474
Glycine	528
Glycylglycine	528
Hibernation	400
Histamine	495
Hypophysectomy	25, 37, 42, 104
Hypothermia	206, 400
Hypothyroidism (propylthiouracil)	207
Immaturity	24, 151, 177, 188, 280, 292, 399, 413, 456, 457, 463, 483, 514, 519
Intermittent exposure	1, 217, 375, 386, 422, 531
Methacholine	178, 181, 185
Oxytyramine	178, 179, 181, 185
Reserpine	27, 28, 365, 373
Serotonin	495
Sodium bicarbonate	338, 430
Sodium diethyldithiocarbamate	131, 175
Sodium lactate	155
Starvation	103, 194, 369
Succinate	429
Thiourea	175
Thyroidectomy	102, 104
Tris aminomethane (THAM)	30, 325, 331, 353, 430
Tryptamine	178, 181, 185
Vitamin E	262, 469, 471, 474

The factors summarized in table 5 have been shown to have a significant effect upon either the degree of pulmonary pathology or the survival time or both of these in animals exposed to toxic oxygen pressures. Individual references may be consulted for descriptions of details such as exposure duration, level of hyperoxia, indices of toxicity and animal species.

Modification of the rate of development of pulmonary oxygen poisoning by various means has been studied for two major purposes. One purpose involves the obtaining of clues relating to potential mechanisms of pulmonary oxygen toxicity; several pertinent papers were reviewed in the previous section. A second major purpose has been concerned with the effects of various agents upon the rate of development of pulmonary oxygen poisoning in patients who breathe oxygen at increased partial pressures for therapeutic reasons. With regard to the latter, the results of animal studies have identified several factors which may be expected to enhance or delay the development of pulmonary oxygen poisoning.

The rate of development of pulmonary intoxication in man has been studied predominantly in normal volunteers who continuously breathed oxygen at increased partial pressures in the absence of other influencing factors (table 3). Therefore, little information is available regarding the quantitative effects of the agents listed in table 5 upon oxygen poisoning in the human lung. It is reasonable to assume, however, that agents which clearly modify pulmonary oxygen poisoning in animals will have similar qualitative effects in man. It is very likely that patients with elevated levels of catecholamines, adrenocortical hormones or thyroid hormones will have an increased susceptibility to pulmonary oxygen toxicity. The pulmonary oxygen tolerance of aged patients may also be decreased. The adverse effects of hyperthermia in animals exposed to hyperoxia suggest that febrile patients may have an increased susceptibility to oxygen poisoning. Hypercapnia is another common clinical entity which definitely enhances pulmonary oxygen poisoning when acute hypercapnia occurs concurrently with exposure to convulsive levels of hyperoxia. The effects of an increased arterial P_{CO_2} during oxygen breathing at atmospheric pressure or after adaptation to hypercapnia are still not known.

Many patients receive oxygen therapy in order to relieve dangerous degrees of arterial hypoxemia caused by inadequate pulmonary function. The work of Winter *et al.* (520) indicates that such patients may be relatively resistant to pulmonary oxygen toxicity, at least at convulsive levels of hyperoxia. However, the results of other investigators (343) suggest that impairment of arterial oxygenation does not provide significant protection against pulmonary damage during oxygen breathing at atmospheric pressure. Since the administration of oxygen partial pressures of 1.0 atm or less to patients with abnormal pulmonary function is one of the most common clinical applications of oxygen therapy, studies are sorely needed to establish conclusively the presence or absence of indirect forms of pulmonary oxygen poisoning at subconvulsive levels of hyperoxia.

Although it has been demonstrated that many drugs can significantly delay the onset or decrease the severity of pulmonary intoxication in animals exposed to hyperoxia (table 5), the prospects of using such drugs to effectively enhance the benefits of oxygen therapy are not encouraging. In some cases, the doses of

the drugs used to provide protection are so high that they cause toxic or other undesirable effects. A few of the drugs protect against some forms of oxygen poisoning while simultaneously enhancing others. For example, barbiturates delay the onset of convulsions and pulmonary pathology, but increase the residual brain damage found in animals exposed to hyperbaric oxygen (18, 19, 219, 249, 493, 496). However, no evidence of residual brain damage has been found in a series of over 200 cancer patients who were deeply anesthetized with pentobarbital and exposed repeatedly to about 4.0 atm of O_2 for an average time of 45 min in conjunction with radiation therapy (496). The observations that pulmonary oxygen tolerance is clearly decreased in vitamin E-deficient rats (262, 469, 471, 474, 508) and increased by administration of antioxidant drugs (257) suggest that such drugs may be of some value as adjuncts to oxygen therapy. The employment of hypothermia as a protective measure may be practical and effective in situations where brief exposures to hyperbaric oxygen pressures are required. Succinate and THAM may also prove to be useful therapeutic adjuncts if the disadvantages of high doses with undesirable side effects can be avoided. In spite of these hopeful possibilities, it is likely that most of the agents listed in table 5 will have very limited clinical applications.

One measure which has been proven to be practical and effective as a means of increasing oxygen tolerance is the intermittent interruption of oxygen breathing by exposure to a normal inspired P_{O_2}. This phenomenon was apparently first observed by Soulie (462) who found no indications of oxygen intoxication in animals exposed for about 6 weeks in alternating 24-hr intervals to about 1.0 atm of O_2 and to air. Paine *et al.* (375) also found that interruption of exposure to about 1.0 atm of O_2 definitely delayed the occurrence of pulmonary oxygen poisoning in dogs. Survival time was greatly prolonged by changing the inspired gas from oxygen to air for a single 45-min interval or for three 15-min intervals each day. In mice exposed to 1.0 atm of O_2 with a daily 4-hr interruption, an equivalent increase in pulmonary oxygen tolerance was obtained when the gas breathed during the interruption was either air at 1.0 atm or pure O_2 at 0.26 atm (531). These results indicate that the extension of pulmonary oxygen tolerance achieved by intermittent exposure is related to reduction of the inspired P_{O_2} to a normal level rather than addition of inert gas to the inspired mixture, and they are consistent with the concept proposed by Haugaard (222, 224) that oxygen poisoning results from oxidation of critical enzymes or cofactors which can be rapidly resynthesized when a non-toxic P_{O_2} is restored.

Several investigators have shown that both pulmonary and CNS oxygen tolerance in animals breathing O_2 at pressures ranging from 2.0 to 5.5 atm can be greatly increased by periodic interruptions of the exposure (1, 217, 282, 386). In an attempt to determine optimum schedules for intermittent oxygen breathing, Hall (217) systematically exposed guinea pigs to 3.0 atm of O_2 for intervals of 10 to 30 min alternately with exposure to 0.21 atm of O_2 for 5 to 20 min. The most efficient schedule in terms of maximum gain in oxygen breathing time for minimum increase of total expended time consisted of 20-min intervals of exposure to 3.0 atm of O_2 alternated with 5-min intervals of exposure to 0.21 atm of O_2. With

this schedule the times for occurrence of gasping respiration, convulsions and death in 25 % of the animals were increased from 5.2, 7.5 and 11.5 hr, respectively, for continuous exposure, to 11.8, 13.0 and 14.7 hr, respectively, for intermittent exposure.

The increase in oxygen tolerance achieved by periodic interruptions of oxygen breathing appears to depend at least partially upon the degree of oxygen intoxication which develops before reduction of the inspired P_{O_2}. For example, Polgar *et al.* (399) found that significant mortality occurred when mice were exposed in alternate 6-hr intervals to 0.95–1.0 atm of O_2 and air, but not when the alternate intervals were 2 or 3 hr in duration. Similarly, the life-span of Drosophila, which was not affected by exposure to 1.0 atm of O_2 for 4 to 6 hr per day, was significantly shortened by extension of the oxygen exposure to 8 hr per day (159). When the flies were exposed intermittently to 1.0 atm of O_2, their life-span was longer than that observed for a continuous exposure to an equivalent "average" oxygen pressure per day. In contrast to this, very brief exposures to 2.0–5.5 atm of O_2 produced a shorter life-span than that associated with continuous exposure to an equivalent, small elevation in the "average" oxygen pressure. Although data obtained in Drosophila are not directly applicable to mammalian lungs, they help to establish the general principle that recovery from the toxic effects of oxygen is more complete when the degree of poisoning is less severe. It has also been observed that the severity of oxygen poisoning in Drosophila increases linearly with duration of exposure even though symptoms are not detectable until the terminal stages of intoxication (159). If this principle is applicable to mammals, it may help to explain how oxygen tolerance can be increased by intermittent exposure, because data obtained in guinea pigs (155) suggest that the rate of recovery from oxygen poisoning is exponential when the inspired P_{O_2} is reduced to a normal level.

Fenn (157) attempted to describe mathematically the rate of recovery from oxygen intoxication in Drosophila exposed intermittently to increased oxygen pressures. Their efforts were frustrated by the extreme variability of the capacity for recovery in different individuals and possibly also by the lack of an appropriate index of oxygen toxicity. The results of these studies suggested that recovery occurred more slowly after the gradual development of oxygen poisoning in flies exposed to 1.0 atm of O_2 than it did after the rapid onset of toxicity at higher oxygen pressures. It would be of great interest to perform similar studies in small mammals exposed intermittently to varying levels of hyperoxia. With quantitative measurements of lung damage and survival time as toxicity indices, such studies could provide information which may apply at least qualitatively to the rate of recovery from pulmonary oxygen poisoning in human lungs. General principles established by these studies could also provide the basis for definitive experiments designed to measure the rate of recovery from early, reversible degrees of pulmonary oxygen poisoning in normal men.

There is very little quantitative information describing the influence of intermittent exposure upon oxygen tolerance in man. During World War II field operations, Lambertsen (282) observed that nearly daily exposures of divers to the

limits of CNS oxygen tolerance over a period of more than a month did not result in evident cumulative toxic effects. Tolerance to increased oxygen pressures at depth could at least in part be re-established acutely without interruption of oxygen breathing by returning to the surface for a short period of time (285). In a large series of subjects, Donald (138) found that multiple exposures to hyperoxia until the onset of CNS symptoms did not cause residual neurologic or pulmonary impairment. In two subjects who breathed oxygen at 2.0 atm for 10.3 and 11.2 hr, the onset of pulmonary symptoms and a progressive decrease in vital capacity appeared to be delayed by periodic, brief reductions of alveolar P_{O_2} to 0.26–1.05 atm (114, 116). During a 24-hr exposure of 30 subjects to 0.75 or 1.0 atm of O_2, however, the incidence of pulmonary symptoms and magnitude of decrease in vital capacity were not consistently reduced by 1 to 15 min of air breathing every 3 hr (120). The only apparent benefits of intermittent exposure were a decreased severity of symptoms in the subjects who breathed oxygen at 0.75 or 1.0 atm with 15-min intermissions and a smaller decrease in vital capacity in the members of this group who were exposed to 1.0 atm of O_2. Carefully controlled studies of the rate of development of pulmonary intoxication in men exposed intermittently to hyperoxia are needed to explain these results and to establish optimum schedules for increasing pulmonary oxygen tolerance by the use of intermittent exposures.

CONCLUDING REMARKS

The studies considered in this review emphasize that prolonged exposure to hyperoxia has adverse effects upon multiple structural components of the lung. Pulmonary cells and tissues are progressively damaged and ultimately destroyed by toxic actions of oxygen which are initiated through the inactivation of essential enzymes and extended by the disruption of cellular metabolism. The nature and sequence of the specific biochemical and pathological processes involved in intracellular oxygen poisoning are not necessarily uniform in different cell types, even within the lung.

Superimposed upon the direct effects of oxygen toxicity upon the lung are neural and hormonal influences related to the development of oxygen intoxication in the central nervous system and possibly in other extrapulmonary sites such as the adrenal and thyroid glands. Although these indirect influences can clearly increase the severity of the overall syndrome of pulmonary oxygen poisoning, it is not known whether they do so by interaction with enzymatic oxygen toxicity or by altering the consequences of cellular intoxication through influences upon vascular and bronchiolar smooth muscle tone, vascular permeability and vagal activity. Similar uncertainties exist regarding the mechanisms of the demonstrated interactions between oxygen intoxication and hypercapnia or inert gas narcosis. Certain of these questions could be resolved by studying the effects of hormones, acidosis, carbon dioxide and inert gases upon the development of oxygen poisoning in preparations devoid of circulatory and neural influences.

In the lungs of intact animals, the diverse mechanisms of oxygen toxicity combine to cause increasingly severe morphological and structural damage with con-

comitant and progressive deterioration of pulmonary function. Although the rates of development of morphological changes have been studied quantitatively in rats and monkeys (especially at 1.0 atm), little is known about the degree of functional impairment associated with specific pathological alterations at various stages of pulmonary oxygen poisoning. Quantitative comparisons of structural and functional changes during the progression of oxygen intoxication would aid identification of the pathological effects responsible for impairment of mechanical properties and gas exchange in oxygen-poisoned lungs. Such studies should be performed at many levels of hyperoxia and in different animal species because the sequence of toxic effects and correlations of structural and functional changes will be affected by alterations in the rate of cellular intoxication, the time available for reaction of damaged tissues, the intensity of neuroendocrine influences and species susceptibility to oxygen toxicity. There are patterns of interaction among the many factors known to contribute to the pathogenesis of pulmonary oxygen poisoning. These will also be partially determined by the inspired P_{O_2} and by the degree of susceptibility of specific cell groups to oxygen toxicity. In animals exposed to convulsive levels of hyperoxia the overt manifestations of pulmonary intoxication are greatly exaggerated by neuroendocrine and hypercapnic influences. However, the role of these factors in the syndrome of pulmonary oxygen poisoning has not been established at oxygen pressures which do not induce convulsions. Since oxygen breathing at 1.0 atm is employed in the therapy of patients with hypoxemia, acidosis and hypercapnia, it is important to determine whether indirect influences such as these affect the development of pulmonary oxygen poisoning at sea level.

Because of widely different susceptibility of animal species to pulmonary damage by oxygen, a precise definition of tolerance in man must be based upon measurements made in human subjects who are exposed to hyperoxia until definite manifestations of pulmonary oxygen poisoning appear. Such studies are limited in number and should be extended to include exposures at several levels of P_{O_2} above atmospheric. It should also be recognized that the minimum level of inspired P_{O_2} which will cause progressive pulmonary damage in man is not yet known. At partial pressures of 0.5 atm or less, normal men can breathe oxygen for many days without significant impairment of pulmonary function, but it cannot be stated unequivocally that adverse effects will not eventually occur after a sufficient duration of exposure. Furthermore, data obtained from normal subjects may not be quantitatively applicable to patients in whom oxygen tolerance may have been altered by disease or by drugs.

At the present time, intermittent exposure to a normal inspired P_{O_2} appears to be the most practical means available for effectively minimizing pulmonary oxygen poisoning while providing useful periods of exposure to oxygen. However, essentially no information exists concerning the quantitative influence of intermittent exposure in slowing the rate of development of pulmonary oxygen poisoning in man.

Optimum schedules for improving oxygen tolerance by periodic alternation of high and normal inspired P_{O_2} should be established for men breathing oxygen

at several levels of ambient pressure. Related experiments should define the rates of recovery from progressive degrees of pulmonary oxygen intoxication. It is conceivable that, eventually, the advantages of intermittent exposure may be even further enhanced by concurrent administration of drugs to retard the rate of development of oxygen poisoning or hasten the rate of recovery. Evaluation of the mechanisms and the practical applications of these protective influences will contribute much to the safe and effective use of oxygen at increased partial pressures in therapy, undersea activity and decompression after diving.

Acknowledgment. This work was supported in part by grants (HE-08184 and HE-08899) from the National Institutes of Health, by a contract (NONR 551) with the Office of Naval Research, and by a contract (NGL 34-010-097) with the National Aeronautics and Space Administration.

