Communication #322 from D. Radford Shanklin, Emeritus Professor, University of Tennessee, Memphis, and member of the corporation, Marine Biological Laboratory, Woods Hole

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Source: Minisymposium: Advances in inflammatory and fibrosing lung diseases. Sunday, April 10, 2011, Experimental Biology 2011, Washington, D.C.

Format: PowerPoint Presentation converted to PDF with brief added remarks for clarification of the PPP frames

Introduction:

Pulmonary fibrosis implies antecedent lung injury which may or may not include inflammatory responses of the ordinary sort. The onset of breathing at mammalian birth is a different kind of lung injury, one occasioned by great physical stretch of the collapsed but moist fetal lung, and immediate exposure to over ten times the level of oxygen resident in the fetal organ. Access to a large archive, the perinatal mortality review from the Chicago Lying-In Hospital, has provided information very relevant to these questions, including the first regular documentation of the pulmonary lesion complex as related to clinical care, beginning in the late 1930s. The lesion complex is called hyaline membrane disease (HMD) from the condensation at the tissue:gas interface of protein exuded from the lung and its circulation. This presentation, titled as above, was more limited to the thyroid factors for want of time, in the following eleven PowerPoint slides, plus a copy of the abstract:

1. Title page and author disclaimer
2. Table with glandular weights over gestational time, 22-39 weeks and a normalized graph showing the progressive relationship between the HMD and control subsets
3. Information on the effect on thyroid cells and mass by birth of southern elephant seal pups into Antarctic circumpolar waters (the only such data available, as is best known)
4. The change of thyroid mass as a gland:body weight ratio, again from the archive, with a clear distinction between HMD and non-HMD cases (obtained off microfische records)
5. Experimental treatment by thyroid factors in an animal model for HMD
6. The histopathology of HMD in premature newborns with the earliest signs of fibrosis
7. Diagram showing the effects of initial breathing on the lung
8. Challenge to an axiom: it is not the partial pressure of oxygen which determines the severity of the lesion but the percentage of oxygen in the mix
9. Flow sheet of probable factors and progress of the lesion
10. Connection to genetic factors and the appearance of the thyroid in such cases; the cover photograph was from our index case
11. Special acknowledgements
12. Abstract from the meeting

THYROID AND ADRENAL FACTORS IN HYALINE MEMBRANE DISEASE

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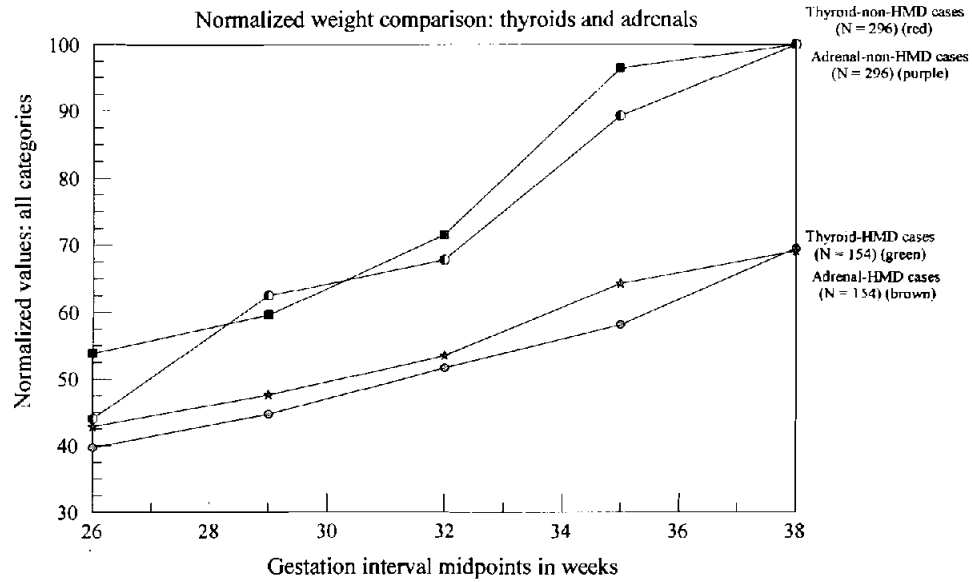
The author has no interests to disclose

