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PREVENTION OF PULMONARY OXYGEN TOXICITY.(U)
1978 R D PAEGLE, W N BERNHARD N00014-72-C-0141

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SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

1. REPORT NUMBER: Final Report
2. GOVT ACCESSION NO.
3. RECIPIENT'S CATALOG NUMBER

4. TITLE (and Subtitle): Prevention of Pulmonary Oxygen Toxicity,
5. TYPE OF REPORT & PERIOD COVERED: Final report. 1971-1978.
6. PERFORMING ORG. REPORT NUMBER

7. AUTHOR(s): Roland D. Paegle, M.D. and William N. Bernhard, M.D.
8. CONTRACT OR GRANT NUMBER(s): N00014-72-C-0140 N00014-72-C-0227 N0014-75-0830

9. PERFORMING ORGANIZATION NAME AND ADDRESS: Department of Anesthesiology, New York University Medical Center, New York, New York
10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS: 1978

11. CONTROLLING OFFICE NAME AND ADDRESS: Underwater Physiology, Physiology Program, Office of Naval Research, Arlington, VA 22217
12. REPORT DATE
13. NUMBER OF PAGES: 28p.

14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)
15. SECURITY CLASS. (of this report): Unclassified
15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

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DISTRIBUTION STATEMENT A
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17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

Unlimited

18. SUPPLEMENTARY NOTES

DDC RECEIVED FEB 22 1979 A

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Acute and chronic oxygen toxicity, pulmonary scarring, emphysema, oxygen hypersensitivity, adaptation to oxygen, respiratory flora, infection.

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Summary of the research conducted at 1) St. Vincent's Hospital, New York City, 2) Jersey City Medical Center, New Jersey and 3) New York University School of Medicine, New York City.

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FINAL TECHNICAL REPORT

PREVENTION OF PULMONARY OXYGEN TOXICITY

1971 - 1978

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This research was sponsored by the Office of Naval Research with funds provided by the Naval Bureau of Medicine and Surgery.

CONTRACT NO. N00014-72-C-0141
N00014-72-C-0227
N00014-75-C-0830

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II. INTRODUCTION

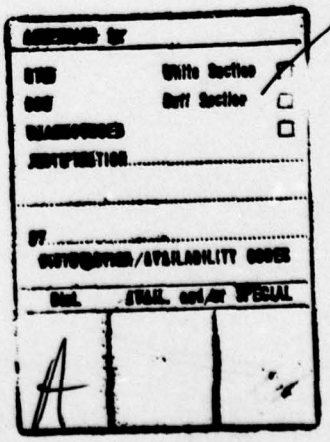
Controlled oxygen therapy is used in hospitals more and more as the appreciation of the need for comprehensive respiratory care becomes more obvious. In view of the large number of patients and military personnel, who are or will be subjected to increased oxygen concentrations, determining the best way to prevent or to minimise oxygen toxicity or other attendant problems is quite important. This project focused on three areas:

A. The main emphasis was on animal studies. An attempt was made to anticipate and resolve some of the problems which might be encountered clinically. These included alterations of microbial flora in upper respiratory tract. Rate of onset and the morphology of acute and chronic phase of pulmonary oxygen toxicity were studied. The optimal regimens for gradual adaptation to increased oxygen concentrations and the efficacy of the intermittent rest periods at lower O_2 concentrations were also determined.

The overall problem of chronic clinical or unsuspected pulmonary fibrosis and emphysema involves Naval personnel located in urban areas with severe air pollution as well as the general public. The basic question concerns the degree of improvement, if any, which could be expected in already scarred lungs if the toxic stimulus were removed or markedly reduced. Exposure of individual city dwellers to those pollutants, which are known to or only suspected to induce pulmonary fibrosis, are so varied and the development of fatal lesions so slow, that such a study would have serious sampling problems as well as take a very long time to complete. In contrast, the animal model system, which evolved during the initial phases of this project, offered an opportunity to get preliminary results relatively quickly.

B. Delivery of oxygen to the patients presents technical problems, including coping with iatrogenic damage to the airways. This portion of our study focused on delineation and reduction of such damage.

C. The usefulness of the research results, obtained by expenditure of ONR funds generated from tax revenues, is determined in part by the rapidity of information dissemination. This part of our project supplemented the publication route of informing the scientific community of the results of contract supported research by the use of lectures and scientific exhibits. This approach markedly enhanced the dissemination of our research findings.



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IV. SUMMARY

A-1) VARIABLE INDIVIDUAL AND COLONY SUSCEPTIBILITIES TO OXYGEN TOXICITY

Despite the risk of oxygen toxicity, the clinical use of hi[illegible] oxygen concentrations for acutely and chronically ill patients is increasing. When a method of therapy becomes widespread, the tendency to standardize it also grows. This may lead to treatment of patients with similar doses for similar time spans. In practice, such an approach may not be too deleterious, provided the sensitivity to such therapy does not vary too widely among the individuals in the group.

It was the aim of this study to determine how different the individual and strain susceptibilities would be among the adult animals from two colonies of Sprague-Dawley rats.

Variations in susceptibility to acute oxygen toxicity were observed among animals from the same colony as well as between two different colonies of Sprague-Dawley rats. Animals from Colony I survived, on the average, 6.7 days in 100 per cent oxygen, while the Colony II rats were considerably more susceptible to 100 per cent oxygen and survived, on the average, only 2.5 days. The survival of individual Colony I rats ranged from three to 20 days, Colony II rats from two to three days.

Because others have described the general lung injuries caused by oxygen as similar in man and rat, one should consider the possibility that some individual human patients may also be excessively sensitive to relatively brief exposures to 100 per cent oxygen.

A-2) ADAPTATION AND THE CHRONIC PHASE OF OXYGEN TOXICITY

This study investigated in more detail the effectiveness of gradual adaptation to increasing concentrations of oxygen (1) as a means to prolong the survival of adult experimental animals in 100 per cent oxygen because the clinical use of elevated oxygen concentrations for acutely and chronically ill patients is increasing.

Additional aims of this study included further delineation of the severe pulmonary changes seen in the chronic phase of oxygen toxicity and investigation of individual and colony susceptibility to different regimens of adaptation.

Some fibrosis and alveolar wall thickening had been observed in animals (2,3) subsequent to prolonged breathing of high oxygen concentrations. Several authors (5-8) have suggested the disturbing possibility that similar fibrosis may be produced in human patients by oxygen therapy. However, these clinical studies involved relatively few patients or the interpretation of findings was complicated by the presence of pre-existing cardiopulmonary diseases and iatrogenic factors, such as mechanical ventilation. Hence, the findings of this study not only helped to interpret the findings of the preceding clinical studies but also allowed better delineation of the lesions resulting from chronic exposure to oxygen.