REFERENCES

1. ACKERMAN, N. B. AND BRINKLEY, F. B.: Cyclical intermittent hyperbaric oxygenation: a method for prolonging survival in hyperbaric oxygen. *In* Proceedings of the Third International Conference on Hyperbaric Medicine, ed. by I. W. Brown, Jr. and B. G. Cox, pp. 200–207, NAS, NRC Publ. No. 1404, Washington, D.C., 1966.
1a. ADAMSON, I. Y. R., BOWDEN, D. H. AND WYATT, J. P.: Oxygen poisoning in mice. Ultrastructural and surfactant studies during exposure and recovery. Arch. Pathol. **90**: 463–472, 1970.
2. AGADZHANIAN, N. A. AND SERGIENKO, A. V.: Acute hypoxia tolerance after prolonged exposure of animals to hyperoxic atmospheres. Fiziol. Zh. S.S.S.R. In. I.M. Sechenova **55**: 1487–1492, 1969.
3. AIKAWA, J. K. AND BRUNS, P. D.: Pulmonary lesions in experimental oxygen poisoning. Amer. J. Dis. Child **91**: 614–620, 1956.
4. ALEXANDER, W. C., SEVER, R. J. AND HOPPIN, F. G.: Hypoxemia induced in man by sustained forward acceleration while breathing pure oxygen in a five pounds per square inch absolute environment. Aerosp. Med. **37**: 372–378, 1966.
5. ALMQVIST, H., ARBORELIUS, M., JR., BARR, P. O., JANSSON, B. AND KALISER, L.: Oxygen toxicity in nitrogen mixtures. Acta Physiol. Scand. **75**: 64–68, 1969.
5a. ALTSCHULE, M. D.: Preliminary observations on the measurement of aminochromes in the blood. *In* Molecular Basis of Some Aspects of Mental Activity, ed. by O. Walaas, vol. 2, pp. 415–433, Academic Press, New York, 1967.
6. AMBRUS, C. M., PICKREN, J. W., WEINTRAUB, D. H., NIEWANDER, K. R., AMBRUS, J. L., RODBARD, D. AND LEVY, J. C.: Studies on hyaline membrane disease *v.* oxygen induced hyaline membrane disease in guinea pigs. Biol. Neonatorum **12**: 246–260, 1968.
7. ARMSTRONG, H. G.: The toxicity of oxygen at decreased barometric pressures. Mil. Surg. **83**: 148–151, 1938.
8. ASCHAN, G.: Oxygen deficiency and oxygen poisoning as stress factors. Acta Soc. Med. Upsal. **58**: 265–268, 1953.
9. ASCHAN, G. AND WALLENIUS, G.: Electrophoretic studies of transudates caused by experimental oxygen poisoning and oxygen deficiency. Acta Soc. Med. Upsala. **58**: 315–320, 1953.
10. ASHTON, N. B., WARD, B. AND SERPELL, G.: Role of oxygen in the genesis of retrolental fibroplasia. Brit. J. Ophthalmol. **37**: 513–520, 1953.
11. ASHTON, N., WARD, B. AND SERPELL, G.: Effect of oxygen on developing retinal vessels with particular reference to the problem of retrolental fibroplasia. Brit. J. Ophthalmol. **38**: 397–432, 1954.
12. ASLAMI, A., RACE, G. J., FINNEY, J. W. AND URSCHEL, H. C.: An unsatisfactory method for experimental production of hyaline membrane disease. Texas Rep. Biol. Med. **26**: 249–251, 1968.
13. BABCHINSKIY, F. V., MALKIN, V. B. AND YUDHNOVSKIY, G. D.: Tolerance of animals to hyperoxia, hypercapnia and high temperature after adaptation to lowered barometric pressure. *In* Problems of Space Biology, vol. 8: Adaptation to Hypoxia and Resistance of an Organism, ed. by V. N. Chernigovskiy, pp. 76–83, NASA TT F-580, 1969.
14. BACK, K. C.: Toxicity studies on animals exposed continuously to a 5 psia 100% oxygen environment for periods up to 235 days. *In* Proceedings of the Second Annual Conference on Atmospheric Contamination in Confined Spaces. Aerospace Medical Research Laboratories Report AMRL-TR-66-120, pp. 80–87, Wright-Patterson Air Force Base, Ohio, 1966.
15. BAHNSON, H. T. AND MATHEWS, C. M.: Blood and tissue gases of animals exposed to one and seven atmospheres of oxygen or air. Amer. J. Physiol. **175**: 87–92, 1953.
16. BALAKHOVSKII, I. S., MANSUROV, A. R. AND YAZDOVSKII, V. I.: The effect of pure oxygen inhalation on the lungs and heart of white rats. Byull. Eksp. Biol. Med. **53**: 43–47, 1962.
17. BALENTINE, J. D.: Pathologic effects of exposure to high oxygen tensions. N. Engl. J. Med. **275**: 1038–1040, 1966.
18. BALENTINE, J. D. AND GUTSCHE, B. B.: Central nervous system lesions in rats exposed to oxygen at high pressure. Amer. J. Pathol. **48**: 107–127, 1966.
19. BALENTINE, J. D. AND GUTSCHE, B. B.: Influence of pentobarbital anesthesia on the distribution of central nervous system lesions in rats exposed to oxygen at high pressure. *In* Proceedings of the Third International Con-

ference on Hyperbaric Medicine, ed. by I. W. Brown, Jr. and B. G. Cox, pp. 145–150, NAS,NRC Publ. No. 1404, Washington, D.C., 1966.

20. Barach, A. L., Eckman, M., Oppenheimer, E. T., Rumsey, C , Jr. and Soroka, M.: Observations on methods of increasing resistance to oxygen poisoning and studies of accompanying physiological effects. Amer. J. Physiol. 142: 462–475, 1944.

20a. Barber, R. E., Lee, J. and Hamilton, W. K.: Oxygen toxicity in man. A prospective study in patients with irreversible brain damage. N. Engl. J. Med. 283: 1478–1484, 1970.

21. Barr, P. O.: Hypoxemia in man induced by prolonged acceleration. Acta Physiol. Scand. 54: 128–137, 1962.

22. Bartek, M. J., Daniels, M. B. and Ulvedal, F.: Growth of the young male rat in a hyperoxic environment. U.S. Air Force School of Aerospace Medicine, Aerospace Medical Division SAM-TR-67-82, Brooks Air Force Base, Texas, September, 1967.

22a. Barter, R. A., Finlay-Jones, L. R. and Walters, M. N.-I.: Pulmonary hyaline membrane: sites of formation in adult lungs after assisted respiration and inhalation of oxygen. J. Pathol. Bacteriol. 95: 481–488, 1968.

23. Bean, J. W.: Effect of high oxygen pressure on carbon dioxide transport, on blood and tissue acidity, on O_2 consumption and pulmonary ventilation. J. Physiol. (London) 72: 27–48, 1931.

24. Bean, J. W.: Effects of oxygen at high pressure Physiol Rev 25: 1–147, 1945.

25. Bean, J. W.: The hypophysis as a determinant in the reaction of the mammal to oxygen at high pressure. Amer. J. Physiol. 170: 508–517, 1952.

26. Bean, J. W.: Hormonal aspects of oxygen toxicity. *In* Proceedings of the Underwater Physiology Symposium ed. by C. J. Lambertsen, pp. 13–19, NAS,NRC Publ. No. 377, Washington, D.C., 1955.

27. Bean, J. W.: Reserpine and reaction to O_2 at high pressure. Fed. Proc. 15: 11–12, 1956.

28. Bean, J. W.: Reserpine, chlorpromazine and the hypothalamus in reactions to oxygen at high pressure. Amer. J. Physiol. 187: 389–394, 1956.

29. Bean, J. W.: Cerebral O_2 in exposures to O_2 at atmospheric and higher pressure, and influence of CO_2. Amer. J. Physiol. 201: 1192–1198, 1961.

30. Bean, J. W.: Tris buffer, CO_2, and sympatho-adrenal system in reactions to O_2 at high pressure. Amer. J. Physiol. 201: 737–739, 1961.

31. Bean, J. W.: General effects of oxygen at high tension. *In* Oxygen in the Animal Organism, ed. by F. Dickens and E. Neil, pp. 455–474, Macmillan, New York, 1964.

32. Bean, J. W.: Problems of oxygen toxicity. *In* Clinical Application of Hyperbaric Oxygen, ed. by I. Boerema W. H. Brummelkamp and N. G. Meijne, pp. 267–276, Elsevier Publ. Co., Amsterdam, 1964.

33. Bean, J. W.: Factors influencing clinical oxygen toxicity, Ann. N.Y. Acad. Sci. 117: 745–755, 1965.

34. Bean, J. W., Baker, B. L. and Johnson, P.: Cytological alterations of adrenal cortex induced by oxygen at high pressure. Fed. Proc. 12: 11, 1953.

35. Bean, J. W. and Bauer, R.: Thyroid in pulmonary injury induced by O_2 in high concentration at atmospheric pressure Proc. Soc. Exp. Biol. Med. 81: 693–694, 1952.

36. Bean, J. W. and Beckman, D. L.: Centrogenic pulmonary pathology in mechanical head injury. J. Appl. Physiol 27: 807–812, 1969.

37. Bean, J. W. and Johnson, P. C.: Influence of hypophysis on pulmonary injury induced by exposure to oxygen at high pressure and by pneumococcus. Amer. J. Physiol. 171: 451–458, 1952.

38. Bean, J. W. and Johnson, P. C.: Adrenocortical response to single and repeated exposure to oxygen at high pressure. Amer. J. Physiol. 179: 410–414, 1954.

39. Bean, J. W. and Johnson, P. C.: Epinephrine and neurogenic factors in the pulmonary edema and CNS reactions induced by O_2 at high pressure. Amer. J. Physiol. 180: 438–444, 1955.

40. Bean, J. W., Johnson, P. and Smith, C. W.: Adrenocortical and medullary factors in O_2 at high pressure. Fed. Proc. 13: 9, 1954.

41. Bean, J. W., Johnson, P., Smith, C. and Bauer, R.: Effects of thyroid and insulin on the pulmonary reaction to oxygen. Fed. Proc. 12: 12, 1953.

42. Bean, J. W. and Smith, C. W.: Hypophyseal and adrenocortical factors in pulmonary damage induced by oxygen at atmospheric pressure. Amer. J. Physiol. 172: 169–174, 1953.

43. Bean, J. W. and Zee, D.: Metabolism and the protection by anesthesia against toxicity of O_2 at high pressure. J. Appl. Physiol. 20: 525–530, 1965.

44. Bean, J. W. and Zee, D.: Influence of anesthesia and CO_2 on CNS and pulmonary effects of O_2 at high pressure. J. Appl. Physiol. 21: 521–526, 1966.

45. Bean, J. W., Zee, D. and Thom, B.: Pulmonary changes with convulsions induced by drugs and oxygen at high pressure. J. Appl. Physiol. 21: 865–872, 1966.

46. Bean, J. W., Zee, D. and Thom, B.: Pulmonary involvement in oxygen toxicity. Jap. Heart J. 8: 734–736, 1967.

47. Becker-Freyseng, H.: Physiological and patho-physiological effects of increased oxygen tension. *In* German Aviation Medicine in World War II, vol. I, pp. 493–514, United States Air Force School of Aviation Medicine, 1950.

48. Becker-Freyseng, H. and Clamann, H. G.: Zur frage der sauerstoffvergiftung. Klin. Wochenschr. 18: 1382–1385, 1939.

49. Beckman, D. L. and Bean, J. W.: Pulmonary damage and head injury. Proc. Soc. Exp. Biol. Med. 130: 5–9, 1969.

50. Beckman, D.L. and Bean, J. W.: Pulmonary pressure-volume changes attending head injury. J. Appl. Physiol. 29: 631–636, 1970.

51. Beckman, D. L., Bean, J. W. and Baslock, D. R.: Head injury and pulmonary compliance in primates. Fed. Proc. 29: 594, 1970.

52. BECKMAN, D. L. AND WEISS, H. S.: Hyperoxia compared to surfactant washout on pulmonary compliance in rats. J. Appl. Physiol. **26:** 700–709, 1969.
53. BEEHLER, C. C.: Oxygen and the eye. Surv. Ophthalmol. **9:** 549–560, 1964.
54. BEEHLER, C. C., NEWTON, N. L., CULVER, J. F. AND TREDICI, T.: Ocular hyperoxia. Aerosp. Med. **34:** 1017–1020, 1963.
55. BEHNKE, A. R., FORBES, H. S. AND MOTLEY, E. P.: Circulatory and visual effects of oxygen at 3 atmospheres pressure. Amer. J. Physiol. **114:** 436–442, 1935.
56. BEHNKE, A. R., JOHNSON, F. S., POPPEN, J. R. AND MOTLEY, E. P.: The effect of oxygen on man at pressures from 1 to 4 atmospheres. Amer. J. Physiol. **110:** 565–572, 1934–35.
57. BEHNKE, A. R., SHAW, L. A., SHILLING, C. W., THOMSON, R. M. AND MESSER, A. C.: Studies on the effects of high pressure O_2. 1. Effect of high oxygen pressure upon the carbon dioxide and oxygen content, the acidity and carbon dioxide combining power of the blood. Amer. J. Physiol. **107:** 13–28, 1934.
58. BENJAMIN, F. B. AND PEYSER, L.: Effect of oxygen on radiation resistance of mice. Aerosp. Med. **35:** 1147–1149, 1964.
59. BENNETT, G. A. AND SMITH, F. J. C.: Pulmonary hypertension in rats living under compressed air conditions. J. Exp. Med. **59:** 181–196, 1934.
60. BENNETT, P. B.: Comparison of the effects of drugs on nitrogen narcosis and oxygen toxicity in rats. Life Sci. **12:** 721–727, 1962.
61. BENNETT, P. B.: Cortical CO_2 and O_2 at high pressures of argon, nitrogen, helium and oxygen. J. Appl. Physiol. **20:** 1249–1252, 1965.
62. BENNETT, P. B.: Hyperbaric oxygen and the significance of increased cerebral oxygen and carbon dioxide tensions. Int. Anesthesiol. Clin. **4:** 41–62, 1966.
63. BENNETT, P. B.: Performance impairment in deep diving due to nitrogen, helium, neon and oxygen. *In* Underwater Physiology, ed. by C. J. Lambertsen, pp. 327–340, Williams & Wilkins, Baltimore, 1967.
64. BERFENSTEM, R., EDLUND, T. AND ZETTERGREN, L.: Hyaline membrane disease. Acta Paediat. **47:** 82–100, 1958.
65. BERFENSTAM, R., EDLUND, T. AND ZETTERGREN, L.: Hyaline membrane disease: influence of high oxygen concentration on ciliary activity in respiratory tract: experimental study on rabbits. Acta Paediat. **47:** 527–533, 1958.
66. BERT, P.: Barometric Pressure; Researches in Experimental Physiology, translated by M. A. Hitchcock and F. A. Hitchcock, College Book Co , Columbus. Ohio, 1943.
67. BERTHARION, G. AND BARTHELEMY, I.: Acute effect of hyperbaric oxygen. Neurophysiological study. Rev. Agressol. **5:** 583–594, 1964.
68. BEZNAK, A. B. L. AND LILJESTRAND, G.: The effect of variations in oxygen tension on the lymph flow. Acta Physiol. Scand. **19:** 170–186, 1949.
69. BINET, L. AND BOCHET, M.: L'adaptation à la vie dans l'oxygene pur. J. Physiol. Pathol. Gén. **38:** 341–349, 1941–1945.
70. BINET, L. AND BOCHET, M.: De l'adaptation a l'hyperoxie. C. R. Hebd. Séances Acad. Sci. Paris **221:** 161–164, 1945.
71. BINET, L. AND BOCHET, M.: Prolonged exposure to pure oxygen. Biol. Med. (Paris) **40:** 85–89, 1951.
72. BINET, L. AND BOCHET, M.: Resistance to hyperoxia of the frog *Rana esculenta* maintained in 100 per cent oxygen for fifty-two days. J. Physiol. (Paris) **55:** 405–412, 1963.
73. BINGER, C. A. L., FAULKNER, J. M. AND MOORE, R. L.: Oxygen poisoning in mammals. J. Exp. Med. **45:** 849–864, 1927.
74. BLENKARN, G. D., SCHANBERG, S. M. AND SALTZMAN, H. A.: Cerebral amines and acute hyperbaric oxygen toxicity. J. Pharmacol. Exp. Ther. **166:** 346–353, 1969.
75. BOLANDE, R. P. AND KLAUS, M. H.: The morphologic demonstration of an alveolar lining layer and its relationship to pulmonary surfactant. Amer. J. Pathol. **45:** 449–462, 1964.
76. BOND, A. N.: An analysis of the response of salamander gills to changes in the oxygen concentration of the medium. Develop. Biol. **2:** 1–20, 1960.
77. BONDURANT, S. AND SMITH, C.: Effect of oxygen intoxication on the surface characteristics of lung extracts. Physiologist **5:** 111, 1962.
78. BORNSTEIN, A. AND STROINK: Regarding oxygen poisoning. Deut. Med. Wochenschr. **38:** 1495–1497, 1912.
79. BOWDEN, D. H., ADAMSON, I. Y. R. AND WYATT, J. P.: Reaction of the lung cells to a high concentration of oxygen. Arch. Pathol. **86:** 671–675, 1968.
80. BOYCOTT, A. E. AND OAKLEY, C. L.: Oxygen poisoning in rats. J. Pathol. Bacteriol. **35:** 468–469, 1932.
81. BRAUER, R. W., PARRISH, D. E., WAY, R. D., PRATT, P. C. AND PESSOTTI, R. L.: Protection by altitude acclimatization against lung damage from exposure to oxygen at 825 mm Hg. J. Appl. Physiol. **28:** 474–481, 1970.
82. BREWIS, R. A.: Oxygen toxicity during artificial ventilation. Thorax **24:** 656–666, 1969.
83. BROOKSBY, G. A., DATNOW, B. AND MENZEL, D. B.: Pulmonary hypertension induced by high partial pressures of oxygen. Physiologist **10:** 134, 1967.
84. BROOKSBY, G. A., DENNIS, R. L., DATNOW, B. AND CLARK, D.: Experimental emphysema. Histologic changes and alterations in pulmonary circulation. Calif. Med. **107:** 391–395, 1967.
85. BROOKSBY, G. A., DENNIS, R. L. AND STALEY, R. W.: Effects of continuous exposure of rats to 100 per cent oxygen at 450 mm Hg for 64 days. Aerosp. Med. **37:** 243–246, 1966.
86. BROOKSBY, G. A., DENNIS, R. L. AND STALEY, R. W.: Effects of prolonged exposures of rats to increased oxygen pressures. *In* Proceedings of the Third International Conference on Hyperbaric Medicine, ed. by I. W. Brown Jr. and B. G. Cox, pp. 208–216, NAS/NRC Publ. No. 1404, Washington, D.C., 1966.