GESTATIONAL PROFILE OF THYROID AND ADRENAL WEIGHTS: HYALINE MEMBRANE DISEASE AND OTHERS

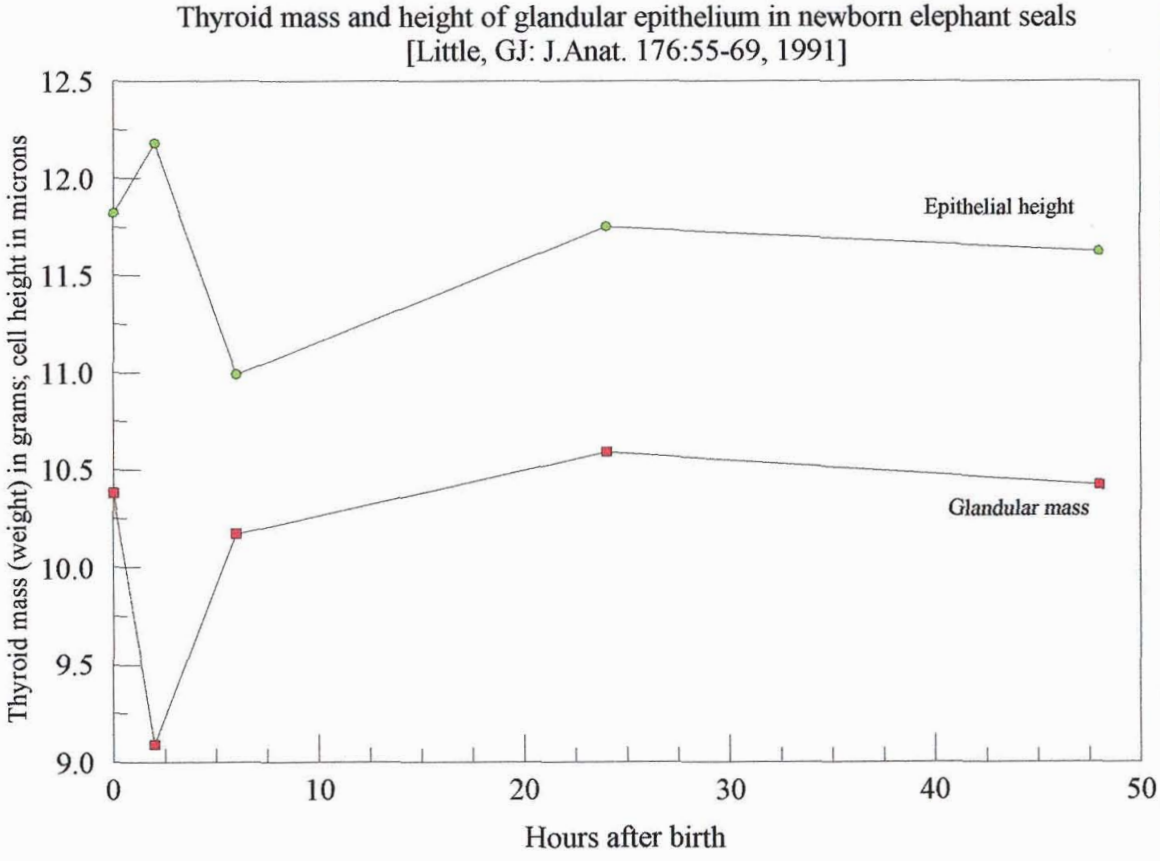
Gestation (weeks)	Number of cases	Males (%)	Mean body weight (grams)	Mean CH length (cm)	Mean CR length (cm)	Mean thyroid weight (grams)
22-27	71 non-HMD 28 HMD	40.6 60.7	886 ± 47 978 ± 13	34.0 ± 0.4 36.0 ± 0.6	23.0 ± 0.4 24.0 ± 0.4	0.76 ± 0.04 0.56 ± 0.05
28-30	50 non-HMD 32 HMD	40.0 50.0	1192 ± 70 1183 ± 75	38.0 ± 0.5 38.0 ± 0.7	26.0 ± 0.4 26.0 ± 0.7	0.84 ± 0.05 0.63 ± 0.04
31-33	50 non-HMD 48 HMD	42.0 60.2	1884 ± 123 1586 ± 45	42.0 ± 0.8 42.0 ± 0.5	29.0 ± 0.7 29.0 ± 0.4	1.01 ± 0.09 0.73 ± 0.03
34-36	44 non-HMD 18 HMD	46.0 55.5	2267 ± 88 1954 ± 103	45.0 ± 0.8 44.0 ± 0.7	31.0 ± 0.4 31.0 ± 0.5	1.36 ± 0.11 0.82 ± 0.06
37-39	81 non-HMD 28 HMD	55.5 67.8	2706 ± 96 2248 ± 91	49.0 ± 0.4 47.0 ± 0.6	34.0 ± 0.3 32.0 ± 0.8	1.41 ± 0.08 0.98 ± 0.07