Experimental animals were used to anticipate and/or delineate more clearly factors that may either facilitate or complicate long-term oxygen therapy. Gradual adaptation, ie, increasing the oxygen concentration in steps (40% and 70%) prolonged survival of adult Sprague-Dawley rats when they were finally exposed to 95 to 100 per cent oxygen. The adaptation had to start at 40 to 70 per cent. Nearly all rats lost weight during their exposure to high oxygen until they died. The partial adaptation or prolonged survival was accompanied by a chronic phase of pulmonary oxygen toxicity, which was characterized by pulmonary scarring, honeycombing, and emphysematous blebs.

The variability in individual susceptibility to oxygen toxicity during the adaptation regimen was less pronounced among Colony I animals than among Colony II animals.

Because a significant number of animals were very sensitive to 70 and 80 per cent oxygen, one should consider the possibility in clinical oxygen therapy that some human patients may also be excessively sensitive to relatively brief exposures to 70 to 80 per cent oxygen. Some patients may be liable to a chronic phase of oxygen toxicity with prolonged exposure to elevated inspired oxygen tensions.

A-3) PULMONARY MORPHOLOGY OF CHRONIC PHASE OF OXYGEN TOXICITY IN ADULT RATS

Previous experiments established that gradual adaptation of rats to high concentrations of oxygen prolonged their survival sufficiently to permit the development of subacute and then chronic phase changes in the lungs. This study delineated in greater detail the development and morphology of the lung changes during the chronic phase in a colony of highly susceptible animals.

Fifty-four adult, 250 to 350 gm Sprague-Dawley (CFE colony, Carworth Farms, N.Y.) male rats of like age were subdivided into four groups. The first and second groups, with ten animals in each, were the normal controls. The first group was killed at the beginning of the experiment and the second group at the end without exposure to increased oxygen.

The third was the acute oxygen toxicity phase control group. Four of the rats were killed after two days in 100 per cent O_2, while the remaining six rats, who were kept as long as possible in the 100 percent O_2 atmosphere, died within three days after being placed in the 100 percent O_2. The lungs of all rats of the third group had the characteristic findings of acute oxygen toxicity, including severe congestion, marked alveolar exudate and interstitial edema. After two to three days this edema was most marked around the medium and large pulmonary vessels.

The remaining 24 rats were exposed to 40 percent O_2 for four days and 70 per cent for four days prior to treatment with 100 percent O_2. The majority of the gradually adapted rats died or were killed within ten days after initiation of 100 percent O_2 and three more died within 10-20 days. The last three of the adapted animals died or were killed after 20-30 days in 100 percent O_2.

The lungs of all were removed and perfusion-fixed overnight (tracheal cannula, 20 cm H_2O pressure) with phosphate buffered (pH 7.2-7.4) 4 percent formaldehyde, then embedded in paraffin and whole sections cut and stained with H&E, Masson's trichrome and Vierhoeff's elastin stains.

The chronic phase was characterized by marked honeycombing and interstitial scarring. The severity was graded by a method previously applied to whole sections of human lung (9). Within three to ten days the majority of the adapted rats had a grade 10 to 20 emphysema, with a predominantly panlobular distribution. The lungs from the rats which survived 20-30 days had large bullous blebs, more marked at the bases of the lungs. In these long-term survivors the emphysema ranged from grade 30 to 60. Regions with thinned alveolar walls alternated with zones of cellular proliferation and intestinal collagen deposition. Large scars and recent, partly organized, thromboemboli were also present. The mild-to-moderate number of interstitial and intra-alveolar inflammatory cells included macrophages, lymphocytes and neutrophils. The intra-alveolar exudate and congestion in the adapted rats appeared less marked during the exposure to 100 percent O_2 than in the acute phase controls, while the perivascular exudate was still very severe. A more exact comparison was not feasible, since the intratracheal perfusion fixation washed out some of the intra-alveolar proteinaceous exudate and compressed the congested vessels. At least a portion of the large scars originated from confluence and organization of the large regions of perivascular exudate. After the initial, relatively acellular phase during the first two days of 100 percent O_2, the numerical increase of fibroblasts in these regions was quite marked.

A-4) PROLONGING RAT SURVIVAL IN 100 PERCENT OXYGEN BY INTERMITTENT EXPOSURE TO 40 PER CENT OXYGEN

This study was designed to investigate in detail the effectiveness of variation in duration and sequence of intermittent 40 percent O_2 as a means for prolonging the survival of experimental animals exposed to 100 percent O_2. Initial experiments showed that gradual adaptation to increasing O_2 concentrations as well as 24- and 48-hour periods of exposure to 40 percent O_2 will prolong survival of the rats exposed to 100 percent O_2.

A range of relatively short intermittent periods of exposure to lowered O_2 tensions for less than an hour during exposure to 100 percent O_2 under hyperbaric conditions of 2 to 3 atmospheres have been evaluated in man and experimental animals (10,11). We evaluated the effect of longer periods of exposure to O_2 at concentrations greater than 21 percent but less than 100 percent at 1 atmosphere, since under clinical conditions 100 percent O_2 is usually used therapeutically at 1 atmosphere.

Prior intermittent exposure to 40 percent O_2 protected rats against fatal O_2 toxicity. Protection was not absolute, however, for the death of most rats in 100 percent O_2 was not prevented but delayed considerably. Furthermore, those rats which did survive exposure to 100 percent O_2 for long periods by virtue of prior adaptation to increased O_2 concentrations had pathologic changes in the lungs typical of chronic O_2 toxicity. The very early demise of some rats indicated that 1 of 12 animals is hypersensitive to high concentrations of inspired O_2.

Series I. -- All animals breathing room air survived 43 days, but all the rats placed from room air directly in 100 percent oxygen died within 3 to 4 days. When experimental animals were subjected to 6 consecutive days in 40 percent O_2 before exposure to 100 percent O_2, average survival time was not prolonged; 4 of 6 rats died within 2 days after being placed in 100 percent O_2, while 1 animal survived 18 days.

Series II. -- When initial and intermittent exposure to 100 percent O_2 was constant at 2 days but the length of the rest period varied from 6 to 48 hours, duration of survival increased markedly. On the average, rats survived 14 days in 100 percent O_2 when the rest periods were 12 to 48 hours long. When the duration of survival of each of the experimental groups was compared to control groups (Student t-test), the differences were significant ($p<0.001$). When rest periods were shortened to only 6 hours, mean survival times decreased insignificantly to 9.6 days ($p<0.10$).