87. Brooksby, G. A. and Staley, R. W.: Static volume-pressure relations in lungs of rats exposed to 100 percent oxygen. Physiologist 9: 144, 1966.
88. Brosemer, R. W. and Rutter, W. J.: The effect of oxygen tension on the growth and metabolism of a mammalian cell. Exp. Cell Res. 25: 101–113, 1961.
89. Bruns, P. D. and Shields, L. V.: The pathogenesis and relationship of the hyaline-like pulmonary membrane to premature neonatal mortality. Amer. J. Obstet. Gynecol. 61: 953–965, 1951.
90. Bruns, P. D. and Shields, L. V.: High O_2 and hyaline-like membranes. Amer. J. Obstet. Gynecol. 67: 1224–1236, 1954.
91. Buckingham, S., Heinemann, H. O., Sommers, S. C. and McNary, W. F.: Phospholipid synthesis in the large pulmonary alveolar cell. Amer. J. Pathol. 48: 1027–1041, 1966.
92. Buckingham, S. and Sommers, S. C.: Pulmonary hyaline membranes. Amer. J. Dis. Child. 99: 216–227, 1960.
93. Buckingham, S., Sommers, S. C. and McNary, W. F.: Sympathetic activation and serotonin release as factors in pulmonary edema after hyperbaric oxygen. Fed. Proc. 25: 566, 1966.
94. Buckingham, S., Sommers, S. C. and McNary, W. F.: Experimental respiratory distress syndrome. I. Central autonomic and humoral pathogenetic factors in pulmonary injury of rats induced with hyperbaric oxygen and the protective effects of barbiturates and trasylol. Biol. Neonatorum 12: 261–281, 1968.
95. Burdick, R. L.: Cited by Forster, R. E. *In* Man's Dependence on the Earthly Atmosphere, ed. by K. E. Schafer, pp. 262–276, Macmillan, New York, 1962.
96. Burger, E. J., Jr.: Pulmonary mechanics associated with oxygen toxicity and a suggested physiological test for susceptibility to the effects of oxygen. Aerosp. Med. 38: 507–513, 1967.
97. Burger, E. J., Jr. and Macklem, P.: Airway closure: demonstration by breathing 100% O_2 at low lung volumes and by N_2 washout. J. Appl. Physiol. 25: 139–148, 1968.
98. Burger, E. J., Jr. and Mead, J.: Static properties of lungs after oxygen exposure. J. Appl. Physiol. 27: 191–197, 1969.
99. Caldwell, P. R. B., Giammona, S. T., Lee, W. L., Jr. and Bondurant, S.: Effect of oxygen breathing at one atmosphere on the surface activity of lung extracts in dogs. Ann. N. Y. Acad. Sci. 121: 823–828, 1965.
100. Caldwell, P. R. B., Lee, W. L., Jr., Schildkraut, H. S. and Archibald, E. R.: Changes in lung volume, diffusing capacity, and blood gases in men breathing oxygen. J. Appl. Physiol. 21: 1477–1483, 1966.
101. Campbell, J. A.: Effects of breathing oxygen at high pressures upon tissue gas tensions. J. Physiol. (London) 68: vii–viii, 1930.
102. Campbell, J. A.: Oxygen poisoning and the thyroid gland. J. Physiol. (London) 90: 91–92P, 1937.
103. Campbell, J. A.: Oxygen poisoning and tumor growth. Brit. J. Exp. Pathol. 18: 191–197, 1937.
104. Campbell, J. A.: Effects of oxygen pressure as influenced by external temperature, hormones and drugs. J. Physiol. (London) 92: 29–31P, 1938.
105. Castleman, B. and McNeely, B. V. (eds.): Case records of the Massachusetts General Hospital. Case 7-1967. N. Engl. J. Med. 276: 401–411, 1967.
106. Castleman, B. and McNeely, B. V. (eds.): Case records of the Massachusetts General Hospital. Case 20-1970. N. Engl. J. Med. 282: 1087–1096, 1970.
107. Cederberg, A., Hellsten, S. and Miörner, G.: Oxygen treatment and hyaline pulmonary membranes in adults. Acta Pathol. Microbiol. Scand. 64: 450–458, 1965.
108. Cedergren, B., Gyllensten, L. and Wersäll, J.: Pulmonary damage caused by oxygen poisoning: electron microscopic study in mice. Acta Paediat. Scand. 48: 477–494, 1959.
109. Chapin, J. L.: Anticonvulsant threshold of CO_2 in oxygen under high pressure. Proc. Soc. Exp. Biol. Med. 90: 663–664, 1955.
110. Chapin, J. L. and Hohl, T. M., Jr.: Cited by Bruns, P. D. and Shields, L. V.: High O_2 and hyaline-like membranes. Amer. J. Obstet. Gynecol. 67: 1224–1236, 1954.
111. Christensen, G. M., Dahlke, L. W., Griffin, J. T., Moutvic, J. C. and Jackson, K. L.: The effect of high-pressure oxygen on acute radiation mortality in mice. Radiat. Res. 37: 283–286, 1969.
112. Churchill-Davidson, I.: The oxygen effect in radiotherapy. Proc. Roy. Soc. Med. 57: 635–638, 1964.
113. Churchill-Davidson, I., Sanger, C. and Thomlinson, R. H.: Oxygenation in radiotherapy. II. Clinical application. Brit. J. Radiol. 30: 406–422, 1957.
114. Clark, J. M.: Derivation of pulmonary oxygen tolerance curves describing the rate of development of pulmonary oxygen toxicity in man, Ph.D. Thesis, Graduate School of Arts and Sciences, University of Pennsylvania, 1970.
115. Clark, J. M. and Lambertsen, C. J.: Pulmonary oxygen tolerance and the rate of development of pulmonary oxygen toxicity in man at two atmospheres inspired oxygen tension. *In* Underwater Physiology, ed. by C. J. Lambertsen, pp. 439–451, Williams & Wilkins, Baltimore, 1967.
116. Clark, J. M. and Lambertsen, C. J.: Rate of development of pulmonary O_2 toxicity in man during O_2 breathing at 2.0 atm abs. J. Appl. Physiol. 30: 739–752, 1971.
117. Clarke, G. M., Sandison, A. T. and Ledingham, I. McA.: Acute pulmonary oxygen toxicity: a pathophysiological study at 1 and 2 atmospheres absolute (ATA) in spontaneously breathing anaesthetised dogs. Brit. J. Anaesth. 41: 558–559, 1969.
118. Cleveland, L. R.: Toxicity of oxygen for protozoa *in vivo* and *in vitro*. Animals defaunated without injury. Biol. Bull. 48: 455–468, 1925.
119. Collier, C. R., Hackney, J. D. and Rounds, D. E.: Alterations of surfactant in oxygen poisoning. Dis. Chest. 48: 233–238, 1965.
120. Comroe, J. H., Jr., Dripps, R. D., Dumke, P. R. and Deming, M.: Oxygen toxicity. The effect of inhalation

of high concentrations of oxygen for twenty-four hours on normal men at sea level and at a simulated altitude of 18,000 feet. J. Amer. Med. Ass. 128: 710–717, 1945.

121. Cook, S. F. and Leon, H. F.: Survival of C-57 mice and squirrel monkeys in high and low pressures of oxygen. USAF Missile Development Center Technical Report 60-21, October 1960.
122. Cross, M. H. and Houlihan, R. T.: Sympathoadrenomedullary response of the rat to high oxygen exposures. J. Appl. Physiol. 27: 523–527, 1969.
123. Dale, W. A. and Rahn, H.: Rate of gas absorption during atelectasis. Amer. J. Physiol. 170: 606–615, 1952.
124. Dalhamn, T. and Rosengren, A.: Oxygen effects on tracheal ciliary activity *in vitro*. Arch. Environ. Health 19: 661–662, 1969.
125. Davies, H. C. and Davies, R. E.: Biochemical aspects of oxygen poisoning. *In* Handbook of Physiology, Section 3: Respiration, vol. II, ed. by W. O. Fenn and H. Rahn, pp. 1047–1058, American Physiological Society, Washington, D.C., 1965.
126. De, T. D. and Anderson, G. W.: The experimental production of pulmonary hyaline-like membranes with atelectasis. Amer. J. Obstet. Gynecol. 68: 1557–1567, 1954.
127. DeClement, F. A. and Smith, C. W.: Alteration of toxicity of oxygen at atmospheric pressure by addition of CO_2 and of N_2. Fed. Proc. 21: 444, 1962.
128. Dejours, P., Labrousse, Y., Raynaud, J. and Teillac, A.: Stimulus oxygène chémoréflexe de la ventilation à basse altitude (50m) chez l'homme. 1. Au repos. J. Physiol. (Paris) 49: 115–120, 1957.
129. deLemos, R., Wolfsdorf, J., Nachman, R., Block, A. J., Leiby, G., Wilkinson, H. A., Allen, T., Haller, J. A., Morgan, W. and Avery, M. E.: Lung injury from oxygen in lambs: the role of artificial ventilation. Anesthesiology 30: 609–618, 1969.
130. Dery, R., Pelletier, J., Jacques, A., Clavet, M. and Houde, J.: Alveolar collapse induced by denitrogenation. Can. Anaesthiol. Soc. J. 12: 531–544, 1965.
131. Dickens, F.: The toxic effect of oxygen on nervous tissue. *In* Neurochemistry, ed. by K. A. C. Elliott, I. H. Page and J. H. Quastel, pp. 851–869, Thomas, Springfield, Ill., 1962.
132. Dickerson, K. H.: Pathophysiology of pulmonic toxicity in rats exposed to 100 percent oxygen at reduced pressures. Aviation Medical Acceleration Laboratory, NADC-ML-6403, U.S. Naval Air Development Center, Johnsville, Pennsylvania, May 1964.
133. Dines, J. H. and Hiatt, E. P.: Prolonged exposure of young rats to oxygen atmosphere at reduced pressure. J. Appl. Physiol. 19: 17–20, 1964.
134. Doležal, V.: The effect of longlasting oxygen inhalation upon respiratory parameters in man. Physiol. Bohemoslov. 11: 149–158, 1962.
135. Doležal, V.: Effects on the body of prolonged inhalation of oxygen during normal barometric pressure. Cesk. Fysiol. 11: 326–355, 1962.
136. Doležal, V.: Some humoral changes in man produced by continuous oxygen inhalation at normal barometric pressure. Riv. Med. Aeronaut. 25: 219–233, 1962.
137. Doležal, V.: Effect on organism of pure oxygen applied by excessive pressure. Cesk. Fysiol. 17: 347–363, 1968.
138. Donald, K. W.: Oxygen poisoning in man. I and II. Brit. Med. J. 1: 667–672, 712–717, 1947.
139. Downes, J. J. and Lambertsen, C. J.: Dynamic characteristics of ventilatory depression in man on abrupt administration of O_2. J. Appl. Physiol. 21: 447–453, 1966.
140. Drastich, L.: Cited by Becker-Freyseng, H.: Physiological and patho-physiological effects of increased oxygen tension. *In* German Aviation Medicine in World War II, vol. I, pp. 493–514, United States Air Force School of Aviation Medicine, 1950.
141. Drinker, C. K. and Field, M. E.: Lymphatics, Lymph and Tissue Fluid. Williams & Wilkins, Baltimore, 1933.
142. DuBois, A. B., Hyde, R. W. and Hendler, E.: Pulmonary mechanics and diffusing capacity following simulated space flight of two weeks duration. J. Appl. Physiol. 18: 696–698, 1963.
143. DuBois, A. B., Turaids, T., Mammen, R. E. and Nobrega, F. T.: Pulmonary atelectasis in subjects breathing oxygen at sea level or at simulated altitude. J. Appl. Physiol. 21: 828–836, 1966.
144. Durfey, J. Q.: Post-mortem pulmonary changes occurring in mice exposed to 100% oxygen at 740 mm Hg for 48 hours. Acta Anaesthesiol. Scand. suppl. 15: 154, 1964.
145. Durfey, J. Q.: Post-mortem pulmonary changes occurring in mice exposed to 100 percent oxygen at 740 mm Hg. Aerosp. Med. 36: 46–50, 1965.
146. Edström, J. E. and Röckert, H.: The effect of oxygen at high pressure on the histology of the central nervous system and sympathetic and endocrine cells. Acta Physiol. Scand. 55: 255–263, 1962.
147. Ernsting, J.: The effect of breathing high concentrations of oxygen upon the diffusing capacity of the lung in man. J. Physiol. (London) 155: 51–52P, 1961.
148. Evans, M. J., Bils, R. F. and Hackney, J. D.: An electron microscopic study of cellular renewal in pulmonary alveolar walls of normal and oxygen poisoned mice. Aspen Emphysema Conf. 11: 33–40, 1968.
149. Faiman, M. D. and Heble, A. R.: The effect of hyperbaric oxygenation on cerebral amines. Life Sci. 5: 2225–2234, 1966.
150. Faibchild, E. J., II.: Eight-month continuous exposure of animals to an oxygen-nitrogen atmosphere at 5 psia. Aerospace Medical Research Laboratories Report AMRL-TR-67-200, pp. 9–28, Wright-Patterson Air Force Base, Ohio, 1967.
151. Faulkner, J. M. and Binger, C. A. L.: Oxygen poisoning in cold blooded animals. J. Exp. Med. 45: 865–871, 1927.
152. Felig, P.: Observations on rats exposed to a space cabin atmosphere for two weeks. Aerosp. Med. 36: 858–863, 1965.

153. FELIG, P.: Oxygen toxicity: ultrastructural and metabolic aspects. Aerosp. Med. 36: 658–662, 1965.
154. FELIG, P., GOLDMAN, J. K. AND LEE, W. L., JR.: Protein-bound iodine in serum of rats breathing 99 percent oxygen. Science 145: 601–602, 1964.
155. FELIG, P. AND LEE, W. L., JR.: Effects of sodium lactate on oxygen toxicity in the rat. Ann. N.Y. Acad. Sci. 121: 829–835, 1965.
156. FENN, W. O.: Inert gas narcosis. Ann. N.Y. Acad. Sci. 117: 760–767, 1965.
157. FENN, W. O.: Interactions of oxygen and inert gases in Drosophila. Resp. Physiol. 3: 117–129, 1967.
158. FENN, W. O., GERSCHMAN, R., GILBERT, D. L., TERWILLIGER, D. AND COTHRAN, F. V.: Mutagenic effects of high oxygen tensions on *Escherichia coli*. Proc. Nat. Acad. Sci. U.S.A. 43: 1027–1032, 1957.
159. FENN, W. O., HENNING, M. AND PHILPOTT, M.: Oxygen poisoning in *Drosophila*. J. Gen. Physiol. 50: 1693–1707, 1967.
160. FENN, W. O., PHILPOTT, M., MEEHAN, C. AND HENNING, M.: Recovery from oxygen poisoning in *Drosophila*. Amer. J. Physiol. 213: 663–670, 1967.
161. FISHER, A. B., HYDE, R. W., PUY, R. J. M., CLARK, J. M. AND LAMBERTSEN, C. J.: Effect of oxygen at 2 atmospheres on the pulmonary mechanics of normal man. J. Appl. Physiol. 24: 529–536, 1968.
162. FRANCK, C., LAMARCHE, M., ARNOULD, P. AND DEMANGE, J. M.: Action de l'hyperoxie sur le taux d'histamine dans le sang et le tissu pulmonaire du cobaye non anesthésié. J. Physiol. (Paris) 49: 176–177, 1957.
163. FRANKENHAEUSER, M., GRAFF-LONNEVIG, V. AND HESSER, C. M.: Effects on psychomotor functions of different nitrogen-oxygen gas mixtures at increased ambient pressures. Acta Physiol. Scand. 59: 400–409, 1963.
164. FRIEDRICH, M. AND GRAYZEL, D. M.: High resistance of rhesus monkeys to 90 plus percent oxygen. Proc. Soc. Exp. Biol. Med. 56: 204–205, 1944.
165. FUJIKURA, T.: Pulmonary hyaline membranes in various strains of mice. Amer. J. Obstet. Gynecol. 87: 1081–1085, 1963.
166. FUJIKURA, T.: Effect of anticoagulant, fibrinolytic and antifibrinolytic agents on experimental hyaline membranes. Amer. J. Obstet. Gynecol. 90: 850–853, 1964.
167. FUJIWARA, T., ADAMS, F. H. AND SETO, K.: Lipids and surface tension of extracts of normal and O_2 treated guinea pig lungs. J. Pediat. 65: 45–52, 1964.
168. FURREY, D. E.: Tolerance of mice X-irradiated in an oxygen-rich environment to explosive decompression. Aerosp. Med. 35: 459–461, 1964.
169. FUSON, R. L., SALTZMAN, H. A., SMITH, W. W., WHALEN, R. E., OSTERHOUT, S. AND PARKER, R. F.: Clinical hyperbaric oxygenation with severe oxygen toxicity. Report of a case. N. Engl. J. Med. 273: 415–419, 1965.
170. GABLE, W. D. AND TOWNSEND, F. M.: Lung morphology of individuals exposed to prolonged intermittent supplemental oxygen. Aerosp. Med. 33: 1344–1348, 1962.
171. GARWACKI, J.: Effect of neuroplegic drugs on changes in the respiratory organs in rats breathing pure oxygen under pressure (1 atm). Acta Physiol. Pol. 11: 73–85, 1960.
172. GERSCHMAN, R.: The biological effects of increased oxygen tension. *In* Man's Dependence on the Earthly Atmosphere, ed. by K. E. Schaefer, pp. 170–179, Macmillan, New York, 1962.
173. GERSCHMAN, R.: Biological effects of oxygen. *In* Oxygen in the Animal Organism, ed. by F. Dickens and E. Neil, pp. 475–494, Macmillan, New York, 1964.
174. GERSCHMAN, R. AND FENN, W. O.: Ascorbic acid content of adrenal glands of rat in oxygen poisoning. Amer. J. Physiol. 176: 6–8, 1954.
175. GERSCHMAN, R., GILBERT, D. L. AND CACCAMISE, D.: Effects of various substances on survival times of mice exposed to different high oxygen tensions. Amer. J. Physiol. 192: 563–571, 1958.
176. GERSCHMAN, R., GILBERT, D. L. AND FROST, J. N.: Sensitivity of *Paramecium caudatum* to high oxygen tensions and its modification by cobalt and manganese ions. Amer. J. Physiol. 192: 572–576, 1958.
177. GERSCHMAN, R., GILBERT, D. L. AND NYE, S. W.: Survival time of newborn rats and mice in high oxygen pressure (HOP). Studies on oxygen poisoning. USAF School of Aerospace Medicine Report No. 10, pp. 35–36, Randolph Field, Texas, 1955.
178. GERSCHMAN, R., GILBERT, D. L. AND NYE, S. W.: The effects of autonomic drugs on oxygen poisoning. USAF School of Aviation Medicine Report No. 56–42, Randolph Air Force Base, Texas, 1956.
179. GERSCHMAN, R., GILBERT, D. L., NYE, S. W., DWYER, P. AND FENN, W. O.: Oxygen poisoning and x-irradiation: a mechanism in common. Science 119: 623–626, 1954.
180. GERSCHMAN, R., GILBERT, D. L., NYE, S. W., NADIG, P. AND FENN, W. O.: Role of adrenalectomy and adrenal cortical hormones in oxygen poisoning. Amer. J. Physiol. 178: 346–350, 1954.
181. GERSCHMAN, R., GILBERT, D. L., NYE, S. W., PRICE, W. E., JR. AND FENN, W. O.: Effects of autonomic drugs and of adrenal glands on oxygen poisoning. Proc. Soc. Exp. Biol. Med. 88: 617–621, 1955.
182. GERSCHMAN, R., GILBERT, D. L., NYE, S. W., PRICE, W. E., JR. AND FENN, W. O.: The role of the adrenal cortical hormones and of dibenzyline in normal and demedullated mice submitted to high oxygen pressure. USAF School of Aviation Medicine Report No. 56–44, Randolph Air Force Base, Texas, 1956.
183. GERSCHMAN, R. AND NADIG, P. W. Stress and oxygen poisoning. Fed. Proc. 12: 50–51, 1953.
184. GERSCHMAN, R., NADIG, P. W., SNELL, A. D., JR. AND NYE, S. W.: Effect of high oxygen concentrations on eyes of newborn mice. Amer. J. Physiol. 179: 115–118, 1954.
185. GERSCHMAN, R., NYE, S. W. AND GILBERT, D. L.: Studies on oxygen poisoning. Further report on the protective effects of drugs of varied chemical nature. USAF School of Aerospace Medicine Report No. 10, pp. 30–34, Randolph Field, Texas, 1955.
186. GERSCHMAN, R., NYE, S. W., GILBERT, D. L., DWYER, P. AND FENN, W. O.: Studies on oxygen poisoning: protective effect of β-mercaptoethylamine. Proc. Soc. Exp. Biol. Med. 85: 75–77, 1954.