Data as means ± SEM

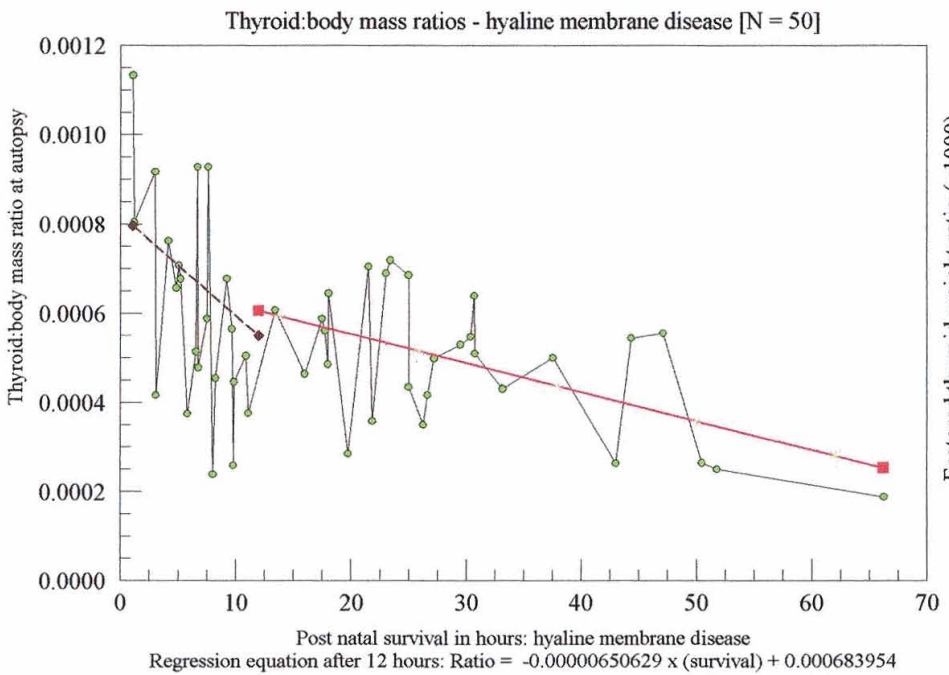
This data set is from the late 1950s through 1966 when neonatal treatment became more regularized but was not intensive with routine intubation and pressure cycled ventilation. There are 296 non-HMD and 154 HMD cases, total = 450.