The rapid death of a small number of experimental rats may be related to O_2 hypersensitivity and not to infection, since no histologic evidence of infection was seen. Prolonged exposure to O_2 altered the tracheal microbial flora but did not necessarily result in pulmonary infection. Variation in individual and colony susceptibility to pulmonary O_2 toxicity was quite marked for Sprague-Dawley rats and for man (12,13). While the pulmonary function measurements of 3 volunteers breathing high F_IO_2 returned to normal within days after cessation of exposure to high inspired O_2, the recovery of the 4th volunteer required weeks (14).

Although the clinical implications of hypersensitivity to O_2 need considerable additional study, it seems likely that early identification of such O_2-sensitive individuals and limitation of their exposure to hyperoxic conditions may be helpful. The clinical or occupational situations where such early identification of O_2 hypersensitivity may be beneficial include (a) early institution of extracorporeal membrane oxygenation (ECMO) for hypersensitive patients; and (b) restrictions on hypersensitive Navy and sports scuba diver exposure to increased torr O_2 during prolonged or very deep dives. Preliminary observations (14) indicate that patients placed on ECMO early in their disease survive more often than those in whom the therapy is instituted late in the course of the acute respiratory insufficiency. Oxygen-hypersensitive patients probably will develop severe acute respiratory insufficiency before other patients if subjected to the same hyperoxic therapeutic regimen.

A-5) MICROBIAL FLORA OF THE LARYNX, TRACHEA, AND LARGE INTESTINE AFTER LONG-TERM INHALATION OF 100 PER CENT OXYGEN

Prolonged exposure to high concentrations of oxygen is now frequently a part of inhalation therapy of critically ill patients. The development of the chronic phase of oxygen toxicity, with attendant pulmonary honeycombing and interstitial scarring, is one of the main complications of prolonged exposure to 100 per cent oxygen. Impairment of the phagocytic activity of alveolar macrophages is another (15). This, in turn, may facilitate microbial proliferation. Enhancement of viral infections in mice following prolonged exposure to high concentrations of oxygen has also been reported (17). On

the other hand, hyperbaric oxygen is used to treat patients infected with anaerobic organisms, such as clostridia, and has also been shown to be bacteriostatic or even bactericidal to aerobic organisms *in vivo* and *in vitro* (18,19).

Since various microorganisms have access to the upper respiratory tract, it was important to determine whether inhalation of high concentration of oxygen could significantly increase or decrease the numbers and types of potentially pathogenic organisms. The experiments were designed to study this in experimental animals. While previous studies *in vivo* and *in vitro* had tested the effects of relatively brief exposures (a few hours to several days) (18,19) to high oxygen concentrations, this study dealt with the effects of a more prolonged exposure to 100 percent oxygen.

Effects of long-term inhalation of 100 per cent oxygen on the microbial flora of the rat larynx, trachea, and large intestine were studied. Rats were kept 14 days in an atmosphere of 100 per cent oxygen after being conditioned to high oxygen concentrations by exposure to three cycles of 100 per cent oxygen (two days) alternating with 40 per cent oxygen (two days). Controls were kept under similar conditions in normal atmosphere. Rats were sacrificed, and at necropsy laryngotracheal swabs and fecal material from the large intestine were obtained and cultured for bacteria and fungi.

Streptobacillus moniliformis, the predominant microorganism in the upper tracheas of controls, was not isolated from the oxygen-treated rats. Alpha-hemolytic streptococcus and *Staphylococcus albus* were present in control rats, but were found less frequently in rats exposed to oxygen. *Pseudomonas* and *Proteus*, infrequently isolated from controls, were predominant and sometimes the only microorganisms isolated from oxygen-treated rats. The data indicate that prolonged exposure of the rat to 100 per cent oxygen shifts the microbial flora in the upper respiratory tract from mainly gram-positive to mainly gram-negative bacteria. In contrast, there was no significant difference between the microbial flora in large intestines of control and oxygen-treated rats.

The possibility that similar changes may occur in man should be considered when prolonged oxygen therapy is contemplated.

A-6) THERMOGRAVIMETRIC ANALYSIS OF RAT LUNGS WITH CHRONIC OXYGEN TOXICITY

Water, glycosaminoglycan (GAG) and the structural protein concentrations were determined in lungs affected by chronic oxygen toxicity. Male, CFE, Sprague-Dawley rats (275-400 g) were randomized into experimental (50 animals) and control groups (16 animals). The rats were subjected to a 10-day regimen in order to prolong their survival in 100% O_2. The regimen consisted of the following sequence of O_2 concentrations: two days in 40% O_2, 2 d.-100%, 2 d.-40%, 2d.-100%, 2 d.-40% O_2. After this regimen, rats were kept in 100% O_2 up to 30 days. The left lung of each animal was processed for histological examination but the right one was lyophilized and analyzed using the MOM derivatograph.

The concentration of glycosaminoglycans in lungs decreased during the first two weeks of exposure to 100% O_2, indicating a significant loss of ground substance. The mean decrease of structurally bound water was -12.7% (S.D. ± 1.3%/p 0.01). This suggested a different behavior between structural water and absorptive water, which is bound by physical forces. The former may be related to structural damage while the latter causes the edema of acute O_2 toxicity. Total collagen content also decreased during the first 2 weeks. Later on, repair resulted in a gradual elevation of its concentration. The changes in the relative amounts of the collagen components of varying thermostability i.e. newly synthesized tropocollagen and mature collagen, suggested alterations in synthesis.

A-7) RATE OF ONSET AND REVERSIBILITY OF ACUTE PULMONARY OXYGEN TOXICITY

Our previous observations indicated that if the inhalation of 100% O_2 was stopped after 2 days, most rats will survive despite the edema and congestion already induced. We wanted to determine the type, the rate of onset as well as how severe this damage had to be before it becomes irreversible. To achieve this we studied sequential changes in lung/thorax compliance during and subsequent to breathing 100 percent oxygen at one atmosphere (ATM).

An attempt was also made to prevent or at least to minimize the pulmonary edema and pleural effusion associated with acute oxygen toxicity by treatment with steroids or Lasix.