187. GERSH, I.: Syndrome of oxygen poisoning in cats. War Med. 8: 221-228, 1945.
188. GERSH, I. AND WAGNER, C. E.: Metabolic factors in oxygen poisoning. Amer. J. Physiol. 144: 270-277, 1945.
189. GERSHENOVICH, Z. S., KRICHEVSKAYA, A. A. AND ALEKSEENKO, L. P.: Adrenaline substance of the brain and suprarenals under increased oxygen pressure. Ukrayins'kyi Biokhim. Zh. 27: 3-11, 1955.
190. GESELL, R.: On the chemical regulation of respiration: regulation of respiration with special reference to the metabolism of the respiratory center and the coordination of the dual function of hemoglobin. Amer. J. Physiol. 66: 5-49, 1923.
191. GIAMMONA, S. T., KERNER, D. AND BONDURANT, S.: Effect of oxygen breathing at atmospheric pressure on pulmonary surfactant. J. Appl. Physiol. 20: 855-858, 1965.
192. GILBERT, D. L.: The role of pro-oxidants and anti-oxidants in oxygen toxicity. Radiat. Res. suppl. 3: 44-53, 1963.
193. GILBERT, D. L.: Atmosphere and evolution. *In* Oxygen in the Animal Organism, ed. by F. Dickens and E. Neil, pp. 641-654, Macmillan, New York, 1964.
194. GILBERT, D. L., GERSCHMAN, R. AND FENN, W. O.: Effects of fasting and x-irradiation on oxygen poisoning in mice. Amer. J. Physiol. 181: 272-274, 1955.
195. GOLDSTEIN, J. R. AND MENGEL, C. E.: Hemolysis in mice exposed to varying levels of hyperoxia. Aerosp. Med. 40: 12-13, 1969.
196. GOTTLIEB, S. F.: Hyperbaric oxygenation. Advan. Clin. Chem. 8: 69-139, 1965.
197. GOTTLIEB, S. F. AND JAGODZINSKY, R. V.: Role of THAM in protecting mice against convulsive episodes caused by exposure to oxygen under high pressure. Proc. Soc. Exp. Biol. Med. 112: 427-430, 1963.
198. GRANDPIERRE, R., GROGNOT, P. AND SENELAR, R.: Modifications des lésions pulmonaires provoquées par l'inhalation d'oxygène après section d'un nerf pneumogastrique. J. Physiol. (Paris) 48: 564-565, 1956.
199. GRANDPIERRE, R., SENELAR, R. AND LOUBIERRE, R.: Sur les mécanismes physiopathologiques de déclenchement de lésions locales dues à l'hyperoxie. J. Physiol. (Paris) 50: 299-301, 1958.
200. GRAY, L. H., CONGER, A. D., EBERT, M., HORNSEY, S. AND SCOTT, O. C. A.: The concentration of oxygen dissolved in tissues at the time of irradiation as a factor in radiotherapy. Brit. J. Radiol. 26: 638-648, 1953.
201. GREEN, I. D.: Synopsis of recent work done on the problem of pulmonary atelectasis associated with breathing 100% oxygen and increased positive 'G'. R.A.F. Institute of Aviation Medicine Report No. 230, Farnborough, Hants, England, 1963.
202. GREENBERG, S. D., GYORKEY, F. AND O'NEAL, R. M.: Pulmonary hyaline membranes in adults receiving oxygen therapy. Texas Rep. Biol. Med. 27: 1005-1012, 1969.
203. GROGNOT, P. AND CHOME, J : Action de la chlorpromasine et du tetrylammonium sur les réactions pulmonaires provoquées par inhalation d'oxygène pur. C.R. Séances Soc. Biol. 148: 1474-1475, 1954.
204. GROGNOT, P. AND CHOME, J.: Action de l'histamine et de antihistaminiques sur les lésions pulmonaires dues à l'inhalation de l'oxygène pur chez le rat et le cobaye. C.R. Séances Soc. Biol. 149: 562-564, 1955.
205. GROSHIKOV, M. A. AND SOROKIN, P. A.: Pathological changes in the lungs of animals under the influence of high oxygen pressures. *In* The Effect of the Gas Medium and Pressure on Body Functions, Collection No. 3, ed. by M. P. Brestkin, pp. 112-121, published for NASA, USA and NSF, Washington, D.C. by Israel Program for Scientific Translations, NASA TTF-358, TT 65-50136, 1965.
206. GROSSMAN, M. S. AND PENROD, K. E.: Relationship of hypothermia to high oxygen poisoning. Amer. J. Physiol. 156: 177-181, 1949.
207. GROSSMAN, M. S. AND PENROD, K. E.: The thyroid and high oxygen poisoning in rats. Amer. J. Physiol. 156: 182-184, 1949.
208. GUPTA, S. R. AND ABRAHAM, S.: Some factors that affect susceptibility to toxic effects of oxygen. Indian J. Med. Res. 57: 739-746, 1969.
209. GUTIERREZ, V. S., BERMAN, I. R., SOLOWAY, H. B. AND HAMIT, H. F.: Relationship of hypoproteinemia and prolonged mechanical ventilation to the development of pulmonary insufficiency in shock. Ann. Surg. 171: 385-393, 1970.
210. GUTSCHE, B. B., HARP, J. R. AND STEPHEN, C. R.: Physiologic responses of the anesthetized dog to oxygen at five atmospheres absolute. Anesthesiology 27: 615-623, 1966.
211. HACKNEY, J. D., COLLIER, C. R. AND ROUNDS, D. E.: Mechanism of pulmonary damage in oxygen poisoning. *In* Drugs and Respiration, ed. by D. Aviado and I. Palecek, vol. XI, pp. 93-103, Macmillan, New York, 1964.
212. HAGEBUSCH, O. E.: Pathology of animals exposed for 235 days to a 5 psia 100% oxygen atmosphere. *In* Proceedings of the Second Annual Conference on Atmospheric Contamination in Confined Spaces. Aerospace Medical Research Laboratories Report AMRL-TR-66-120, pp. 103-107, Wright-Patterson Air Force Base, Ohio, 1966.
213. HÄGGENDAL, J.: The effect of high pressure air or oxygen with and without carbon dioxide added on the catecholamine levels of rat brain. Acta Physiol. Scand. 69: 147-152, 1967.
214. HALE, H. B., WILLIAMS, E. W., ANDERSON, J. E. AND ELLIS, J. P., JR.: Endocrine and metabolic effects of short-duration hyperoxia. Aerosp. Med. 35: 449-451,1964.
215. HALL, A. L. AND KELLY, H. B., JR.: Cited by Roth, E. M.: Selection of space cabin atmospheres. I. Oxygen toxicity. NASA Technical Note D-2008, Washington, D.C., 1963.
216. HALL, A. L. AND MARTIN, R. J.: Prolonged exposure in the Navy full pressure suit at "space equivalent" altitudes. Aerosp. Med. 31: 116-122, 1960.
217. HALL, D. A.: The Influence of the Systematic Fluctuation of P_{O_2} upon the Nature and Rate of the Development of Oxygen Toxicity in Guinea Pigs, M.S. Thesis, Graduate School of Arts and Sciences, University of Pennsylvania, 1967.
218. HALL, P., MATSUYAMA, Y., WILLIAMS, K. R., GELFAND, R. AND LAMBERTSEN, C. J.: Effect of oxygen at 0.2, 1

and 3.5 atm abs on carotid chemoreceptor discharge in the cat at various levels of carbon dioxide. Fed. Proc. 26: 379, 1967.

219. HARP, J. R., GUTSCHE, B. B. AND STEPHEN, C. R.: Effect of anesthetics on central nervous system toxicity of hyperbaric oxygen. Anesthesiology 27: 608-614, 1966.
220. HARPER, D. T., JR. AND ROBINSON, F. R.: Pathology of animals exposed for periods up to 92 days to a pure oxygen atmosphere at reduced pressure. Aerosp. Med. 38: 340-344, 1967.
221. HARRIS, J. W. AND VAN DEN BRENK, H. A. S.: Comparative effects of hyperbaric oxygen and pentylenetetrasol on lung weight and non-protein sulfhydryl content of experimental animals. Biochem. Pharmacol. 17: 1181-1188, 1968.
222. HAUGAARD, N.: Effect of high oxygen tensions upon enzymes. *In* Proceedings of the Underwater Physiology Symposium, ed. by L. G. Goff, pp. 8-12, and p. 47, NAS/NRC Publ. 377, Washington, D.C., 1955.
223. HAUGAARD, N.: The toxic action of oxygen on metabolism and the role of trace metals. *In* Oxygen in the Animal Organism, ed. by F. Dickens and E. Neil, pp. 495-505, Macmillan, New York, 1964.
224. HAUGAARD, N.: Poisoning of cellular reactions by oxygen. Ann. N.Y. Acad. Sci. 117: 736-744, 1965.
225. HAUGAARD, N.: Cellular mechanisms of oxygen toxicity. Physiol. Rev. 48: 311-373, 1968.
226. HAWKER, J. M., REYNOLDS, E. D. R. AND TAGHIZADEH, A.: Pulmonary surface tension and pathological changes in infants dying after respirator treatment for severe hyaline membrane disease. Lancet 2: 75-77, 1967.
227. HEDERER, C. AND ANDRE, L.: De l'intoxication par les hautes pressiôns d'ôxygene. Bull. Acad. Nat. Med. (Paris) 123: 294-307, 1940.
228. HELLSTRÖM, B. AND NERGÅRDH, A.: The effect of high oxygen concentrations and hypothermia on the lung of the newborn mouse. Acta Paediat. Scand. 54: 457-466, 1965.
229. HELVEY, W. M., ALBRIGHT, G. A., BENJAMIN, F. B., GALL, L. S., PETERS, J. M. AND RIND, H.: Effects of prolonged exposure to pure oxygen on human performance. Republic Aviation Corporation, Report 393-1, NASA Contr. NASr-92, 1962.
230. HEMINGWAY, A. AND WILLIAMS, W. L.: Pulmonary edema in oxygen poisoning. Proc. Soc. Exp. Biol. Med. 80: 331-334, 1952.
231. HEMPLEMAN, H. V.: Effect of pre-exposure to carbon dioxide upon resistance to acute oxygen poisoning in the rat. Great Britain MRC-RNPRC, R.N.P. 56/860, U.P.S. 156, March 1956.
232. HENDLER, E.: Physiological effects of a simulated spaceflight profile. Fed. Proc. 22: 1060-1063, 1963.
233. HERLOCHER, J. E., QUIGLEY, D. G., BEHAR, V. S., SHAW, E. G. AND WELCH, B. E.: Physiologic response to increased oxygen partial pressure: I. Clinical observations. Aerosp. Med. 35: 613-618, 1964.
234. HILL, G. B., OSTERHOUT, S. AND O'FALLON, W. M.: Variation in response to hyperbaric oxygen among inbred strains of mice. Proc. Soc. Exp. Biol. Med. 129: 687-689, 1968.
235. HILL, L.: Influence of CO_2 in production of oxygen poisoning. Quart. J. Exp. Physiol. Cog. Med. Sci. 23: 49-50, 1933.
236. HOULIHAN, R. T.: Adaptation to chronic hyperbaric oxygen pressures. Final Scientific Report. Contr. Nonr. 656-36. USAF School of Aerospace Medicine, September 1969.
237. HOULIHAN, R. T.: Rheomelanin accumulation in the blood and lungs and hemolysis in rats poisoned by hyperbaric oxygen. J. Amer. Osteopath. Ass. 69: 1040, 1970.
238. HOULIHAN, R. T., ALTSCHULE, M. D. AND HEGEDUS, Z. L.: Indole metabolism of catecholamines during exposure to hyperbaric oxygen. Preprints of Annual Scientific Meeting of Aerospace Medical Association, pp. 192-193, 1969.
239. HOULIHAN, R. T., ALTSCHULE, M. D., HEGEDUS, Z. L. AND CROSS, M. H.: Oxidative cyclization of catecholamines following exposure to hyperbaric oxygen. Fourth International Congress on Hyperbaric Medicine (Program), Sapporo, Japan, pp. 14-15, 1969.
240. HOULIHAN, R. T., WEINER, R. E. AND ZAVODNI, J.: Adrenocortical response to simulated high altitude and to oxygen at high pressure. Physiologist 9: 206, 1966.
241. HOULIHAN, R. T., ZAVODNI, J. J. AND CROSS, M. H.: Adaptation to increased oxygen tension at ambient pressure. Aerosp. Med. 38: 995-997, 1967.
242. HOULIHAN, R. T., ZAVODNI, J. AND CROSS, M.: Effects of increased oxygen pressure on adrenal steroid and catecholamine release. *In* Aviation and Space Medicine, ed. by B. Hannisdahl and C. W. Sem-Jacobsen, pp. 68-73, Universitetsforlaget, Oslo, 1969.
243. HUDSON, L. H. AND ERDMANN, R. R.: Pulmonary vascular changes in newborn mice following exposure to increased oxygen tensions under moderate hyperbaric conditions. Angiology 17: 819-824, 1966.
244. HULPIEU, H. R. AND COLE, V. V.: The effect of humidity and temperature on oxygen toxicity. J. Lab. Clin. Med. 29: 1134-1138, 1944.
245. HYDE, R. W. AND RAWSON, A. J.: Unintentional iatrogenic oxygen pneumonitis—response to therapy. Ann. Intern. Med. 71: 517-531, 1969.
246. IGARASHI, S., HASEGAWA, K., KAWAKAMI, F., SUGASE, Z. AND NISHIKAWA, M.: Effect of hyperbaric oxygen on adrenocortical function. Folia Endocrinol. Jap. 44: 358, 1968.
247. ISHIZUKA, R. A.: Surface tension study of the animal lungs: influence of O_2 toxicity due to hyperbaric oxygenation. Jap. J. Thorac. Surg. 19: 578-585, 1966.
247a. ISHIZUKA, R., MIYAKAWA, K., MAEKAWA, T., IMAMURA, B., AKASHI, T., TANAKA, N., KASAI, Y., JOCKIN, H. C. AND BERNHARD, W. F.: Pulmonary surface characteristics in oxygen toxicity. *In* Proceedings of the Fourth International Congress on Hyperbaric Medicine, ed. by J. Wada and T. Iwa, pp. 16-21, Williams & Wilkins, Baltimore, 1970.
248. JAILER, J. W.: Adrenocorticotropin content of the immature rat pituitary gland. Endocrinology 49: 826-827, 1951.