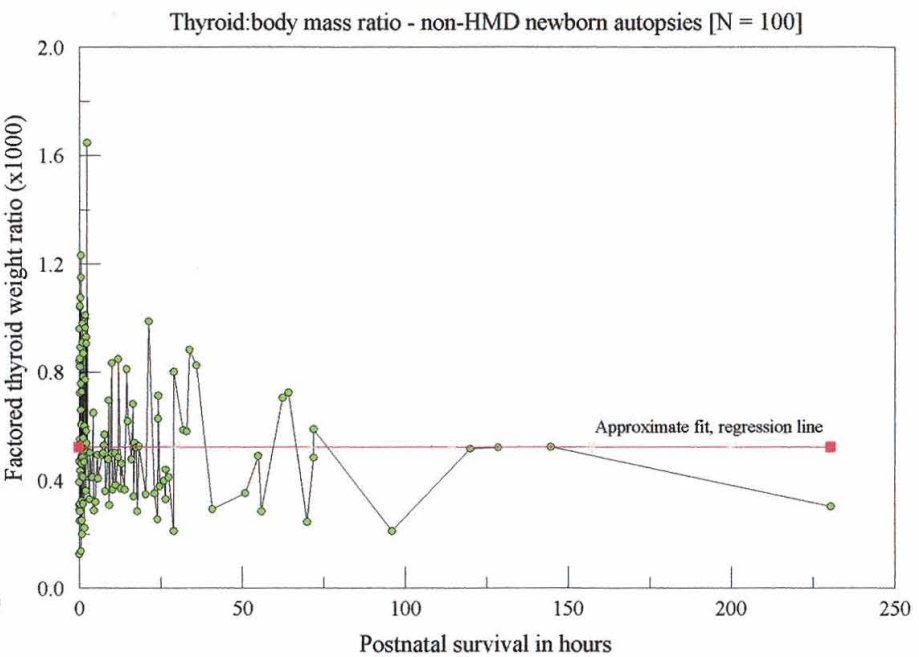


NORMALIZATION SHOWED A 30% DECREASE IN BOTH THYROID AND ADRENAL WEIGHTS FOR INFANTS WITH HYALINE MEMBRANE DISEASE; THUS, IT BECAME IMPORTANT TO DETERMINE WHETHER THIS IS AN ANTENATAL OR POSTNATAL DEVELOPMENT. POSTNATAL THERMAL ADAPTATION HAS BEEN FOUND TO OCCUR IN NEWBORN PUPS OF THE SOUTHERN ELEPHANT SEAL, EXPOSED TO A NEAR FREEZING ENVIRONMENT BY BIRTH ON MACQUARIE ISLAND IN THE FAR SOUTH PACIFIC OCEAN:



THE POSTNATAL HUMAN EXPERIENCE SEEMS DIFFERENT:





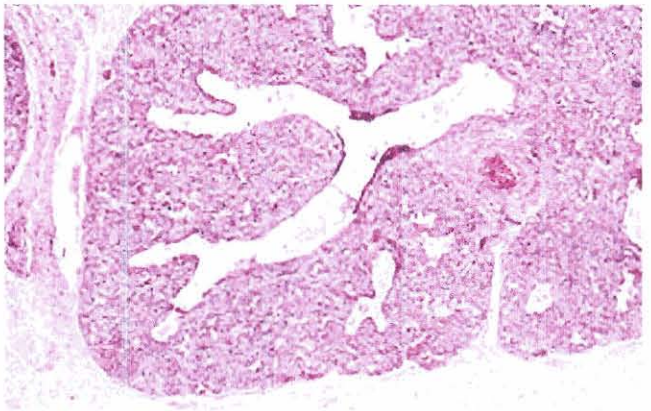
The thyroid:body mass ratio in non-HMD cases is essentially flat with wide variation only in the first hour or so. This group includes many neonates with failed resuscitation, born with cardiac pulse but apneic. By contrast hyaline membrane cases have a distinctive biphasic decline in relative thyroid size with the change fairly consistent after 12 hours postnatal. These patterns support the prospect there is something special about the metabolic challenge through lung injury following the onset of air breathing. The thermal challenge is much less than that for circumpolar seal pups. The data are from 1934-1942, a period when neonatal care was both primitive and minimalist.

A PARADOX REFERENT THYROID FACTORS AND LUNG INJURY?

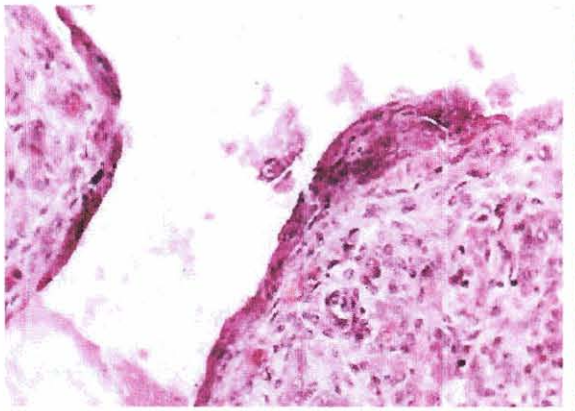
Conditions/Time interval	0-3 hours	3-10 hours	10+ hours
Controls in air	3.95 ± 0.89%	35.92 ± 9.34%	37.0 + 12.74%
Thyroxine pre-BCV 1 mg/kg	8.33%	No Δ	No Δ
Thyroxine pre-BCV 10 mg/kg	20.77%	No Δ	No Δ
Thyroxine pre-BCV 100 mg/kg	25.70%	No Δ	No Δ
Thyrotropin 1 unit/kg	3.00 - 4.00%	73%	72%

Thyroxine prior to induction by bilateral cervical vagotomy shortened the life span of the experimental group but the severity of lung injury increased only in the first phase, 0-3 hours post induction, suggesting an early effect which resulted from the single dose. Thyrotropin had the reverse effect, no change in the early result but an effective doubling in the second and third phases. It seems by stimulating the thyroid to produce more thyroxine in a more or less physiological way, lung injury is worsened. While this might seem paradoxical *ab initio* referent the lower weight of the human thyroid in cases of hyaline membrane disease, taken together the loss of weight in a biphasic manner is consistent with hyperstimulation through the hypothalamic-pituitary axis making the lesion more conspicuous in the latter part of the course of disease, and possibly through other modulating and reinforcing pathways, including stimulation of the adrenal cortex, with mass loss there as well.