Groups of 300-400 gram CFE strain male, Sprague-Dawley rats (Colony II) were placed in a 300 liter acrylic environmental chamber supplied with either 750 ml/min/animal 100 percent oxygen, 40 percent oxygen, or room air at one atmosphere. Chamber oxygen concentration was measured at least once daily with a Beckman D-2 oxygen analyzer. Relative humidity, measured with a Precision Instruments Hygrometer, varied between 70 and 100 percent. Chamber temperature, controlled with room air conditioning, averaged 75°. Carbon dioxide was absorbed with soda lime. Fresh wood shavings, food and water were supplied daily. This was done through an air lock in order to maintain the environmental oxygen tension constant. Full arm gloves were built into the chamber to distribute food, water, shavings and rats within the chamber. Lung/thorax compliance was determined on the animals after 0, 24, 36, 60, and 72 hours (only 3 animals lasted that long) breathing 100 percent oxygen, and on 9 control rats breathing compressed air in the chamber for 72 hours.

Rats were anesthetized with 10 mg Ketamine and 1.25 mg Inapsine given intramuscularly, pinned supine to a cork board, exanguinated through a 21 gauge needle inserted visually into the abdominal aorta and volume pressure points measured through a 2 mm O.D. cannula tied into the trachea. Lungs were inflated with 0.5 ml increments of air to 7 ml and then deflated in similar decrements to 0 ml. Lung/thorax compliance was measured twice on each rat. Following thoracotomy, pleural effusion was removed and measured, and open chest lung compliances were measured twice on each animal as previously described. Volume/pressure loops were graphed, and highest compliance point plotted.

After compliance measurements were done, trachea and both lungs were excised, right lung weighed, and left lung expanded with 4 ml of phosphate-buffered formaldehyde. Both lungs, heart, trachea, spleen, and one kidney were immersed in 4% formaldehyde. After fixation, all tissues were embedded in paraffin, cut into 5-7 micron sections, and stained with hematoxylin and eosin. Lung sections were also treated with Verhoeff's and Masson's Trichrome stains. The severity of emphysema was graded by the method previously applied to whole sections of human lungs (9).

Lasix was given via drinking water (40 mg/bottle) or intramuscularly (1 mg q 12 h) after the rats had been breathing 100% for 24 and 48 hours, respectively; 5 mg of Depomedrol were given IM upon initiation of 100% O_2, followed 48 hours later by 5 mgm of Solumedrol.

Closed chest lung/thorax compliance measurements were lower than open chest lung compliance, but differences between the two diminished as compliance decreased.

Figure 2 shows lung/thorax compliance had decreased only slightly after 24, 36, and 48 hours in 100% oxygen, but had decreased precipitiously after rats had breathed 100 percent oxygen for 60 and 72 hours. Large amounts of pleural effusion did not appear until after 48 hours of 100 percent oxygen. After 60 and 72 hours of hyperoxic exposure up to 8 ml of effusion had accumulated on each side. Microscopic sections of lungs showed interstitial edema and intra-alveolar proteinaceous exudate. The perivascular edema and exudates were most marked after 48 hours.

Lasix in drinking water did not prolong survival significantly but when it was combined with IM Lasix and a rest period (one hour in 40% oxygen after every 12 hours in 100% O_2), the survival increased to 68 hours, compared to 56 hours for the controls ($p < .0025$). Steroids, however, did not prolong the survival significantly.

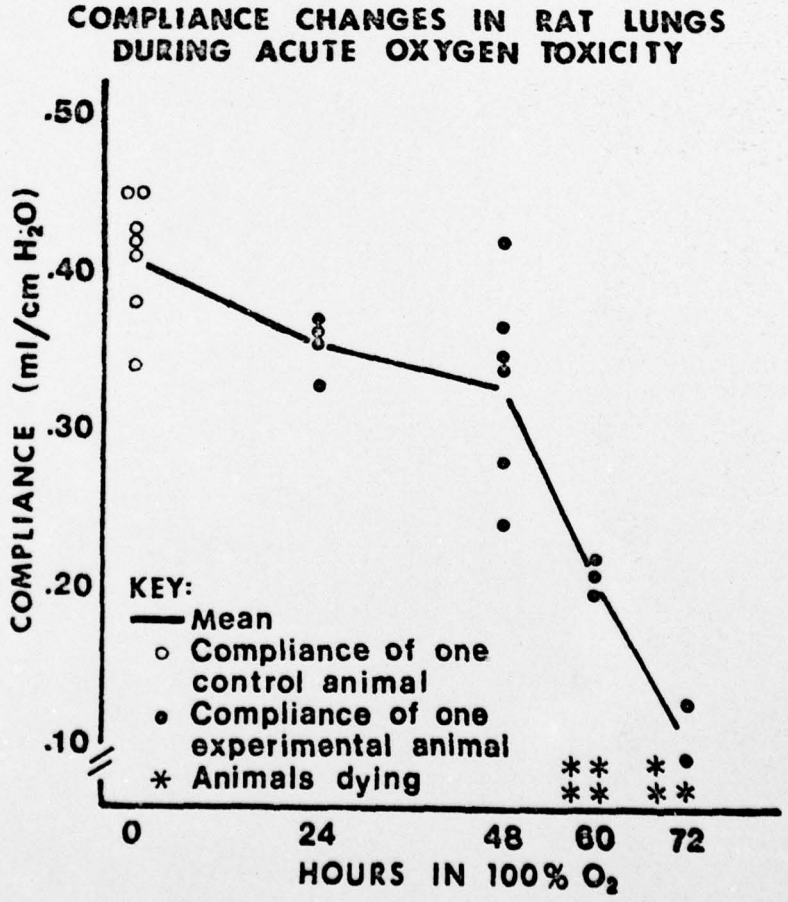
The experimental animals, who were in the end stages of acute oxygen toxicity, had labored breathing. This suggested that the work of breathing was increased. Restrictive lung defects can arise from changes in the thoracid structures, pleural effusion, or loss of elasticity of alveoli. Any of these restrictive defects alone, or in combination could have caused decreased compliance of the lung-thorax system. The fact that the lungs of the experimental animals were much stiffer than the controls, even after opening the thorax and removing the fluid, indicated that the loss of compliance in acute oxygen toxicity resulted from restriction due to pleural effusion (extrapulmonary restriction) as well as loss of elasticity of alveoli (intra-pulmonary restriction). Both the decrease of compliance and accumulation of pleural effusion occured at approximately the same time (48 to 72 hours). Rats were exanguinated to obviate any effect that pulmonary vascular congestion might have had on compliance measurements.