249. JAMIESON, D.: Potentiation of HPO paralysis in rats. *In* Clinical Application of Hyperbaric Oxygen, ed. by I. Boerema *et al.*, pp. 319–323, Elsevier Publ. Co., Amsterdam, 1964.
250. JAMIESON, D.: The effect of anaesthesia and CO_2 on survival time and lung damage in rats exposed to high pressure oxygen. Biochem. Pharmacol. **15**: 2120–2122, 1966.
251. JAMIESON, D.: Role of central nervous system and pulmonary damage as cause of respiratory failure in rats exposed to hyperbaric oxygen. *In* Proceedings of the Third International Conference on Hyperbaric Medicine, ed. by I. W. Brown, Jr. and B. G. Cox, pp. 89–96, NAS/NRC Publ. 1404, Washington, D.C., 1966.
252. JAMIESON, D. AND CASS, N.: CNS and pulmonary damage in anesthetized rats exposed to hyperbaric oxygen. J. Appl. Physiol. **23**: 235–242, 1967.
253. JAMIESON, D., LADNER, K. AND VAN DEN BRENK, H. A. S.: Pulmonary damage due to high pressure oxygen breathing in rats. 4. Quantitative analysis of sulfhydryl and disulphide groups in rat lungs. Aust. J. Exp. Biol. Med. Sci. **41**: 491–497, 1963.
254. JAMIESON, D. AND VAN DEN BRENK, H. A. S.: Pulmonary damage due to high pressure oxygen breathing in rats. 2. Changes in dehydrogenase activity of rat lung. Aust. J. Exp. Biol. Med. Sci. **40**: 51–56, 1962.
255. JAMIESON, D. AND VAN DEN BRENK, H. A. S.: Pulmonary damage due to high pressure oxygen breathing in rats. 3. Quantitative analysis of fluid changes in rat lungs. Aust. J. Exp. Biol. Med. Sci. **40**: 309–314, 1962.
256. JAMIESON, D. AND VAN DEN BRENK, H. A. S.: Measurement of oxygen tensions in cerebral tissues of rats exposed to high pressures of oxygen. J. Appl. Physiol. **18**: 869–876, 1963.
257. JAMIESON, D. AND VAN DEN BRENK, H. A. S.: The effects of antioxidants on high pressure oxygen toxicity. Biochem. Pharmacol. **13**: 159–164, 1964.
258. JAMIESON, D. AND VAN DEN BRENK, H. A. S.: Pulmonary damage due to high pressure O_2 breathing in rats. 5. Changes in the surface active lung alveolar lining. Aust. J. Exp. Biol. Med. Sci. **42**: 483–490, 1964.
259. JOFFE, N. AND SIMON, M.: Pulmonary oxygen toxicity in the adult. Radiology **92**: 460–465, 1969.
260. JOHNSON, P. C. AND BEAN, J. W.: Carbon dioxide and the sympathoadrenal system in O_2 at high pressure (OHP). Fed. Proc. **14**: 81, 1955.
261. JOHNSON, P. C. AND BEAN, J. W.: Effect of sympathetic blocking agents on the toxic action of O_2 at high pressure. Amer. J. Physiol. **188**: 593–598, 1957.
262. KANN, H. E., JR., MENGEL, C. E., SMITH, W. AND HORTON, B.: Oxygen toxicity and vitamin E. Aerosp. Med. **35**: 840–844, 1964.
263. KAPANCI, Y., WEIBEL, E. R., KAPLAN, H. P. AND ROBINSON, F. R.: Pathogenesis and reversibility of the pulmonary lesions of oxygen toxicity in monkeys. II. Ultrastructural and morphometric studies. Lab. Invest. **20**: 101–118, 1969.
264. KAPLAN, H. P.: Hematologic effects of increased oxygen tensions. *In* Proceedings of the Second Annual Conference on Atmospheric Contamination in Confined Spaces. Aerospace Medical Research Laboratories Report AMRL-TR-66-120, pp. 200–222, Wright-Patterson Air Force Base, Ohio, 1966.
265. KAPLAN, H. P., ROBINSON, F. R., KAPANCI, Y. AND WEIBEL, E. R.: Pathogenesis and reversibility of the pulmonary lesions of oxygen toxicity in monkeys. I. Clinical and light microscopic studies. Lab. Invest. **20**: 94–100, 1969.
266. KARSNER, H. T.: Pathological effects of atmospheres rich in oxygen. J. Exp. Med. **23**: 149–170, 1916.
267. KARSNER, H. T. AND ASH, J. E.: Further study of pathological effects of atmospheres rich in oxygen. J. Lab. Clin. Med. **2**: 254–255, 1916.
268. KATSAROS, B., LOESCHCKE, H. H., LERCHE, D., SCHÖNTHAL, H. AND HAHN, N.: Wirkung der Bicarbonat-Alkalose auf die Lungenbelüftung beim Menschen. Bestimmung der Teilwirkungen von pH und CO_2-Druck auf die Ventilation und Vergleich mit den Ergebnissen bei Acidose. Pflügers Arch. Gesamte Physiol. Menchen Tiere **271**: 732–747, 1960.
269. KENNEDY, J. H.: Hyperbaric oxygenation and pulmonary damage. The effect of exposure at two atmospheres upon surface activity of lung extracts in the rat. Med. Thoracalis **23**: 27–35, 1966.
270. KING, C. T. G.: Carbon dioxide and certain aspects of adrenal function. *In* Man's Dependence on the Earthly Atmosphere, ed. by K. E. Schaefer, pp. 117–126, Macmillan, New York, 1962.
271. KING, C. T. G., WILLIAMS, E. E., MEGO, J. L. AND SCHAEFER, K. E.: Adrenal function during prolonged exposure to low concentration of carbon dioxide. Amer. J. Physiol. **183**: 46–52, 1955.
272. KISTLER, G. S., CALDWELL, P. R. B. AND WEIBEL, E. R.: Quantitative electron microscopic studies of murine lung damage after exposure to 98.5% oxygen at ambient pressure: a preliminary report. *In* Proceedings of the Third International Conference on Hyperbaric Medicine, ed. by I. W. Brown, Jr. and B. G. Cox, NAS/NRC Publ. 1404, Washington, D.C., 1966.
273. KISTLER, G. S., CALDWELL, P. R. B. AND WEIBEL, E. R.: Development of fine structural damage to alveolar and capillary lining cells in oxygen-poisoned rat lungs. J. Cell Biol. **32**: 605–628, 1967.
274. KISTLER, G. S., WEIBEL, E. R. AND CALDWELL, P. R. B.: Electron microscopic and morphometric study of rat lungs exposed to 97 percent oxygen at 258 torr (27,000 feet). *In* Proceedings of the Second Annual Conference on Atmospheric Contamination in Confined Spaces, Aerospace Medical Research Laboratories Report AMRL-TR-66-120, pp. 147–161, Wright-Patterson Air Force Base, Ohio, 1966.
275. KISTLER, G. S., WEIBEL, E. R. AND CALDWELL, P. R. B.: Electron microscopic investigations of oxygen effects on lung tissue. I. Electron microscopic and morphometric study of rat lungs exposed to 98.5 percent oxygen at atmospheric pressure. *In* Proceedings of the Second Annual Conference on Atmospheric Contamination in Confined Spaces. Aerospace Medical Research Laboratories Report AMRL-TR-66-120, pp. 108–146, Wright-Patterson Air Force Base, Ohio, 1966.
276. KLAUS, M., REISS, O. K., TOOLEY, W. H., PIEL, C. AND CLEMENTS, J. A.: Alveolar epithelial cell mitochondria as source of the surface active lung lining. Science **137**: 750–751, 1962.

277. KYDD, G. H.: The gas exchange of animals exposed to 100 percent oxygen at atmospheric pressure. NADC-ML-6503, U.S. Naval Air Development Center, June 1965.
278. KYDD, G. H.: Lung changes resulting from prolonged exposure to 100 percent oxygen at 550 mm Hg. Aerosp. Med. 38: 918–923, 1967.
279. KYDD, G. H.: Survival of rats exposed to 10 psia oxygen to further exposure at one atmosphere oxygen. Aerosp. Med. 39: 739–744, 1968.
280. KYLE, J. D.: The effects of 100% oxygen inhalation on adult and newborn rat lungs. S. Med. J. 58: 1592, 1965.
281. LABORIT, H., BROUSSOLLE, B. AND PERIMOND-TROUCHET, R.: Essais pharmacologiques concernant le mécanisme des convulsions dues à l'oxygène pur en pression chez la souris. J. Physiol. (Paris) 49: 953–962, 1957.
282. LAMBERTSEN, C. J.: Respiratory and circulatory actions of high oxygen pressure. *In* Proceedings of the Underwater Physiology Symposium, ed. by L. G. Goff, NAS/NRC Publ. 377, Washington, D.C., 1955.
283. LAMBERTSEN, C. J.: Physiological effects of oxygen. *In* Proceedings of the Second Symposium on Underwater Physiology, ed. by C. J. Lambertsen and L. J. Greenbaum, Jr., pp. 171–187, NAS/NRC Publ. 1181, Washington, D.C., 1963.
284. LAMBERTSEN, C. J.: Effects of oxygen at high partial pressure. *In* Handbook of Physiology, Section 3: Respiration, vol. II, ed. by W. O. Fenn and H. Rahn, pp. 1027–1046, American Physiological Society, Washington, D.C., 1965.
285. LAMBERTSEN, C. J.: Floor discussion. *In* Proceedings of the Third International Conference on Hyperbaric Medicine, ed. by I. W. Brown, Jr. and B. G. Cox, p. 207, NAS/NRC Publ. 1404, Washington, D.C., 1966.
286. LAMBERTSEN, C. J.: Oxygen toxicity. *In* Fundamentals of Hyperbaric Medicine, pp. 21–32, NAS/NRC Publ. 1298, Washington, D.C., 1966.
287. LAMBERTSEN, C. J.: Physiological effects of oxygen inhalation at high partial pressures. *In* Fundamentals of Hyperbaric Medicine, pp. 12–20, NAS/NRC Publ. 1298, Washington, D.C., 1966.
288. LAMBERTSEN, C. J.: Chemical control of respiration at rest. *In* Medical Physiology, ed. by V. B. Mountcastle, vol. I, pp. 713–763, Mosby, St. Louis, 1968.
288a. LAMBERTSEN, C. J. AND CLARK, J. M.: Derivation of pulmonary and central nervous system oxygen tolerance curves in man. Manuscript in preparation.
289. LAMBERTSEN, C. J., EWING, J. H., KOUGH, R. H., GOULD, R. AND STROUD, M. W., III: Oxygen toxicity. Arterial and internal jugular blood gas composition in man during inhalation of air, 100% O_2 and 2% CO_2 in O_2 at 3.5 atmospheres ambient pressure. J. Appl. Physiol. 8: 255–263, 1955.
290. LAMBERTSEN, C. J., HALL, P., WOLLMAN, H. AND GOODMAN, M. W.: Quantitative interactions of increased P_{O_2} and P_{CO_2} upon respiration in man. Ann. N.Y. Acad. Sci. 109: 731–741, 1963.
291. LAMBERTSEN, C. J., KOUGH, R. H., COOPER, D. Y., EMMEL, G. L., LOESCHCKE, H. H. AND Schmidt, C. F.: Comparison of relationship of respiratory minute volume to P_{CO_2} and pH of arterial and internal jugular blood in normal man during hyperventilation produced by low concentrations of CO_2 at 1 atmosphere and by O_2 at 3.0 atmospheres. J. Appl. Physiol. 5: 803–813, 1953.
292. LAMBERTSEN, C. J., KOUGH, R. H., COOPER, D. Y., EMMEL, G. L., LOESCHCKE, H. H. AND SCHMIDT, C. F.: Oxygen toxicity. Effects in man of oxygen inhalation at 1 and 3.5 atmospheres upon blood gas transport, cerebral circulation and cerebral metabolism. J. Appl. Physiol. 5: 471–486, 1953.
293. LAMBERTSEN, C. J., SEMPLE, S. J. G., SMYTH, M. G. AND GELFAND, R.: H^+ and pCO_2 as chemical factors in respiratory and cerebral circulatory control. J. Appl. Physiol. 16: 473–484, 1961.
294. LAMBERTSEN, C. J., STROUD, M. W., III, EWING, J. H. AND MACK, C.: Oxygen toxicity. Effects of oxygen breathing at increased ambient pressure upon P_{CO_2} of subcutaneous gas depots in men, dogs, rabbits and cats. J. Appl. Physiol. 6: 358–368, 1953.
295. LAMBERTSEN, C. J., STROUD, M. W., III, GOULD, R. A., KOUGH, R. H., EWING, J. H. AND SCHMIDT, C. F.: Oxygen toxicity. Respiratory responses of normal men to inhalation of 6 and 100 percent oxygen under 3.5 atmospheres pressure. J. Appl. Physiol. 5: 487–494, 1953.
296. LANGDON, D. E. AND REYNOLDS, G. E.: Postflight respiratory symptoms associated with 100 percent oxygen and G-forces. Aerosp. Med. 32: 713–718, 1961.
297. LANPHIER, E. H.: Use of nitrogen-oxygen mixtures in diving. *In* Proceedings of the Underwater Physiology Symposium, ed. by L. G. Goff, pp. 74–78, NAS/NRC Publ. 377, Washington, D.C., 1955.
298. LANPHIER, E. H.: Influence of increased ambient pressure upon alveolar ventilation. *In* Proceedings of the Second Symposium on Underwater Physiology, ed. by C. J. Lambertsen and L. J. Greenbaum, Jr., pp. 124–133, NAS/NRC Publ. 1181, Washington, D.C., 1963.
299. LARKIN, E. C., ADAMS, J. D., WILLIAMS, W. T. AND DUNCAN, D. M.: The hematologic responses to hypobaric hyperoxia. Will be submitted to Blood.
300. LAURENZI, G. A., YIN, S. AND GUARNERI, J. J.: Adverse effect of oxygen on tracheal mucus flow. N. Engl. J. Med. 279: 333–339, 1968.
301. LEE, C.-J., LYONS, J. H., KONISBERG, S., MORGAN, F. AND MOORE, F. D.: Effects of spontaneous and positive-pressure breathing of ambient air and pure oxygen at one atmosphere pressure on pulmonary surface characteristics. J. Thorac. Cardiovasc. Surg. 53: 759–769, 1967.
302. LEE, C.-J., LYONS, J. H. AND MOORE, F. D.: Cardiovascular and metabolic responses to spontaneous and positive-pressure breathing of 100 percent oxygen at one atmosphere pressure. J. Thorac. Cardiovasc. Surg. 53: 770–780, 1967.
303. LEVINE, B. E. AND JOHNSON, R. P.: Surface activity of saline extracts from inflated and degassed normal lung. J. Appl. Physiol. 19: 333–335, 1964.
304. LEVINE, B. E. AND JOHNSON, R. P.: Effects of atelectasis on pulmonary surfactant and quasi-static lung mechanics. J. Appl. Physiol. 20: 859–864, 1965.