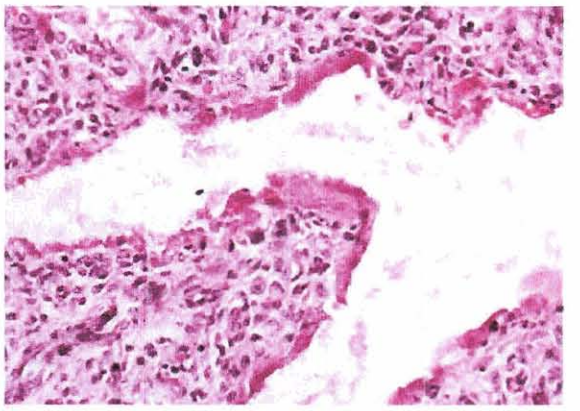
HISTOPATHOLOGY OF HYALINE MEMBRANE DISEASE



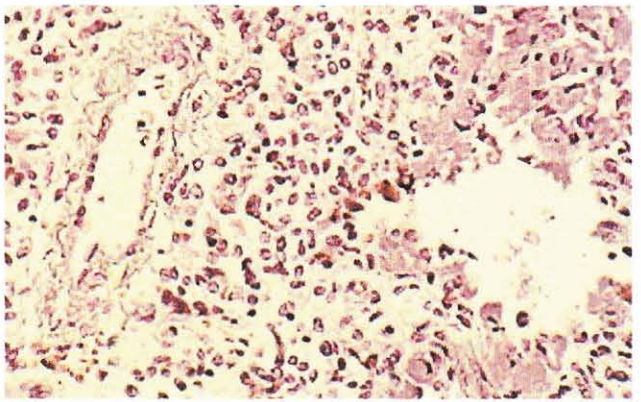
"Lucky" random section across lung lobule . 40X



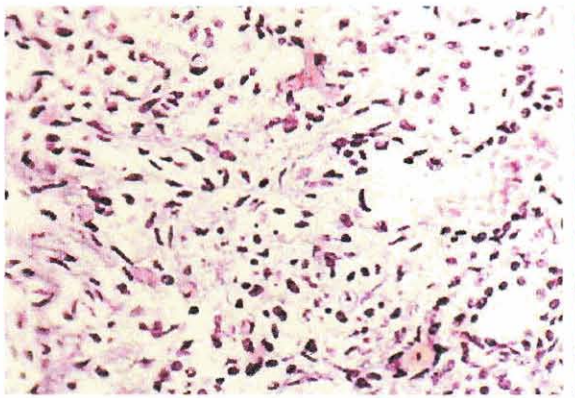
Detail: proximal injury site. 100X



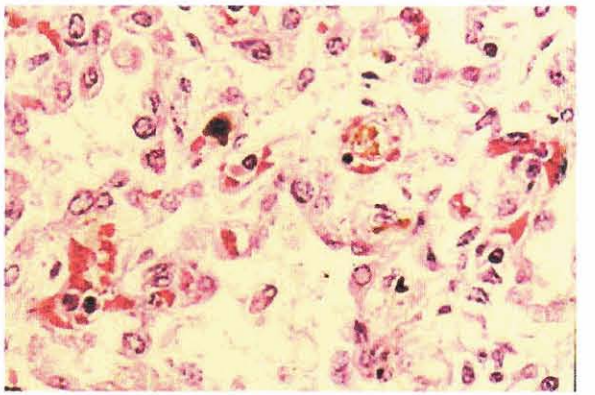
Detail: distal injury site. 100X



Initial enhancement of interstitial reticulin begins in the perivascular zone (left) while remnant hyaline membranes (right). 250X