We chose to follow closed chest compliance measurements not only because they were easily reproduced and compared to open chest measurements but also because they could be compared with clinical data. Lung/thorax compliance measurements in mechanically ventilated patients are not routinely done, even

though their use has been recommended and the procedure is noninvasive, and easily accomplished. Clinically, compliance measurements may also be used to determine the optimum end-expiratory airway pressure. Perhaps such compliance measurements can also be used in patients to identify oxygen hypersensitivity and then initiate remedial measures, including reduction of O_2 tension. Although most first class respiratory care departments are quite aware of the dangers of using 100% oxygen, some situations can be envisioned where it may be necessary to resort to such an extreme concentration. For example, acute lung injury in humans due to blunt trauma, such as car or airplane crashes, may injure large regions of lungs and severely compromise pulmonary function. This may necessitate using up to 100% oxygen just to keep the blood oxygenated. Since the onset of the injuries in such instances is very rapid, there will be no chance for gradual adaptation to the toxic oxygen concentration. Hence, intermittent rest period regimen may be of use to limit the damage and help tide the patient over the critical phase, especially if it appears that such a patient is hypersensitive to oxygen.

The abrupt alteration (Figure 1) of the compliance at 48 hours in rats suggests that the pulmonary damage accelerates at this point and may well become irreversible soon after. If a similar phenomenon exists in humans, patients could be monitored for onset of the severe phase of oxygen toxicity by careful scrutiny of pulmonary compliance changes.

Figure 1.



A-8) THORACIC AND LUNG COMPLIANCE DURING AND AFTER INDUCTION OF PULMONARY EMPHYSEMA BY 100% OXYGEN

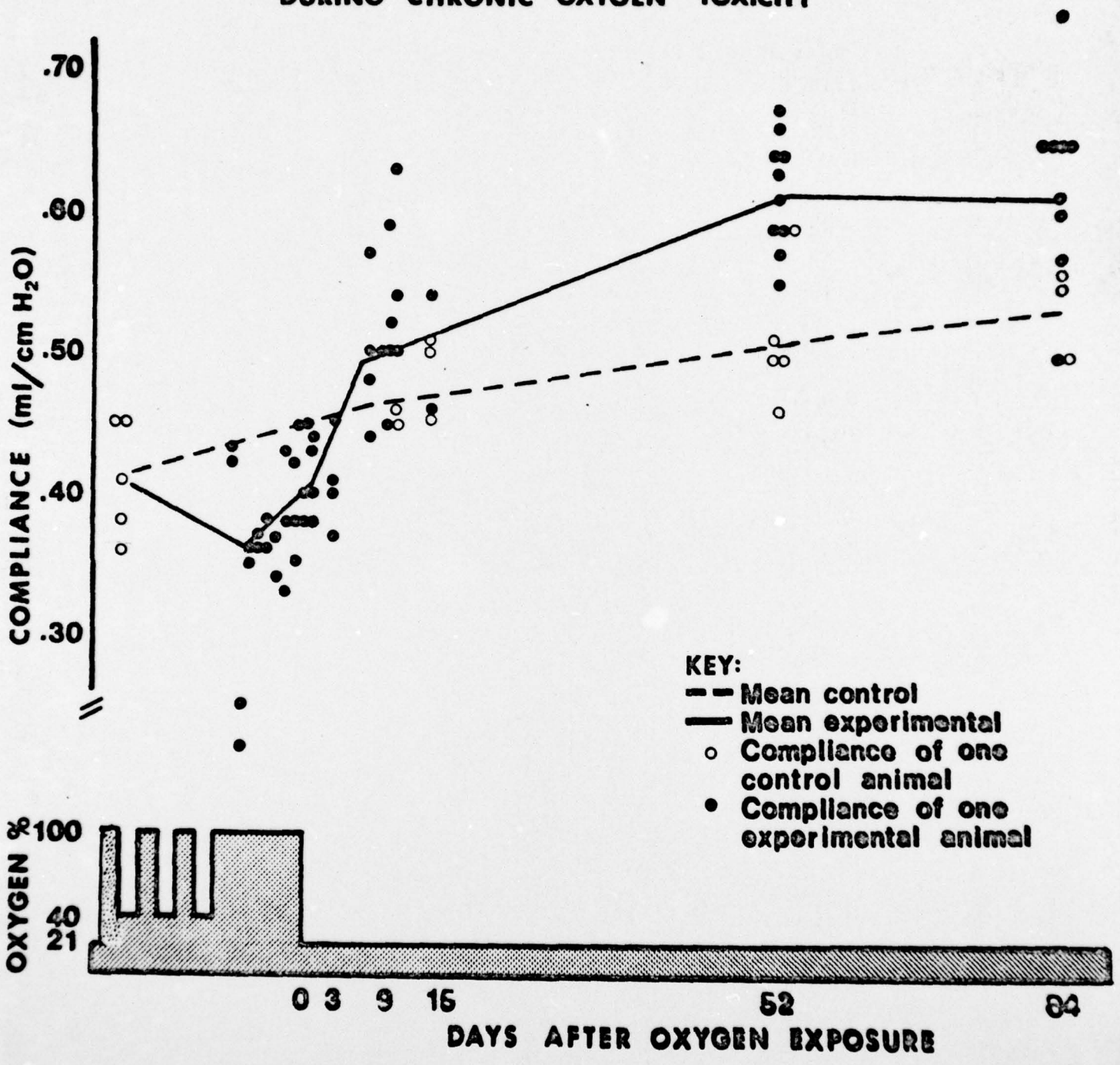
Determination of the degree of improvement, if any, which can be expected in severe chronic pulmonary scarring and emphysema, if the toxic stimulus is removed, was the main aim of this part of the project. The regimen of inducing chronic lesions, which are comparable to human emphysema, was developed during the initial phase of this project. This regimen was adapted and used for determining to what degree, if any, can resolution and reduction of the severe pulmonary scarring take place if the animals are allowed to recuperate in room air after exposure to the toxic oxygen concentrations.

The long term survival and the degree of invalidism of the animals with the chronic lung damage was compared to their littermates; 300-400 gram, male Sprague-Dawley rats of the CFE strain (Colony II) were subjected in batches to the regimen which produced the severe scarring of the chronic phase of oxygen toxicity. The technique consisted of 48 hour long recuperation periods inserted between the initial, two day long exposures to 100% O_2 (Fig. 2). The chest wall and lung compliance measurements were determined by the method described in Section A-7.

Lung inflation and perfusion fixation was performed as follows: The thorax and neck were opened up to the chin. A tie was placed and tied firmly around the mainstem bronchus leading to the 4-5 lobes of the right lung. A glass cannula, made from Pasteur pipettes, was inserted and tied securely into the trachea at mid neck level. 3.8% formaldehyde, buffered to pH. 7.2-7.4 with sodium phosphate, was instilled into the trachea via the cannula at 15-20 cm water pressure. The left lung was checked for leaks, then carefully resected together with the cannula from other mediastinal structures. The perfusion fixation was continued for 2-24 hours. After this time the left bronchus was also tied without deflating the lung. The isolated lung was cut free from the trachea. All the tissues were fixed further in fresh, buffered formaldehyde solution. The right lung and the heart were resected after inflation of the left lung. The excess blood was removed by blotting before the right lung and the heart were weighed and fixed. After fixation all tissues were embedded into paraffin, cut into 5-7 μ thick sections and stained with hematoxylin and eosin. Only the lung sections were stained with Verhoeff's elastin and Masson's Trichrome stains.