305. LEVY, P. M., JAEGER, E. A., STONE, R. S. AND DOUDNA, C. T.: Aeroatelectasis: a respiratory syndrome in aviators. Aerosp. Med. 33: 988–994, 1962.
306. LEWERENZ, M., SCHWINGER, G., WEIBEL, E. R. AND KAPLAN, H. P.: Electron microscopic and morphometric evaluation of lungs from animals exposed continuously for eight months to 5 psia, 100% oxygen. Aerospace Medical Research Laboratories Report AMRL-TR-67-200, pp. 89–105, Wright-Patterson Air Force Base, Ohio, 1967.
307. LIDDLE, H. V.: Role of oxygen in development of pulmonary hypertension. Surg. Forum 15: 186–188, 1964.
308. LIDDLE, H. V. AND FYLER, D. C.: Etiology of pulmonary vascular disease. Evidence for oxygen as an etiologic agent (II). Guthrie Clin. Bull. 33: 151–160, 1964.
309. LIEBERMAN, J.: A unified concept and critical review of pulmonary hyaline membrane formation. Amer. J. Med. 35: 443–449, 1963.
310. LIEBERMAN, J. AND KELLOGG, F.: Hyaline membrane formation and pulmonary plasminogen-activator activity in various strains of mice. Pediatrics 39: 75–81, 1967.
311. LLOYD, B. B., JUKES, M. G. M. AND CUNNINGHAM, D. J. C.: The relation between alveolar oxygen pressure and the respiratory response to carbon dioxide in man. Quart. J. Exp. Physiol. 43: 214–227, 1958.
312. LOTTSFELDT, F. I., SCHWARTZ, S. AND KRIVIT, W.: Hyperbaric oxygen, whole-body X-irradiation and cyclophosphamide combination therapy in mouse leukemia L1210. J. Natl. Cancer Inst. 36: 37–43, 1966.
313. LOUBIERE, R. AND PFISTER, A.: Acute and chronic lesions of normobaric hyperoxia in rats. Arch. Anat. Pathol. (Paris) 14: 171–175, 1966.
314. LOUBIERE, R., PFISTER, A., FABRE, J. AND VIOLETTE, C.: Recent data on experimental hyperoxia lesions. Rev. Med. Aeronaut. (Paris) 4: 8–11, 1965.
315. LOVE, T. L., SCHNURE, J. J., LARKIN, E. C., LIPMAN, R. L. AND LECOCQ, F. R.: Glucose intolerance in man during prolonged exposure to a hypobaric-hyperoxic environment. Diabetes, in press.
316. LYNCH, M. J. G.: Hyaline membrane disease of lungs. Further observations. J. Pediat. 48: 165–179, 1956.
317. LYNCH, M. J. G., MELLOR, L. D. AND BADGERY, A. R.: Hyaline membrane disease. Its nature and etiology. The poisonous metabolic effects of excess oxygen. Neural control of electrolytes. J. Pediat. 48: 602–632, 1956.
318. MACDONALD, G. F., DINES, D. E., SESSLER, A. D. AND TITUS, J. L.: Prolonged oxygen therapy and mechanical ventilation. Associated pulmonary abnormalities. Minn. Med. 52: 1745–1748, 1969.
319. MACEWEN, J. D. AND HAUN, C. C.: Oxygen toxicity at near ambient pressures. *In* Proceedings of the Second Annual Conference on Atmospheric Contamination in Confined Spaces. Aerospace Medical Research Laboratories Report AMRL-TR-66-120, pp. 65–72, Wright-Patterson Air Force Base, Ohio, 1966.
320. MACHATTIE, L. AND RAHN, H.: Survival of mice in absence of inert gas. Proc. Soc. Exp. Biol. Med. 104: 772–775, 1960.
321. MCCURDY, W. C., III, BELLER, J. J., COALSON, J. J. AND GREENFIELD, L. J.: Pulmonary oxygen toxicity in hemorrhagic shock. Surg. Forum 20: 49–50, 1969.
322. MCGAVIN, D., GUPTA, R. K., WINTER, P. M. AND LANPHIER, E. H.: Effect of inert gas on high-pressure oxygen toxicity in rats. Physiologist 9: 242, 1966.
323. MCSHERRY, C. K. AND GILDER, H.: Pulmonary oxygen toxicity and surfactant. *In* Proceedings of the Fourth International Congress on Hyperbaric Medicine, ed. by J. Wada and T. Iwa, pp. 10–15, Igakushoin Ltd., Tokyo, 1970.
324. MCSHERRY, C. K., PANOSSIAN, A., JAEGER, V. J. AND VEITH, F. J.: Effects of hyperbaric oxygen, the hyperbaric state, and rapid decompression on pulmonary surfactant. J. Surg. Res. 8: 334–340, 1968.
325. MCSHERRY, C. K. AND VEITH, F. J.: The relationship between the central nervous system and pulmonary forms of oxygen toxicity: effect of THAM administration. Surg. Forum 19: 33–35, 1968.
326. MAKLÁRI, E., KELLNER, M., KÁDÁR, A., KOVÁCH, A. G. B. AND GOTTSEGEN, GY.: Studies in experimental pulmonary oedema. I. Pathomechanism of pulmonary oedema induced by hyperoxygenation. Acta Med. Acad. Sci. Hung. 23: 25–30, 1966.
327. MAKLÁRI, E., KELLNER, M., KOVÁCH, A. G. B. AND GOTTSEGEN, GY.: Studies in experimental pulmonary oedema. II. Effect of dibenzyline on pulmonary oedema induced by hyperoxygenation. Acta Med. Acad. Sci. Hung. 23: 31–36, 1966.
328. MARCOZZI, G., MESSINETTI, A., COLOMBATI, M., MOCAVERO, G. AND ZELLI, G. P.: Oximetric variations and pulmonary lesions induced by inhalation of oxygen concentrations higher than that of the atmosphere. Arch. de Vecchi Anat. Patol. Med. Clin. 32: 609–636, 1960.
329. MARGOLIS, G. AND BROWN, I. W., JR.: Hyperbaric oxygenation: the eye as a limiting factor. Science 151: 466–468, 1966.
330. MARIN, M. G. AND MORROW, P. E.: Effect of changing inspired O_2 and CO_2 levels on tracheal mucociliary transport rate. J. Appl. Physiol. 27: 385–388, 1969.
331. MARITANO, M., CABRAI, M., MARCHIARO, G., MARGARIA, E. AND PATTONO, R.: The activity of THAM during OHP. Acta Anesthesiol. Scand. Suppl. 24: 353–362, 1966.
332. MARITANO, M., CABRAI, M., PATTONO, R. AND MARCHIARO, G.: Apropos of various vascular and respiratory manifestations with the use of adrenolytic substances during hyperbaric oxygenation in rats. Acta Anesthesiol. Scand. Suppl. 24: 343–352, 1966.
333. MAROTTA, S. F., HIRAI, K. AND ATKINS, G.: Adrenocortical secretion in anesthetized dogs during hyperoxia, hypoxia and positive pressure breathing. Proc. Soc. Exp. Biol. Med. 118: 922–926, 1965.
334. MARSHALL, J. R. AND LAMBERTSEN, C. J.: Interactions of increased P_{O_2} and P_{CO_2} effects in producing convulsions and death in mice. J. Appl. Physiol. 16: 1–7, 1961.
335. MARSHALL, R. B., ROBERTS, D. K, TURNER, R. A AND GORDON, D. L.: Electron microscopic studies on ani-

mals exposed to differential potential spacecraft environments. SAM-TR-69-34, USAF School of Aerospace Medicine, 1969.

336. Massart, L.: Sur une prétendue relation entre l'oxydose et l'acidose gaseuse. C. R. Séances Soc. Biol. 117: 265–266, 1934.

337. Matsuda, T.: Experimental studies on hyperbaric oxygenation. I. The oxygen poisoning by hyperbaric oxygenation. Jap. J. Anesthesiol. 18: 620–629, 1969.

338. Matteo, R. S. and Nahas, G. G.: Sodium bicarbonate: increase in survival rate of rats inhaling oxygen. Science 141: 719–720, 1963.

339. Mengel, C. E., Kann, H. E., Jr., Lewis, A. M. and Horton, B.: Mechanisms of *in vivo* hemolysis induced by hyperoxia. Aerosp. Med. 35: 857–860, 1964.

340. Menzel, D. B.: Toxicity of osone, oxygen and radiation. Annu. Rev. Pharmacol. 10: 379–394, 1970.

341. Meschan, I.: DeArmas, C. R. and Scharyj, M.: Adult bronchopulmonary dysplasia: the similarity in roentgen and histopathologic appearance between some cases of oxygen toxicity, radiation pneumonitis, and postcytotoxic nonspecific bronchopneumonia. Radiology 92: 612–615, 1969.

341a. Michel, E. L., Lahgevin, R. W. and Gell, C. F.: Effect of continuous human exposure to oxygen tension of 418 mm Hg for 168 hours. Aerosp. Med. 31: 138–144, 1960.

342. Miller, D. A. and Bondurant, S.: Surface characteristics of vertebrate lung extracts. J. Appl. Physiol. 16: 1075–1077, 1961.

343. Miller, W. M., Waldhausen, J. A. and Rashkind, W. J.: Comparison of oxygen poisoning of the lung in cyanotic and acyanotic dogs. N. Engl. J. Med. 282: 943–947, 1970.

344. Morehouse, R., Richardson, D. and Rush, B. F.: The effect of 100% oxygen on resistance to pulmonary edema. Surg. Forum 19: 262–263, 1968.

345. Morgan, A. P.: The pulmonary toxicity of oxygen. Anesthesiology 29: 570–579, 1968.

346. Morgan, T. E., Jr., Cutler, R. G., Shaw, E. G., Ulvedal, F., Hargreaves, J. J., Moyer, J. E., McKenzie, R. E. and Welch, B. E.: Physiologic effects of exposure to increased oxygen tension at 5 psia. Aerosp. Med. 34: 720–726, 1963.

347. Morgan, T. E., Finley, T. N., Huber, G. L. and Fialkow, H.: Alterations in pulmonary surface active lipids during exposure to increased oxygen tension. J. Clin. Invest. 44: 1737–1744, 1965.

348. Morgan, T. E., Jr., Ulvedal, F., Cutler, R. G. and Welch, B. E.: Effects on man of prolonged exposure to oxygen at a total pressure of 190 mm Hg. Aerosp. Med. 34: 589–592, 1963.

349. Morgan, T. E., Jr., Ulvedal, F. and Welch, B. E.: Observations in the SAM two-man space cabin simulator. II. Biomedical aspects. Aerosp. Med. 32: 591–602, 1961.

350. Moss, W. T. and Haddy, F. J.: The relationship between oxygen tension of inhaled gas and the severity of acute radiation pneumonitis. Radiology 75: 55–58, 1960.

351. Motlagh, F. A., Kaufman, S. Z., Giusti, R., Cramer, M., Garzon, A. A. and Karlson, K. E.: Electron microscopic appearance and surface tensions properties of the lungs ventilated with dry or humid air or oxygen. Surg. Forum 20: 219–220, 1969.

352. Nahas, G. G.: The pharmacology of tris (hydroxymethyl) aminomethane (THAM). Pharmacol. Rev. 14: 447–472, 1962.

353. Nahas, G. G.: Control of acidosis in hyperbaric oxygenation. Ann. N.Y. Acad. Sci. 117: 774–786, 1965.

354. Nair, C. S.: Effects of breathing 100 percent oxygen at ground level on blood clotting time and platelet count. Indian J. Med. Res. 55: 123–127, 1967.

355. Nairn, J. R., Power, G. G., Hyde, R. W., Forster, R. E., Lambertsen, C. J. and Dickson, J.: Diffusing capacity and pulmonary capillary blood flow at hyperbaric pressures. J. Clin. Invest. 44: 1591–1599, 1965.

356. Nash, G., Blennerhassett, J. B. and Pontoppidan, H.: Pulmonary lesions associated with oxygen therapy and artificial ventilation. N. Engl. J. Med. 276: 368–374, 1967.

356a. Nash, G., Bowen, J. A. and Langlinais, P. C.: "Respirator lung": a misnomer. Arch. Pathol. 21: 234–240, 1971.

357. Nasseri, M. and Bücherl, E. S.: Light and electron-microscopic studies of structural changes in the lung following hyperbaric oxygenation. Virchows Arch. Pathol. Anat. Physiol. Klin. Med. 242: 190–198, 1967.

358. Nasseri, M., Kirstaedter, H. J. and Bücherl, E. S.: Experimentelle Untersuchungen über das Allgemeinverhalten und die morphologischen Veränderungen unter hohem Sauerstoffdruck. Virchows Arch. Pathol. Anat. Physiol. Klin. Med. 341: 148–154, 1966.

359. Newman, D. and Naimark, A.: Palmitate-^{14}C uptake by rat lung: effect of altered gas tensions. Amer. J. Physiol. 214: 305–312, 1968.

360. Nichols, C. W. and Lambertsen, C. J.: Effects of high oxygen pressures on the eye. N. Engl. J. Med. 281: 25–30, 1969.

361. Noell, W. K.: Effects of high and low oxygen tension on the visual system. *In* Environmental Effects on Consciousness, ed. by K. E. Schaefer, pp. 3–18, Macmillan, New York, 1962.

362. Northway, W. H., Jr. and Rosan, R. C.: Radiographic features of pulmonary oxygen toxicity in the newborn: bronchopulmonary dysplasia. Radiology 91: 49–58, 1968.

363. Northway, W. H., Jr., Rosan, R. C. and Porter, D. Y.: Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. N. Engl. J. Med. 276: 357–368, 1967.

364. Northway, W. H., Jr., Rosan, R. C., Shahinian, L., Jr., Castellino, R. A., Gyepes, M. T. and Durbridge, T.: Radiologic and histologic investigation of pulmonary oxygen toxicity in newborn guinea pigs. Invest. Radiol. 4: 148–155, 1969.

365. Novelli, G. P., Pagni, E., Pirani, A., Ariano, M. and Pallini, C.: La cosiddetta tossicita dell' ossigeno iper-

barico come fenomeno adrenergico. Proposta di interpretasione patogenetica. Acta Anaesthesiol. (Padova) 18: 801–831, 1967.

366. Ogawa, J. and Saito, H.: Hyaline membrane in the lung of premature newborn mammals. Study on the etiological factors. Nagoya Med. J. 7: 44, 1961.

367. Ohlsson, W. T. L.: A study on oxygen toxicity at atmospheric pressure. Acta Med. Scand. suppl. 190, 1947.

367a. Ohta, Y., Kawashiro, T. and Yokoyama, T.: Tissue gas tensions of the rats' subcutaneous gas pockets and the oxygen intoxication. *In* Proceedings of the Fourth International Congress on Hyperbaric Medicine, ed. by J. Wada and T. Iwa, pp. 32–36, Williams & Wilkins, Baltimore, 1970.

368. Oliver, J. H., Little, J. M. and Pirch, J. H.: Strain differences in CNS and lethal effects of hyperbaric oxygen in mice. Proc. Soc. Exp. Biol. Med. 132: 666–669, 1969.

369. Ozorio de Almeida, A.: Recherches sur l'action toxique des hautes pressions d'oxygène. C. R. Séances Soc. Biol. 116: 1225–1227, 1934.

370. Pace, D. M., Thompson, J. R. and van Camp, W. A.: Effects of oxygen on growth in several established cell lines. J. Nat. Cancer Inst. 28: 897–909, 1962.

371. Pagni, E., Palumbo, D. and Cortesini, C.: Influenza della medullectomia surrenalica sulla comparsa delle lesioni da ossigeno iperbarico. Boll. Soc. Med.-Chir. Pisa 34: 1, 1966.

372. Pagni, E., Zampolini, M. and Frullani, F.: Blocking of *alpha*-adrenergic receptors as a method of prevention of lesions from hyperbaric oxygen. Minerva Anesthesiol. 33: 49–54, 1967.

373. Pagni, E., Novelli, G. P. and Patumi, F.: Catecholamine depletion induced by reserpine as a means of preventing hyperbaric oxygen injuries. Osp. Ital. Chir. 17: 233–246, 1967.

374. Paine, J. R., Lynn, D. and Keys, A.: Manifestations of oxygen poisoning in dogs confined in atmospheres of 80 to 100 percent oxygen. Amer. J. Physiol. 133: 406–407, 1941.

375. Paine, J. R., Lynn, D. and Keys, A.: Observations on the effects of prolonged administration of high oxygen concentration to dogs. J. Thorac. Cardiovasc. Surg. 11: 151–168, 1941.

376. Parienté, R., Legrand, M. and Brouet, G.: Ultrastructural aspects of the lung in oxygen poisoning at atmospheric pressure in the rat. Presse Med. 77: 1073–1076, 1969.

377. Patel, Y. Z. and Gowdey, C. W.: Effects of single and repeated exposures to oxygen of high pressure on normal rats. Can. J. Physiol. Pharmacol. 42: 245–264, 1964.

378. Paton, W. D. M.: Experiments on the convulsant and anesthetic effects of oxygen. Brit. J. Pharmacol. Chemother 29: 350–366, 1967.

379. Patrick, R. L.: Pathology of animals exposed for 240 days to a 5 psia 70% oxygen and 30% nitrogen atmosphere. Aerospace Medical Research Laboratories Report AMRL-TR-67-200, pp. 106–108, Wright-Patterson Air Force Base, Ohio, 1967.

380. Patrick, R. L.: Histopathology after exposure to mixed gas at 5 psia for eight months. Aerospace Medical Research Laboratories Report AMRL-TR-69-130, pp. 201–207, Wright-Patterson Air Force Base, Ohio, 1969.

381. Patrick, T. R.: Effects of hyperbaric oxygen on pulmonary phospholipids. Presented at First Annual Western Conference on Hyperbaric Medicine, Hospital of the Good Samaritan Medical Center, Los Angeles, Calif., Jan., 1970.

382. Pattle, R. E.: Surface lining of lung alveoli. Physiol. Rev. 45: 48–79, 1965.

383. Pattle, R. E. and Burgess, F.: The lung lining film in some pathological conditions. J. Pathol. Bacteriol. 82: 315–331, 1961.

384. Patz, A., Eastham, A., Higginbotham, D. H. and Kleh, T.: Oxygen studies in retrolental fibroplasia. II. The production of the microscopic changes of retrolental fibroplasia in experimental animals. Amer. J. Ophthalmol. 36: 1511–1522, 1953.

385. Pautler, S., Cimons, I. M., Cauna, D., Totten, R. and Safar, P.: Pulmonary oxygen toxicity at one ata. Acta Anaesthesiol. Scand. suppl. 24: 51–56, 1966.

386. Penrod, K. E.: Effect of intermittent nitrogen exposures on tolerance to oxygen at high pressure. Amer. J. Physiol. 186: 149–151, 1956.