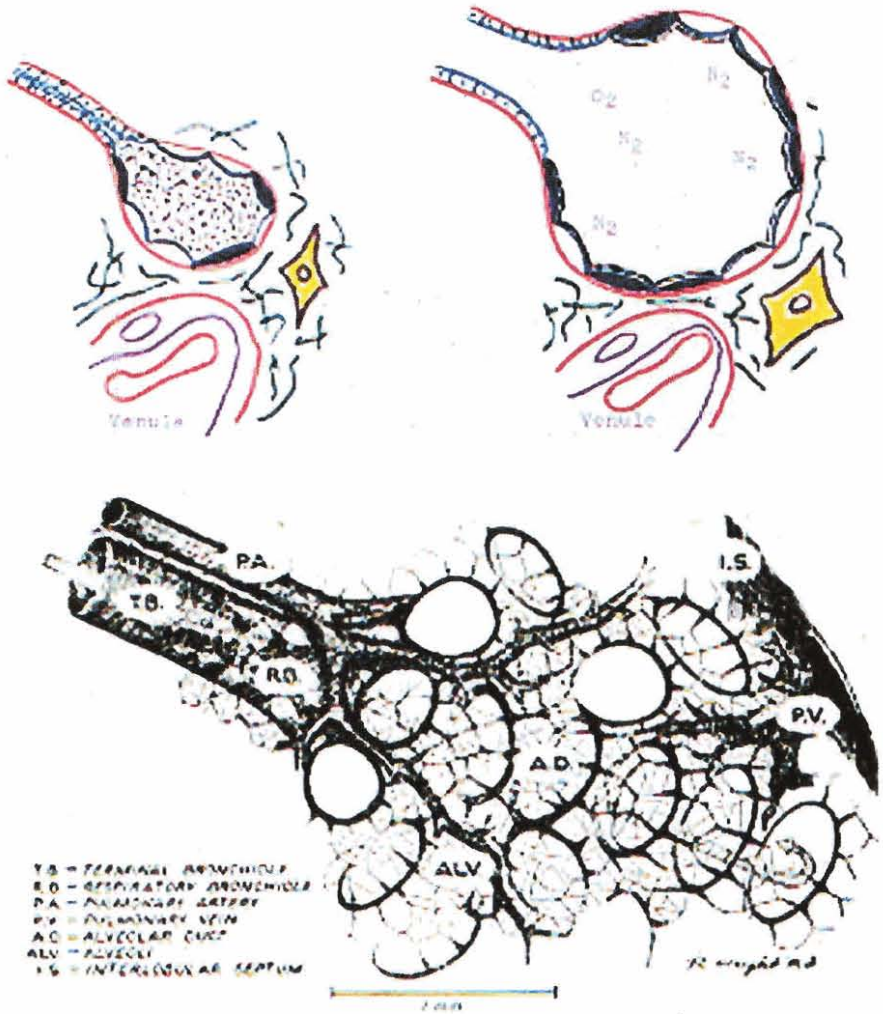


The initial reaction in very immature lungs is interstitial hypercellularity. Reticulin stain. 250X



By 7 days much membrane is gone but cells lining terminal air spaces are prominent as well. H&E. 400X

THE LUNG BEFORE AND AFTER ONSET OF BREATHING



The intrapulmonary oxygen tension before the onset of respiration is 11.33 ± 0.33 Torr (Exp.Molec.Pathol.89:36-45, 2010) and, with the limited volume of respiratory dead space as buffer in the premature neonatal lung, the terminal air spaces quickly acquire values in the 110-120 Torr range. This 10-fold change is a major challenge to the antioxidant defenses of the lung. Hyaline membrane disease has a close histomorphic similarity to influenzal pneumonia and hot gas inhalant burns found in victims of major facility fires (e.g., The Cocoanut Grove fire). These are injuries of the air:lung interface with all of the attendant systemic factors which relate to lung integrity. This includes pulmonary levels of ascorbic acid (Arch.Pathol. 84:451-459, 1967; Nature 210: 1329-1331, 1966) which also involves the adrenal cortex. The diagram to the left is of the interstitial reticulin network of a mature adult lung.