Lung/thorax compliance decreased during oxygen adaptation (intermittent rest regimen) and during the early part of the ten consecutive days in 100 percent oxygen (Fig. 2). Compliance returned to normal four days after cessation of 100 percent oxygen breathing and then stabilized at above normal 7, 10, 14, 52, and 83 days post hyperoxic exposure (Figure 2).

Figure 2


COMPLIANCE CHANGES IN RAT LUNGS
DURING CHRONIC OXYGEN TOXICITY
COMPLIANCE (ml/cm H2O)
.70
.60
.50
.40
.30
KEY:
Mean control
Mean experimental
Compliance of one control animal
Compliance of one experimental animal
OXYGEN %
100
40
21
0 3 9 15 52 84
DAYS AFTER OXYGEN EXPOSURE

Pleural effusion accumulated during the early phase of adaptation while breathing 100 percent oxygen but was not seen thereafter. After compliance measurements, high compliance lungs contained white avascular scarred areas and transparent blebs. Microscopic sections of these lungs revealed varying amounts of interstitial honeycombing and scarring. The histology and sequence of morphologic changes are shown and described in greater detail in earlier portions of this study (A-3, A-4).

Lung weight increased as compliance decreased and decreased again as compliance increased. The stabilization of the compliance of the emphysematous lungs at a level above that of the control group (which had not been exposed to 100% O_2), indicated that the emphysema neither regressed nor became worse once the noxious stimulus (100% O_2), had been removed. The increase in lung/thorax compliance during 100 percent oxygen breathing after adaptation is most likely due to resorption of both interstitial pulmonary edema fluid and pleural effusion. Pleural effusion was noted during adaptation (intermittent rest regimen) when compliance was low but was not seen thereafter. The volume of interstitial edema fluid appeared to decrease and become organized as honeycombing and fibrosis developed with prolonged exposure (total 14 days) to 100 percent oxygen. The increase in compliance coincided with the morphologic change from edematous to emphysematous lungs. The predominance of enlarged air spaces and thin walls over scarring and thick alveolar walls correlated with the increase in compliance above normal. The compliance increase was further substantiated by the decrease in lung weight which occurred with the development of emphysematous changes in the lungs (chronic pulmonary oxygen toxicity).

A decrease in lung/thorax compliance is certainly not specific for acute pulmonary oxygen toxicity. But, when compliance decreases during high concentration oxygen therapy, one should consider that fluid may be accumulating in the lung and/or pleural space. When compliace increases after long term exposure to high oxygen tensions, one must include in the differential diagnosis development of the emphysematous changes seen in chronic pulmonary oxygen toxicity. Routine measurement of lung/thorax compliance should be done in patients mechanically ventilated with elevated oxygen tensions in an effort to detect early pulmonary and pleural changes which might be caused by oxygen as well as to detect oxygen hypersensitive individuals.

A-9) FAILURE OF SEVERAL ANTIOXIDANTS TO PREVENT ONSET OF ACUTE PULMONARY OXYGEN TOXICITY

The antioxidants, vitamin E, ascorbic acid and butylated hydroxyanisol decreased the mortality of choline deficient rats (4). Short term protection of mice by antioxidants has also been reported. Several antioxidants were tried in this study in an attempt to prevent or at least diminish acute pulmonary oxygen toxicity in experimental animals.

Rats receiving an antioxidant were kept in 100% oxygen at 1 ATM until they died. The Sprague-Dawley male and female rats (Colony I) were ex-breeders . After arrival at animal quarters, they were kept in a separate room, so as to delay or minimize crossinfection from other strains or rats. Each antioxidant was injected into a group of six rats. The concentrations of the drugs injected daily into the rats were:

Antioxidant	Daily dose	Solvent
Butylated hydroxyanisol (Nutritional Biochemicals Corporation).	20 mg	0.5cc Sesame oil
Vitamin E (α-tocopherol)	20 mg	0.5cc Sesame oil
Vitamin-C (Ascorbic acid in aqueous buffer in ampules, the Vitarine Co.)	500 mg	2 cc buffer
Vitamin-C (Sodium ascorbate, Nutritional Biochemicals Corp.)	562 mg	2 cc dist. H_2O

Most of the control rats kept in room air gained some weight despite the relatively high doses of the antioxidant drugs while the six controls exposed to 100% oxygen died in 6-20 days.

Although BHA appeared to have a mild protective effect (5-30 day survival in 100% O_2), none of the drugs tested had a significant success in preventing the pulmonary damage and prolonging the survival of the rats in 100% O_2.

A-10) NON-FATAL OXYGEN TOXICITY AND ADAPTATION TO LONG TERM 50% AND 70% OXYGEN

Since prolonged use of 40 to 70% oxygen is occasionally necessary for patients, this study was designed to test the response of an oxygen sensitive colony of adult male Sprague-Dawley rats to comparable long term oxygen concentrations.

Twenty-four rats were placed into 50% oxygen for twenty-one weeks, and twenty-four animals into another chamber with 70% O_2 for sixteen weeks. Control group 1 was kept in room air for twenty-two weeks while control 2 was placed directly into 100% oxygen. None of the control group 1 animals died, while all of the control group 2 animals died within 3-4 days, with pulmonary edema and other signs of acute oxygen toxicity.

The experimental rats kept on 50% oxygen gained weight more slowly than the room air controls; none died. Initially the animals in 70% O_2 lost weight but then their weights also increased.

Three of the 70% animals died early (3-5 weeks) with signs of acute oxygen toxicity. The other animals survived in 70% oxygen the full sixteen weeks, when these animals were sacrificed. Microscopic examination of lungs revealed only mild emphysema and honeycombing (chronic oxygen toxicity).

It appears that the nonfatal range of oxygen for the hypersensitive animals in this colony of rats is above 50% but below 70% oxygen at 1 ATM.