387. Penrod, K. E.: Nature of pulmonary damage produced by high oxygen pressures. J. Appl. Physiol. 9: 1–4, 1956.

388. Penrod, K.: Lung damage by oxygen using differential catheterization. Fed. Proc. 17: 123, 1958.

389. Pepelko, W. E.: Long-term effects of an oxygen environment on a rat colony at 210 mm Hg absolute. SAM-TR-66-90, USAF School of Aerospace Medicine, 1966.

390. Pepelko, W. E.: Adrenocortical steroids, body organ weights, and hematology of rats exposed to a pure oxygen environment at 210 mm Hg absolute. SAM-TR-67-78, USAF School of Aerospace Medicine, 1967.

391. Perkins, G. F., Wood, C. D., Koerner, T. A. and Seager, L. D.: Effect of amphetamine on hypertension and pulmonary edema produced by hyperbaric O_2. Preprints of Annual Scientific Meeting of Aerospace Medical Association, p. 104, 1970.

392. Perot, P. L., Jr. and Stein, S. N.: Conduction block in peripheral nerve produced by oxygen at high pressure. Science 123: 802–803, 1956.

393. Perot, P. L., Jr. and Stein, S. N.: Conduction block in mammalian nerve produced by O_2 at high pressure. Amer. J. Physiol. 197: 1243–1246, 1959.

394. Pfeiffer, C. C. and Gersh, I.: The prevention of the convulsions of oxygen poisoning by means of drugs. U. S. Navy NMRI, Project X-192, Report 2, 1944.

395. Pfister, A. M., Fabre, J., Coudert, G., Pingannaud, M. and Miro, L.: Normobaric hyperoxia in the rat. Anesth. Analg. Reanim. 24: 387–403, 1967.

396. Phillips, L. L., Wyte, S. R., Weeks, D. B. and Soloway, H. B.: Fibrinolytic deficit in oxygen intoxicated guinea pigs. Aerosp. Med. 40: 744–746, 1969.

397. PICHOTKA, J.: Morphology and morphogenesis of pulmonary changes due to oxygen poisoning. *In* German Aviation Medicine in World War II, vol. I, pp. 515–525, USAF School of Aviation Medicine, 1950.
398. PIZZARELLO, D. J. AND SHIRCLIFFE, A. C.: Protection against hyperbaric oxygen toxicity after feeding N,N-diphenyl-*p*-phenylene diamine. Experientia (Basel) **24**: 188–189, 1968.
399. POLGAR, G., ANTAGNOLI, W., FERRIGAN, L. W., MARTIN, E. A. AND GREGG, W. P.: The effect of chronic exposure to 100% oxygen in newborn mice. Amer. J. Med. Sci. **252**: 580–587, 1966.
400. POPOVIC, V., GERSCHMAN, R. AND GILBERT, D. L.: Effects of high oxygen pressure on ground squirrels in hypothermia and hibernation. Amer. J. Physiol. **206**: 49–50, 1964.
401. PRATT, P. C.: Pulmonary capillary proliferation induced by oxygen inhalation. Amer. J. Pathol. **34**: 1033–1050, 1958.
402. PRATT, P. C.: The reaction of the human lung to enriched oxygen atmosphere. Ann. N.Y. Acad. Sci. **121**: 809–822, 1965.
403. PRATT, P. C.: Oxygen toxicity as a factor. J. Trauma **8**: 854–866, 1968.
404. PREKLADOVIZKII, S. I.: Toxic effect of high oxygen tension on the animal organism. Fiziol. Zh. S.S.S.R. im. I.M. Sechenova **20**: 518–533, 1936.
405. PUY, R. J. M., HYDE, R. W., FISHER, A. B., CLARK, J. M., DICKSON, J. AND LAMBERTSEN, C. J.: Alterations in the pulmonary capillary bed during early O_2 toxicity in man. J. Appl. Physiol. **24**: 537–543, 1968.
405a. RACE, G. J., MATTHEWS, J. L., FINNEY, J. W. AND MARTIN, J. H.: Ultrastructural changes in rat adrenal cortex following hyperbaric oxygen (OHP). *In* Proceedings of the Fourth International Congress on Hyperbaric Medicine, ed. by J. Wada and T. Iwa, pp. 170–178, Williams & Wilkins, Baltimore, 1970.
406. RAHN, H. AND FARHI, L. E.: Gaseous environment and atelectasis. Fed. Proc. **22**: 1035–1041, 1963.
407. REHBOCK, D. J., OLDT, M. R. AND DIXON, H. M.: Effect of exposure to high oxygen tension on the lungs and heart of the rat. Arch. Pathol. **30**: 1172–1177, 1940.
408. RICHARDS, D. W. AND BARACH, A. L.: Prolonged residence in high oxygen atmospheres. Effects on normal individuals and on patients with chronic cardiac and pulmonary insufficiency. Quart. J. Med. **3**: 437–466, 1934.
409. REICHERT, W.: Beitrag zum cardiazol-lungenödem. Naunyn-Schmiedebergs. Arch. Pharmakol. Exp. Pathol. **197**: 620–628, 1941.
410. RIESEN, W. H., GROSS, A. M. AND O'NEILL, H. J.: Effects of oxygen exposure on the production of surfactant phospholipids in the rabbit lung. Preprints of Annual Scientific Meeting of Aerospace Medical Association, pp. 112–113, 1970.
411. ROBERTSON, W. G., HARGREAVES, J. J., HERLOCHER, J. E. AND WELCH, B. E.: Physiologic response to increased oxygen partial pressure: II. Respiratory studies. Aerosp. Med. **35**: 618–622, 1964.
412. ROBERTSON, W. G. AND FARHI, L. E.: Rate of lung collapse after airway occlusion on 100% O_2 at various ambient pressures. J. Appl. Physiol. **20**: 228–232, 1965.
413. ROBINSON, F. R. AND HARPER, D. T.: Pathological evaluation of oxygen toxicity at near-ambient pressures. *In* Proceedings of the Second Annual Conference on Atmospheric Contamination in Confined Spaces. Aerospace Medical Research Laboratories Report AMRL-TR-66-120, pp. 73–79, Wright-Patterson Air Force Base, Ohio, 1966.
414. ROBINSON, F. R., HARPER, D. T., JR. AND KAPLAN, H. P.: Comparison of strains of rats exposed to oxygen at various pressures. Lab. Anim. Care **17**: 433–441, 1967.
415. ROBINSON, F. R., HARPER, D. T., JR., THOMAS, A. A. AND KAPLAN, H. P.: Proliferative pulmonary lesions in monkeys exposed to high concentrations of oxygen. Aerosp. Med. **38**: 481–486, 1967.
416. ROBINSON, F. R., SOPHER, R. L., CARTER, V. L. AND WITCHETT, C. E.: Pulmonary lesions in monkeys exposed to 100% oxygen at 258 and 750 mm Hg pressure. Aerospace Medical Research Laboratories Report AMRL-TR-68-175, pp. 237–249, Wright-Patterson Air Force Base, Ohio, 1968.
417. ROBINSON, F. R., SOPHER, R. L. AND WITCHETT, C. E.: Pathology of normobaric oxygen toxicity in primates. Aerosp. Med. **40**: 879–884, 1969.
418. ROBINSON, F. R., THOMAS, A. A. AND RENDON, L.: Analysis of pleural effusions from rats exposed to high concentrations of oxygen. Clin. Chem. **14**: 1066–1073, 1968.
419. ROSENBAUM, R. M., WITTNER, M. AND LENGER, M.: Mitochondrial and other ultrastructural changes in great alveolar cells of oxygen-adapted and poisoned rats. Lab. Invest. **20**: 516–528, 1969.
420. ROSENBERG, E. AND MACLEAN, L. D.: Effect of high oxygen tensions on diffusing capacity for CO and Krogh's K. J. Appl. Physiol. **23**: 11–17, 1967.
421. ROSENGREN, K.: Hyaline membrane disease. A radiological investigation in rabbits. Acta Radiol. Suppl. **262**: 1–64, 1967.
422. ROTH, E. M.: Selection of space cabin atmospheres. I. Oxygen toxicity. NASA Technical Note D-2008, Washington, D.C., 1963.
423. ROUGHTON, F. J. W. AND FORSTER, R. E.: Relative importance of diffusion and chemical reaction rates in determining rate of exchange of gases in the human lung, with special reference to true diffusing capacity of pulmonary membrane and volume of blood in the lung capillaries. J. Appl. Physiol. **11**: 290–302, 1957.
424. ROWLAND, R. AND NEWMAN, C. G. H.: Pulmonary complications of oxygen therapy. J. Clin. Pathol. **22**: 192–198, 1969.
425. RUCCI, F. S., SATTA, U. AND CAMPODONICO, A.: Effects of adrenal medullectomy on acute intoxication due to O_2 in rats. Acta Anaesthesiol. (Padova) **16**: 265–286, 1965.
426. RUECKERT, R. R. AND MUELLER, G. C.: Effect of oxygen tension on HeLa cell growth. Cancer Res. **20**: 944–949, 1960.
427. SAID, S. I., AVERY, M. E., DAVIS, R. K., BANERJEE, C. M. AND EL-GOHARY, M.: Pulmonary surface activity in induced pulmonary edema. J. Clin. Invest. **44**: 458–464, 1965.

428. SAIKI, H.: Physiological influences of high oxygen respiration in close environmental systems. Nineteenth Congress of the International Astronautical Federation, B183, New York, October 13–19, 1968.
429. SANDERS, A. P., HALL, I. H. AND WOODHALL, B.: Succinate: protective agent against hyperbaric oxygen toxicity. Science 150: 1830–1831, 1965.
430. SANGER, C., NAHAS, G. G., GOLDBERG, A. R. AND D'ALLESIO, G. M.: Effects of 2-amino-2-hydroxymethyl-1,3-propanediol on oxygen toxicity in mice. Ann. N.Y. Acad. Sci. 92: 710–723, 1961.
431. SCHAEFER, K. E., KLEIN, H. AND ZINCK, K. H.: Experimentelle Untersuchungen über den Zusammenhang von Mark und Rinde der Nebenniere unter langdauernder CO_2-Einwirkung. Klin. Wochenschr. 28: 179–184, 1950.
432. SCHAFFNER, F., FELIG, P. AND TRACHTENBERG, E.: Structure of rat lung after protracted oxygen breathing. Arch. Pathol. 83: 99–107, 1967.
433. SCHULZ, H.: Über den Gestaltwandel der Mitochondrien in Alveolorepithel unter CO_2 und O_2 Atmung. Naturwissenschaften 9: 205, 1956.
434. SEELKOPF, K.: Cited by Becker-Freyseng, H.: Physiological and patho-physiological effects of increased oxygen tension. *In* German Aviation Medicine in World War II, vol. I, pp. 493–514, United States Air Force School of Aviation Medicine, 1950.
435. SEELKOPF, K. AND VON WERTZ, R.: Über die Rolle der Kohlensäure bei der Sauerstoffvergiftung. Naunyn-Schmiedebergs Arch. Pharmakol. Exp. Pathol. 205: 351–366, 1948.
436. SHANKLIN, D. R.: The influence of intermediate oxygen percentages on experimental hyaline membrane disease. S. Med. J. 57: 1473, 1964.
437. SHANKLIN, D. R.: The influence of total pressure on the pulmonary toxicity of oxygen. Amer. J. Pathol. 50: 46a, 1967.
438. SHANKLIN, D. R.: A general theory of oxygen toxicity in man. Perspect. Biol. Med. 13: 80–100, 1969.
439. SHANKLIN, D. R.: Initiating cause of hyaline membrane disease. Fed. Proc. 28: 654, 1969.
440. SHANKLIN, D. R.: On the pulmonary toxicity of oxygen. I. The relationship of oxygen content to the effect of oxygen on the lung. Lab. Invest. 21: 439–448, 1969.
441. SHANKLIN, D. R. AND BERMAN, P. A.: The influence of hyperbaric oxygen on hyaline membrane disease in newborn rabbits. S. Med. J. 56: 1443, 1963.
442. SHANKLIN, D. R. AND BERMAN, P. A.: An experimental model for hyaline membrane disease. Biol. Neonatorum 6: 340–360, 1964.
443. SHANKLIN, D. R. AND CUNNINGHAM, J. J.: Vagotomy—oxygen synergism in the pathogenesis of hyaline membrane disease. Amer. J. Pathol. 46: 27a, 1965.
444. SHANKLIN, D. R., CUNNINGHAM, J. J., SOTELO-AVILA, C. AND CRUSSI, F.: Oxygen, ascorbic acid, and the lung participation of adrenal ascorbic acid in response to oxygen challenge of the lung. Arch. Pathol. 84: 451–459, 1967.
445. SHANKLIN, D. R. AND LESTER, E.: Role of nitrogen in pulmonary oxygen toxicity. S. Med. J. 61: 1338, 1968.
446. SHANKLIN, D. R. AND SOTELO-AVILA, C.: The effects of components of vagotomy on the lung and the effects of anesthesia on vagotomy-induced lung change. Biol. Neonatorum 11: 61–86, 1967.
447. SHANKLIN, D. R. AND WOLFSON, S. L.: Therapeutic oxygen as a possible cause of pulmonary hemorrhage in premature infants. N. Engl. J. Med. 277: 833–837, 1967.
448. SHAW, L. A., BEHNKE, A. R. AND MESSER, A. C.: The role of carbon dioxide in producing the symptoms of oxygen poisoning. Amer. J. Physiol. 108: 652–661, 1934.
448a. SHERMETA, D. W., WHITE, J. J., DE LEMOS, R. AND HALLER, J. A., JR.: Pulmonary effects of lethal and sublethal oxygen exposure in lambs. Amer. Surg. 36: 721–723, 1970.
449. SHILLING, C. W. AND ADAMS, B. H.: A study of the convulsive seizures caused by breathing oxygen at high pressure. U.S. Naval Med. Bull. 31: 112–121, 1933.
450. SIEGEL, B. V.: Effects of long-term periodic administration of hyperbaric oxygen on body and organ weights, histology and hematology of the mouse. Aerosp. Med. 38: 399–401, 1967.
450a. SINGER, M. M., WRIGHT, F., STANLEY, L. K., ROE, B. B. AND HAMILTON, W. K.: Oxygen toxicity in man. A prospective study in patients after open-heart surgery. N. Engl. J. Med. 283: 1473–1478, 1970.
451. SJÖSTRAND, J.: The effect of oxygen at high pressure on thyroid function in the rat. Acta Physiol. Scand. 62: 94–100, 1964.
452. SMITH, C. W. AND BEAN, J. W.: Adrenal factors in toxic action of O_2 at atmospheric pressure. Fed. Proc. 14: 140, 1955.
453. SMITH, C. W. AND BEAN, J. W.: Influence of CO_2 on toxicity of O_2 at atmospheric pressure. Amer. J. Physiol. 183: 662, 1955.
454. SMITH, C. W., BEAN, J. W. AND BAUER, R.: Thyroid influence in reactions to O_2 at atmospheric pressure. Amer. J. Physiol. 199: 883–888, 1960.
455. SMITH, C. W., LEHAN, P. H. AND MONKS, J. J.: Cardiopulmonary manifestations with high O_2 tensions at atmospheric pressure. J. Appl. Physiol. 18: 849–853, 1963.
456. SMITH, F. J. C., BENNETT, G. A., HEIM, J. W., THOMSON, R. M. AND DRINKER, C. K.: Morphological changes in the lungs of rats living under compressed air conditions. J. Exp. Med. 56: 79–93, 1932.
457. SMITH, F. J. C., HEIM, J. W., THOMSON, R. M. AND DRINKER, C. K.: Bodily changes and development of pulmonary resistance in rats living under compressed air conditions. J. Exp. Med. 56: 63–78, 1932.
458. SMITH, G., LEDINGHAM, I. M. AND SANDISON, A. T.: Pulmonary oxygen toxicity-pathophysiology and effects of N_2 mixture. Clin. Sci. (London) 38: 12P, 1970.
459. SMITH, J. L.: The pathological effects due to increased oxygen tension in the air breathed. J. Physiol. (London) 24: 19–35, 1899.