RISK OF OXYGEN TOXICITY AS COMMONLY USED

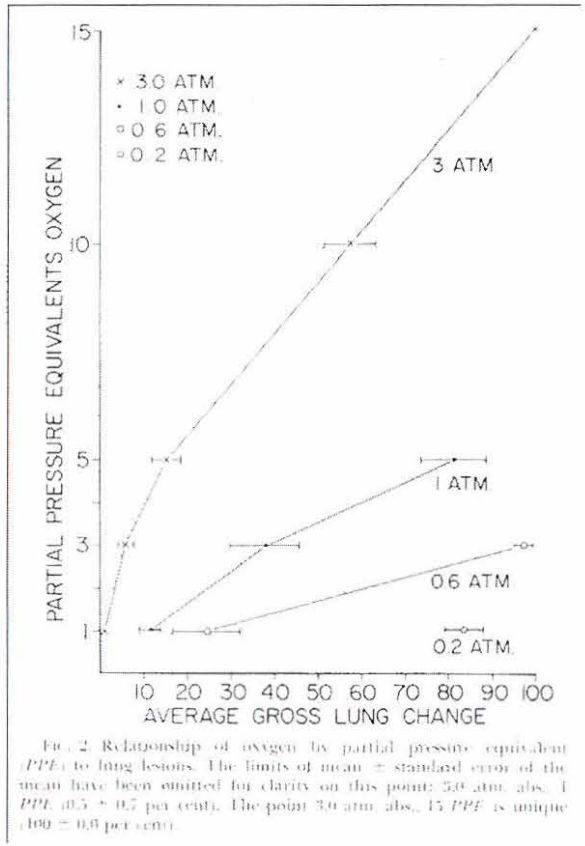


FIG. 2. Relationship of oxygen by partial pressure equivalent (*PPE*) to lung lesions. The limits of mean ± standard error of the mean have been omitted for clarity on this point: 5.0 atm. abs., 1 *PPE*, (0.5 ± 0.7 per cent). The point 3.0 atm. abs., 15 *PPE* is unique (100 ± 0.0 per cent).

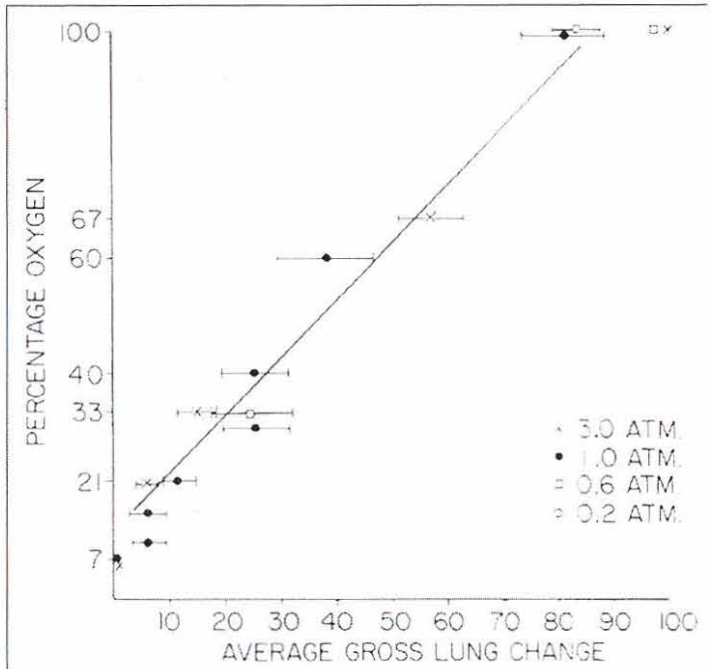
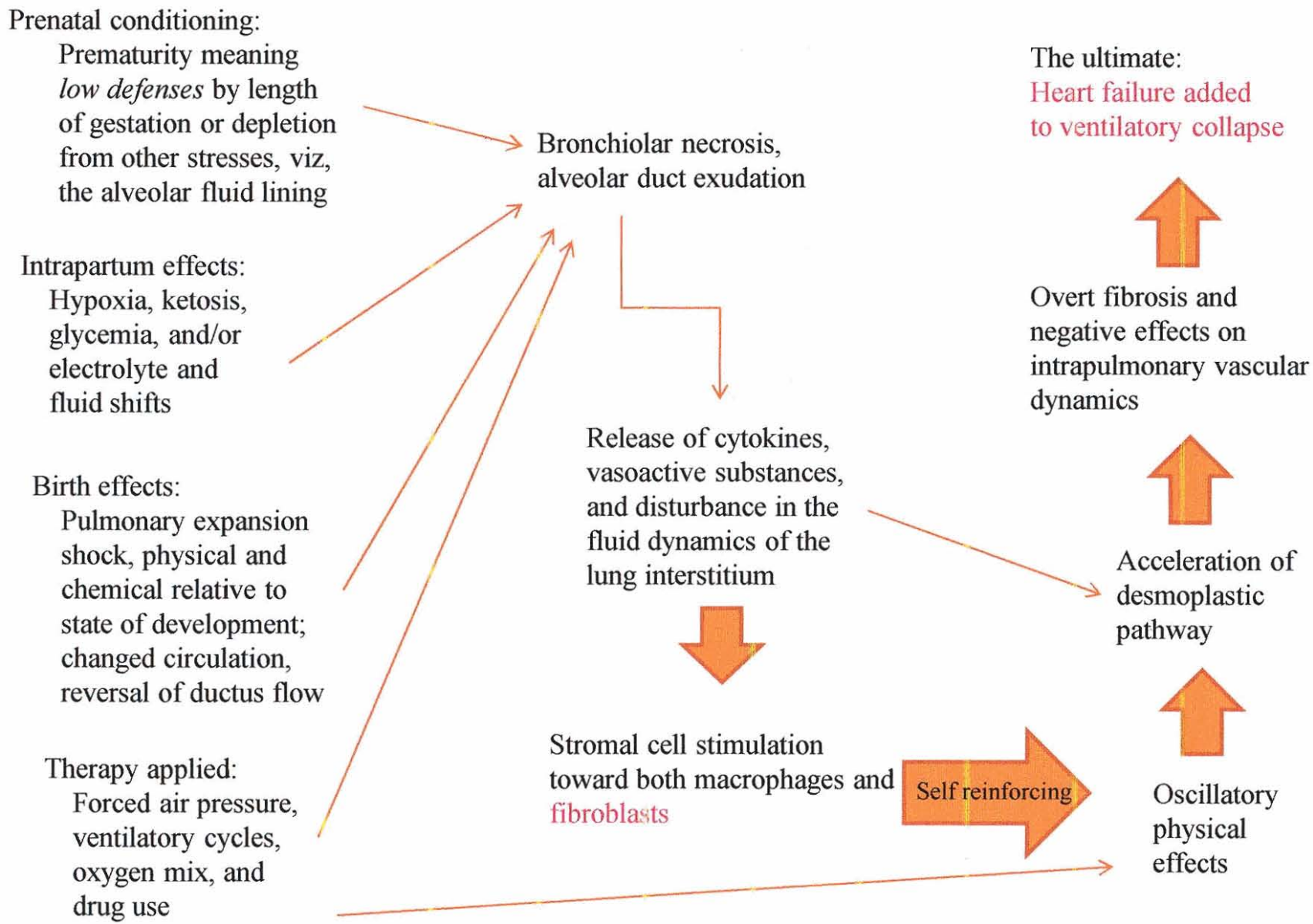