B-1) RAPID TRACHEAL INJURY BY CUFFED AIRWAYS AND HEALING WITH LOSS OF CILIATED EPITHELIUM

Laryngeal and tracheal lesions were being seen with great frequency in patients managed with respirators while giving high inspired oxygen. These lesions may limit ultimate survival or complicate recovery (20-22). For example, up to 15% of patients who survived after prolonged ventilatory assistance developed tracheal stenosis (22)

Previous studies (23-27) concentrated on the determination of the severity of the acute erosions and the accompanying symptoms as well as on the long-term changes produced by scarring and stenosis. The emphasis in this study was on the determination of the rapidity of onset of the lesions and the evaluation of the healing of the tracheal wounds, especially the epithelial regeneration over the tracheal scars.

In 54 patients examined at autopsy, the acute tracheal erosions produced by two types of commercially available endotracheal tubes with low volume, high pressure inflatable cuffs were similar to those induced by two types of cuffed tracheostomy tubes. The erosions exposed portions of the tracheal cartilages within 12 to 48 hours.

Healing of the circumferential tracheal erosions often was accompanied by the loss of the submucosal mixed mucous and serous glands and the replacement of the normal ciliated epithelium by stratified squamous epithelium. Such a zone in a long-term survivor may become a substantial barrier to removal of particulate matter from the tracheobronchial tree.

Additional complications of controlled ventilation included mediastinal and subcutaneous air dissection, tension pneumothorax, perforation of the esophagus, bronchial obstruction, hemorrhage, and signs suggestive of adult oxygen toxicity. Hemorrhage appeared to be more common in patients receiving anticoagulants.

B-2) SQUAMOUS METAPLASIA OF TRACHEAL EPITHELIUM ASSOCIATED WITH HIGH-VOLUME, LOW PRESSURE AIRWAY CUFFS

Healing of the circumferential tracheal erosions induced by the older-style endotracheal and tracheostomy airways (20), which were equipped with LVHP cuffs, was often accompanied by a variety of complcations, including stenosis, scarring (20-22), loss of the submucosal mixed mucous and serous glands, and the not-infrequent replacement of the normal ciliated epithelium by stratified squamous epithelium. The decrease in damage achieved by switching to a variety of the newer-style HVLP cuffed tubes has been documented repeatedly (28-30).

More recent work has been centered on comparing advantages of foam-filled with air-filled endotracheal-tube cuffs (31). Therefore, we concentrated our investigation on other aspects: the effect of HVLP cuffs on tracheal epithelium and the submucosa. Since the materials used in the previous study (B-1) of the LVHP cuffs were still available, they were reviewed and compared with the specimens obtained from patients intubated with the HVLP-cuffed airways.

The tracheas of 12 patients, intubated from 2 hours to 20 days with tracheal airways equipped with the newer style, high-volume, low-pressure (HVLP) cuffs, were examined at autopsy. The type and severity of iatrogenic damage to the epithelium and submucosa was determined and compared to that seen in a previous study of 54 patients, who had been intubated with the older-style low-volume, high-pressure (LVHP) cuffed airways.

The tracheal epithelial and submucosal damage due to intubation with the HVLP cuffed airways was considerably less than that with LVHP cuffs. The submucosal glands were often spared, and some of the tracheal epithelium even survived 20 days of exposure to the "soft" cuffs. However, the pseudostratified ciliated epithelium, which normally lines the trachea, was often replaced by stratified squamous epithelium.

If such a zone of nonciliated epithelium remains in the trachea of a long-term survivor, its determinental effect on the removal of particulate matter from the tracheobronchial tree may have to be considered.

B-3) PHYSICAL CHARACTERISTICS OF AND RATES OF NITROUS OXIDE DIFFUSION INTO TRACHEAL TUBE CUFFS

Concern over high cuff-to-tracheal wall pressure and reports of aspiration past low-pressure cuffs (32) prompted changes in cuff design and introduction of cuff pressure-regulating devices (33,34). Nitrous oxide and other gases diffused into air-inflated tracheal tube cuffs and increased volume and pressure in all cuffs unless the cuff-inflating tube was open to atmosphere (35-39). This study was done to measure rates of nitrous oxide diffusion into commonly used tracheal tube cuffs and to compare their physical characteristics.

Physical characteristics and time-related volume changes in air-inflated tracheal tube cuffs exposed to nitrous oxide were measured in an environmental chamber. Cuff wall diameter thickness, residual volume, and length were also measured. Gas volumes in most air-inflated tracheal tube cuffs increased 1.7 to 7 ml within 30 min of exposure to pure nitrous oxide. Diffusion rates into most cuffs varied inversely with cuff thickness and directly with the partial pressure of nitrous oxide. There were significant differences in diffusion rates among cuffs of the same composition with different densities or porosities as well as among cuffs of different compositions. Cuff diameters ranged from 13.8 to 32 mm; thicknesses from .033 to .55 mm; residual volumes from .22 to 19.4 ml; lengths from 23.1 to 49.1 mm.

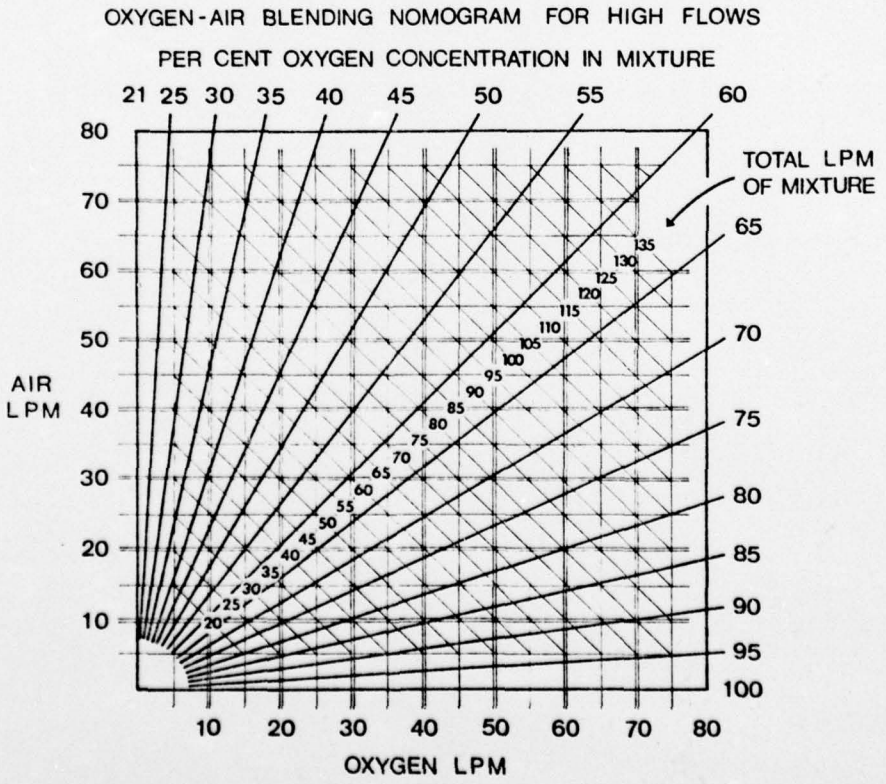
Intracuff volume and pressure increase related to gas diffusion into air-inflated cuffs should be preiodically adjusted or pressure automatically controlled during nitrous oxide anesthesia. Large diameter, thin walled cuffs are recommended.