460. SOBEL, H.: Follow-up on mice exposed to 1.08 ATS of oxygen in nitrogen for a substantial portion of life span. Aerosp. Med. 41: 524–529, 1970.
461. SOLOWAY, H. B., CASTILLO, Y. AND MARTIN, A. M., JR.: Adult hyaline membrane disease: relationship to oxygen therapy. Ann. Surg. 168: 937–945, 1968.
462. SOULIE, P.: Modifications expérimentales de la résistance individuelle de certains animaux à l'action toxique de l'oxygène. C. R. Séances Soc. Biol. 130: 541–542, 1939.
463. SPERLING, D. R.: Hyperbaric oxygen toxicity in newborn and developing mice. J. Appl. Physiol. 29: 472–474, 1970.
464. STADIE, W. C., RIGGS, B. C. AND HAUGAARD, N.: Oxygen poisoning. Amer. J. Med. Sci. 207: 84–114, 1944.
465. STADIE, W. C., RIGGS, B. C. AND HAUGAARD, N.: Oxygen poisoning. III. The effect of high oxygen pressures upon the metabolism of brain. J. Biol. Chem. 160: 191–208, 1945.
466. STADIE, W. C., RIGGS, B. C. AND HAUGAARD, N.: Oxygen poisoning. IV. The effect of high oxygen pressures upon the metabolism of liver, kidney, lung and muscle tissue. J. Biol. Chem. 160: 209–216, 1945.
467. SZAM, I.: Pathogenesis of hyperbaric oxygen intoxication. Experimental studies on the significance of CO_2 and NH_3 accumulation in the central nervous system for the pathogenesis of hyperbaric pulmonary edema. Anaesthetist 18: 39–43, 1969.
468. SZILÁGYI, T., TÓTH, S., MILTÉNYI, L. AND JÓNA, G.: Oxygen poisoning and thyroid function. Acta Physiol. Acad. Sci. Hung. 35: 59–61, 1969.
469. TAYLOR, D. W.: Effects of vitamin E deficiency on oxygen toxicity in the rat. J. Physiol. (London) 121: 47P, 1953.
470. TAYLOR, D. W.: Effects of high oxygen pressures on adrenalectomized, treated and untreated rats. J. Physiol. (London) 125: 46–47P, 1954.
471. TAYLOR, D. W.: The effects of vitamin E and methylene blue on the manifestations of oxygen poisoning in the rat. J. Physiol. (London) 131: 200–206, 1956.
472. TAYLOR, D. W.: Changes in cardiac and respiratory rates, and in carbon dioxide pressure and pH of arterial blood, in anaesthetized rats exposed to oxygen under high pressure. J. Physiol. (London) 143: 149–164, 1958.
473. TAYLOR, D. W.: Effects of adrenalectomy on oxygen poisoning in the rat. J. Physiol. (London) 140: 23–36, 1958.
474. TAYLOR, D. W.: Effects of tocopherols, methylene blue, and glutathione on the manifestations of oxygen poisoning in vitamin E-deficient rats. J. Physiol. (London) 140: 37–47, 1958.
475. TAYLOR, D. W.: Changes in cardiac and respiratory function, and in blood carbon dioxide pressure and pH, in cats exposed to oxygen under high pressure. J. Physiol. (London) 152: 506–514, 1960.
476. TAYLOR, H. J.: The effect of breathing oxygen at atmospheric pressure on tissue oxygen and carbon dioxide tensions. J. Physiol. (London) 108: 264–269, 1949.
477. TAYLOR, H. J.: The role of carbon dioxide in oxygen poisoning. J. Physiol. (London) 109: 272–280, 1949.
478. TENNEKOON, G. E.: Pulmonary edema due to thiosemicarbaside. J. Pathol. Bacteriol. 67: 341–347, 1954.
478a. THOMAS, A. N., KETCHUM, S. A., III, HALL, A. D., AND ZUBRIN, J. R.: A protective effect of venous admixture on chronic pulmonary oxygen toxicity. *In* Proceedings of the Fourth International Congress on Hyperbaric Medicine, by J. Wada and T. Iwa, pp. 22–28, Williams & Wilkins, Baltimore, 1970.
479. THOMAS, J. J., JR., BAXTER, R. C. AND FENN, W. O.: Interactions of oxygen at high pressure and radiation in *Drosophila*. J. Gen. Physiol. 49: 537–549, 1966.
480. THOMPSON, R. E. AND AKERS, T. K.: Influence of sodium pentobarbital on mice poisoned by oxygen. Aerosp. Med. 41: 1025–1027, 1970.
481. THOMPSON, R. E., NIELSEN, T. W. AND AKERS, T. K.: Synergistic oxygen-inert gas interactions in laboratory rats in a hyperbaric environment. Submitted to Aerosp. Med.
482. TIISALA, R.: Stress reaction to oxygen poisoning in newborn, growing, and adult rats. Ann. Pediat. Fenn. 5: 59–66, 1959.
483. TIISALA, R.: Endocrine response to hyperoxia and hypoxia in the adult and newborn rat. An experimental study with radioactive phosphorus. Ann. Acad. Sci. Fenn. Ser. A V Med. 95: 1–141, 1962.
484. TRECIOKAS, L. J.: The effect of "oxygen poisoning" on alveolar cell mitochondria as revealed by electron microscopy. Aerosp. Med. 30: 674–677, 1959.
485. TROSHIKHIN, G. V.: Effect of prolonged exposure to a hyperoxic atmosphere on gas exchange in white mice. Bull. Eksp. Biol. Med. 62: 46–49, 1966.
486. TURAIDS, T., NOBREGA, F. T. AND GALLAGHER, T. J.: Absorptional atelectasis breathing oxygen at simulated altitude: prevention using inert gas. Aerosp. Med. 38: 189–192, 1967.
487. ULVEDAL, F.: Preliminary observations on testicular function in roosters and mice exposed to increased partial pressure of oxygen. SAM-TR-66-40, USAF School of Aerospace Medicine, 1966.
488. ULVEDAL, F. AND BROWN, H. E.: Physiologic and biochemical observations on the rhesus *Macaca mulatta* exposed to oxygen-rich atmospheres. USAF School of Aerospace Medicine, Aerospace Medical Division, SAM-TR-67-86, Brooks Air Force Base, Texas, September 1967.
489. ULVEDAL, F., CUTLER, R. G. AND WELCH, B. E.: The effects of high concentrations of carbon dioxide and diet on the urinary excretion of steroids and catecholamines. Aerosp. Med. 34: 923–929, 1963.
490. ULVEDAL, F. AND ROBERTS, A. J.: Endocrine functions in an oxygen atmosphere at reduced total pressure. Aerospace Med. 39: 1218–1224, 1968. See also: Aviation and Space Medicine, pp. 56–67, Universitetsforlaget, Oslo, 1969.
491. VAN BREEMEN, V. L., NEUSTEIN, N. B. AND BURNS, P. D.: Pulmonary hyaline membranes studied with the electron microscope. Amer. J. Pathol. 33: 769–789, 1957.
492. VAN DEN BRENK, H. A. S.: Lung damage in rats due to radical X radiation in high-pressure oxygen. Aust. Radiol. 10: 375–382, 1966.
493. VAN DEN BRENK, H. A. S. AND JAMIESON, D.: Potentiation by anesthetics of brain damage due to breathing high-pressure oxygen in mammals. Nature (London) 194: 777–778, 1962.

494. VAN DEN BRENK, H. A. S. AND JAMIESON, D.: Pulmonary damage due to high pressure oxygen breathing in rats. 1. Lung weight, histological and radiological studies. Aust. J. Exp. Biol. Med. Sci. 40: 37–49, 1962.
495. VAN DEN BRENK, H. A. S. AND JAMIESON, D.: Studies of mechanisms of chemical radiation protection *in vivo*. II. Effect of high pressure oxygen on radio-protection *invivo* and its relationship to 'oxygen poisoning'. Int. J. Radiat. Biol. 4: 379–402, 1962.
496. VAN DEN BRENK, H. A. S. AND JAMIESON, D.: Brain damage and paralysis in animals exposed to high pressure oxygen: pharmacological and biochemical observations. Biochem. Pharmacol. 13: 165–182, 1964.
497. VAN DEN BRENK, H. A. S., KERR, R. C., RICHTER, W. AND PAPWORTH, M. P.: Enhancement of radiosensitivity of skin of patients by high pressure oxygen. Brit. J. Radiol. 38: 857–864, 1965.
498. VAN DEN BRENK, H. A. S. AND MOORE, R.: Effect of high oxygen pressure on the protective action of cystamine and 5-hydroxytryptamine in irradiated rats. Nature (London) 183: 1530–1531, 1959.
499. VAN DE WATER, J. M., KAGEY, K. S., MILLER, I. T., PARKER, D. A., O'CONNER, N. E., SHEH, J.-M., MACARTHUR, J. D., ZOLLINGER, R. M., JR. AND MOORE, F. D.: Response of the lung to six to 12 hours of 100 percent oxygen inhalation in normal man. N. Engl. J. Med. 283: 621–626, 1970.
500. VAN TASSEL, P. V.: Effect of dimercaprol on oxygen toxicity in rats. J. Appl. Physiol. 20: 531–533, 1965.
501. VINOGRADOV, V. N. AND BABCHINSKIY, F. V.: Electron microscope observations of changes in the lungs of rats after repeated exposure to pure oxygen. Space Biol. Med. 2: 40–45, 1969.
502. WADA, J. AND IWA, T. (ed.): Proceedings of the Fourth International Congress on Hyperbaric Medicine, Igaku-shoin Ltd., Tokyo, 1970.
503. WALKER, J. B.: The involvement of carbon dioxide in the toxicity of oxygen at high pressure. Can. J. Biochem. Physiol. 39: 1803–1809, 1961.
504. WARSHAW, L. J., MOLOMUT, N. AND SPAIN, D. M.: Cortisone effect on pneumonitis produced in mice by exposure to a high oxygen atmosphere. Proc. Soc. Exp. Biol. Med. 80: 341–344, 1952.
505. WEBB, W. R., LANIUS, J. W., ASLAMI, A. AND REYNOLD, R. C.: Effects of oxygen tensions on pulmonary surfactant in guinea pigs and rats. J. Amer. Med. Ass. 195: 279–280, 1966.
506. WEIBEL, E. R.: Morphometry of the Human Lung. Academic Press, New York, 1963.
507. WEIBEL, E. R.: Discussion. Aerospace Medical Research Laboratories Report AMRL-TR-68-175, p. 246, Wright-Patterson Air Force Base, Ohio, 1968.
508. WEIBEL, E. R. AND CONRADI, C. R.: Pulmonary pathology of oxygen toxicity. Aerospace Medical Research Laboratories Report AMRL-TR-69-130, pp. 227–260, Wright-Patterson Air Force Base, Ohio, 1969.
509. WEIBEL, E. R. AND ELIAS, H.: Quantitative Methods in Morphology, Springer-Verlag, New York, 1967.
510. WEIBEL, E. R., LEWERENZ, M. AND KAPLAN, H. P.: Electron microscopic and morphometric study of rat, monkey and dog lungs exposed to 68% O_2 and 32% N_2 at 258 torr for eight months. Aerospace Medical Research Laboratories Report AMRL-TR-68-175, pp. 189–212, Wright-Patterson Air Force Base, Ohio, 1968.
511. WEIR, F. W., BATH, D. W., YEVICH, P. AND OBERST, F. W.: Study of effects of continuous inhalation of high concentrations of oxygen at ambient pressure and temperature. Aerosp. Med. 36: 117–120, 1965.
512. WEISS, H. S., BECKMAN, D. L. AND WRIGHT, R. A.: Delayed mortality in adult chickens exposed to 1 atmosphere oxygen. Nature (London) 206: 1003–1004, 1965.
513. WEISS, H. S. AND WRIGHT, R. A.: Force feeding on the response of Japanese quail to oxygen toxicity. Comp. Biochem. Physiol. 25: 95–106, 1968.
514. WEISS, H. S., WRIGHT, R. A. AND HIATT, E. P.: Reaction of the chick to one atmosphere of oxygen. J. Appl. Physiol. 20: 1227–1231, 1965.
515. WELCH, B. E., MORGAN, T. E., JR. AND CLAMANN, H. G.: Time-concentration effects in relation to oxygen toxicity in man. Fed. Proc. 22: 1053–1056, 1963.
516. WESTGATE, H. D., FISCH, R. O., LANGER, L. O., JR. AND STAUB, H. P.: Pulmonary and respiratory function changes in survivors of hyaline-membrane disease. Dis. Chest. 55: 465–470, 1969.
516a. WHALEN, R. E., SALTZMAN, H. A., HOLLOWAY, D. H., JR., MCINTOSH, H. D., SIEKER, H. O. AND BROWN, I. W., JR.: Cardiovascular and blood gas responses to hyperbaric oxygenation. Amer. J. Cardiol. 15: 638–646, 1965.
517. WIDDICOMBE, J. G.: Respiratory reflexes. *In* Handbook of Physiology, Section 3: Respiration, vol. 1, ed. by W. O. Fenn and H. Rahn, American Physiological Society, Washington, D.C., 1965.
518. WILDERMUTH, O.: Hybaroxic radiation therapy in cancer management. Radiology 82: 767–777, 1964.
519. WILLIAMS, C. M. AND BEECHER, H. K.: Sensitivity of Drosophila to poisoning by oxygen. Amer. J. Physiol. 140: 566–573, 1944.
520. WINTER, P. M., GUPTA, R. K., MICHALSKI, A. H. AND LANPHIER, E. H.: Modification of hyperbaric oxygen toxicity by experimental venous admixture. J. Appl. Physiol. 23: 954–963, 1967.
521. WITTNER, M. AND ROSENBAUM, R. M.: Pathophysiology of pulmonary oxygen toxicity. *In* Proceedings of the Third International Conference on Hyperbaric Medicine, ed. by I. W. Brown, Jr. and B. G. Cox, pp. 179–188, NAS/NRC Publ. 1404, Washington, D.C., 1966.
522. WOOD, C. D. AND PERKINS, G. F.: Factors influencing hypertension and pulmonary edema produced by hyperbaric O_2. Aerosp. Med. 41: 869–872, 1970.
523. WOOD, C. D., PERKINS, G. F., SEAGER, L. D. AND KOERNER, T. A.: Pulmonary edema resulting from oxygen toxicity in divers. J. Louisiana State Med. Soc. 122: 219–221, 1970.
524. WOOD, C. D., SEAGER, L. D. AND PERKINS, G.: Blood pressure changes and pulmonary edema in the rat associated with hyperbaric oxygen. Aerosp. Med. 38: 479–481, 1967.
525. WOOD, J. D.: Development of a strain of rats with greater than normal susceptibility to oxygen poisoning. Can. J. Physiol. Pharmacol. 44: 259–265, 1966.
526. WOOD, J. D., STACEY, N. E. AND WATSON, W. J.: Pulmonary and central nervous system damage in rats exposed

to hyperbaric oxygen and protection therefrom by *gamma*-aminobutyric acid. Can. J. Physiol. Pharmacol. **43**: 405–410, 1965.

527. WOOD, J. D. AND WATSON, W. J.: Protective action of γ-aminobutyric acid against oxygen toxicity. Nature (London) **195**: 296, 1962.
528. WOOD, J. D. AND WATSON, W. J.: Molecular structure-activity relationships of compounds protecting rats against oxygen poisoning. Can. J. Physiol. Pharmacol. **42**: 641–646, 1964.
529. WOOD, J. D., WATSON, W. J. AND CLYDESDALE, F. M.: *Gamma*-aminobutyric acid and oxygen poisoning. J. Neurochem. **10**: 625–633, 1963.
530. WRIGHT, R. A., HIATT, E. P. AND WEISS, H. S.: Mortality and histopathology of germ-free rats and mice exposed to 100% oxygen. Proc. Soc. Exp. Biol. Med. **122**: 446–448, 1966.
531. WRIGHT, R. A., WEISS, H. S., HIATT, E. P. AND RUSTAGI, J. S.: Risk of mortality in interrupted exposure to 100 percent O_2: role of air *vs.* lowered P_{O_2}. Amer. J. Physiol. **210**: 1015–1020, 1966.
532. YAMAMOTO, E., WITTNER, M. AND ROSENBAUM, R. M.: Resistance and susceptibility to oxygen toxicity by cell types of the gas-blood barrier of the rat lung. Amer. J. Pathol. **59**: 409–436, 1970.
533. YARBROUGH, I. D., WELHAM, W., BRINTON, E. S. AND BEHNKE, A. R.: Symptoms of oxygen poisoning and limits of tolerance at rest and at work. U.S. Naval Experimental Diving Unit, Proj. X-337, Sub. No. 62, Report No. 1, 1947.
534. YHAP, E. O., ZELLER, J. A., LEVIN, P. M. AND SOLIS, R. T.: The effects of high inspired oxygen tension and its relationship to oxygen toxicity. Presented at Society of University Surgery, New Haven, Conn., Feb. 1971.
535. YORK, E.: Post-flight discomfort in aviators: aero atelectasis. Aerosp. Med. **38**: 192–194, 1967.
536. ZAL'TSMAN, G. L., ZINOV'EVA, I. D. AND KUMANICHKIN, S. D.: Increased individual predisposition of a subject to the effect of high partial oxygen pressure. *In* The Effect of the Gas Medium and Pressure on Body Functions, Collection No. 3, ed. by M. P. Brestkin, pp. 287–290, published for NASA, USA and NSF, Washington, D.C. by Israel Program for Scientific Translations, NASA TT F-358, TT 65-50136, 1965.
537. ZAL'TSMAN, G. L., ZINOV'EVA, I. D., KUMANICHKIN, S. D. AND TURYGINA, A. V.: Experience in the comprehensive study of the conditions of some systems of the human body under increased oxygen pressure. *In* The Effect of the Gas Medium and Pressure on Body Functions, Collection No. 3, ed. by M. P. Brestkin, pp. 148–155, published for NASA, USA and NSF, Washington, D.C. by Israel Program for Scientific Translations, NASA TT F-358, TT 65-50136, 1965.
538. ZEINER, F. N.: Sixty-day exposure to artificial atmospheres. Aerosp. Med. **37**: 492–494, 1966.
539. ZELAC, R. E. AND CROMBOY, H. L.: Variation of rat radiosensitivity with increased oxygen partial pressure of inspired gas. Health Phys. **18**: 227–231, 1970.
540. ZUBRIN, J. R., KETCHUM, S. A., III., THOMAS, A. N. AND HALL, A. D.: A protective effect of venous admixture on chronic pulmonary oxygen toxicity. Preprints of Annual Scientific Meeting of Aerospace Medical Association, pp. 211–212, 1968.