B-4) OXYGEN-AIR BLENDING NOMOGRAMS FOR MEDIUM AND HIGH FLOW RATES

In our institutions the use of intermittent mandatory ventilation (IMV) and continuous positive airway pressure (CPAP) was increasing, and we were faced with increasing need for accurate oxygen concentrations. In addition to using commercial blenders we were mixing oxygen and air for these circuits with two flowmeters. To speed computation of the oxygen-air mix at the bedside we constructed two nomograms (Fig 3). Each integrated four variables: (1) total flow of mixture, (2) oxygen concentration of mixture, (3) oxygen flow, and (4) air flow.

Nomograms, tables and slide rules for oxygen-air mixing were available, but these were generally guides for supplemental oxygen to specific ventilators (40,41). Others lacked precision or ease of operation (42,43). Our nomograms have universal application for any system requiring accurately controlled oxygen concentrations, and they are easy to use. In addition, our nomograms differ from those previously published in that they solve the oxygen-air mix problem in the order most logical for IMV and CPAP, ie, (1) desired oxygen concentrations, (2) total flow desired, (3) air flow, and (4) oxygen flow. One nomogram (Fig. 3) is limited to the flow range of 0 to 15 LPM per flowmeter because most flowmeters currently in use have this range. The second nomogram (Fig. 3) covers the flow range of 0 to 80 LPM per flowmeter and is useful when high flow rates are desired. Because the relationships are linear, flow ranges beyond the limits of both nomograms may be calculated as multiple of the indicated flows.

Figure 3

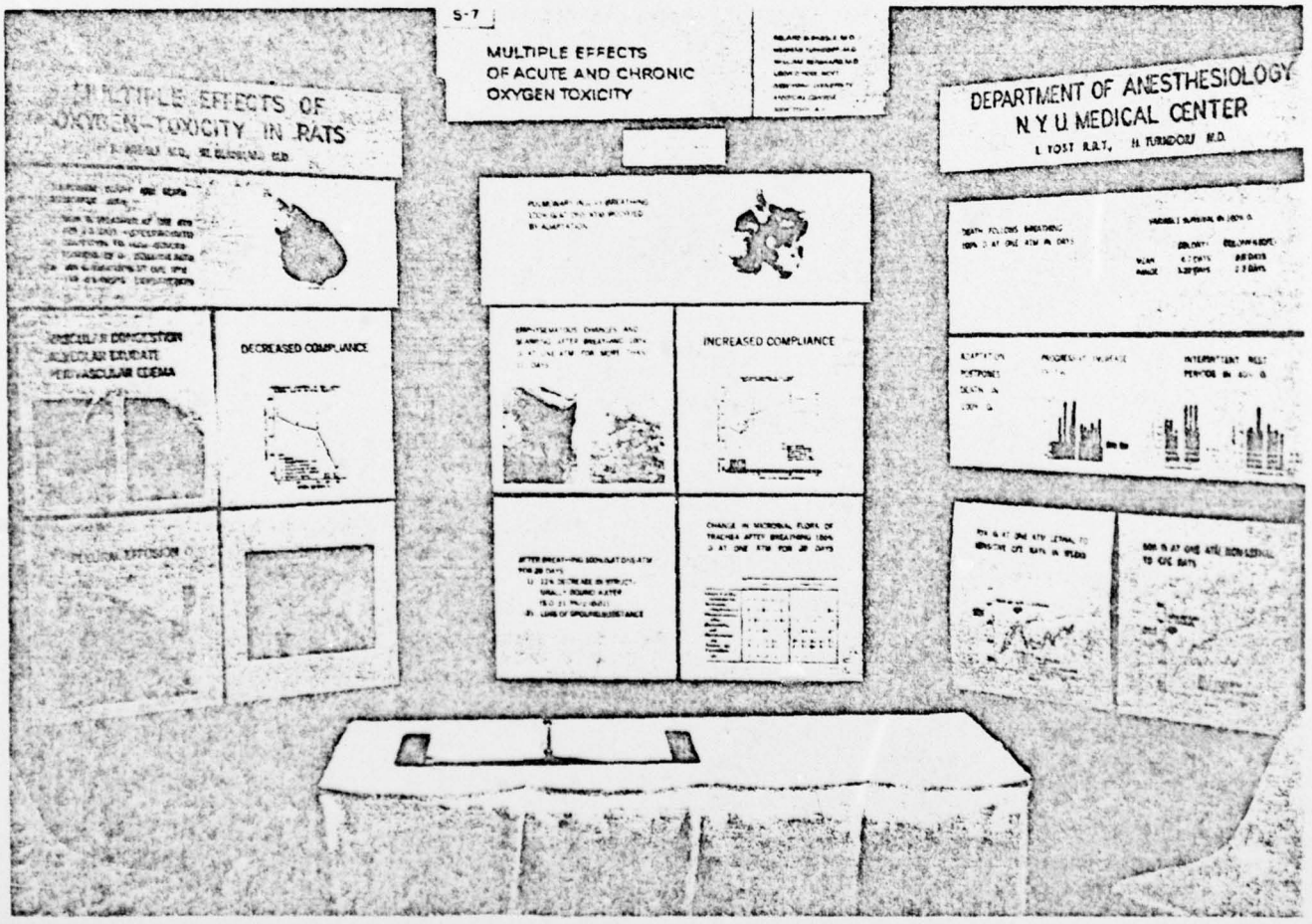


C) COMMUNICATION OF RESULTS TO SCIENTIFIC COMMUNITY

Informing the scientific community of the results of contract supported research can be markedly enhanced by supplementing the publication route with lectures and scientific exhibits. The latter reach an especially large number of professionals, including Navy personnel, who attend national meetings for anesthesiologists, acute care physicians and respiratory care therapists.

Results of our studies were incorporated into three scientific exhibits (See Publication Section items L, M, and P, and Fig. 4). Each has been shown at a number of meetings. This practice of disseminating information was supplemented by guest lectures at other institutions and during Continuing Medical Education seminars at the hospitals where each of the investigators was employed.

Figure 4



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