FIG. 3. Relationship of oxygen by percentage to lung lesions. The limits of mean ± standard error of the mean have been omitted for clarity on these points: (1) 0.6 atm. abs., 100 per cent oxygen (97.2 ± 2.2 per cent); (2) 1.0 atm. abs., 7 per cent oxygen (0.2 ± 0.2 per cent); and (3) 3.0 atm. abs., 7 per cent oxygen (0.5 ± 0.7 per cent). The point 3.0 atm. abs., 100 per cent oxygen is unique (100 ± 0.0 per cents.

The principle of gas effect according to its partial pressure is an artefact of sea level physiology. When the oxygen-nitrogen mixture of which air is the *baseline* of respiratory therapy is altered by oxygen enrichment it overrides the protective effect of nitrogen. When related to lung injury in the bilateral cervical vagotomy model in newborn rabbits the result is clearly due to atomic competition based on percentage, not partial pressure. When the oxygen content is taken below 21% (air) animal survival declines dramatically, to just a few hours. By contrast, as little as 3% oxygen in argon results in survivals so long many experimental runs had to be terminated at 72+ hours (data not shown). The data are consistent with a biatomic receptor mechanism which does not distinguish oxygen from nitrogen. From: Lab.Invest. 21:439-448, 1969.

Interrelationships in perinatal lung injury leading to interstitial fibrosis



Pulmonary fibrosis is one consequence of genetic mutation of regulatory genes, as shown in this October 2008 paper from the University of Tennessee:

Experimental and Molecular Pathology 85 (2008) 112–116

Contents lists available at ScienceDirect

Experimental and Molecular Pathology

journal homepage: www.elsevier.com/locate/yexmp

Cerebropulmonary dysgenetic syndrome

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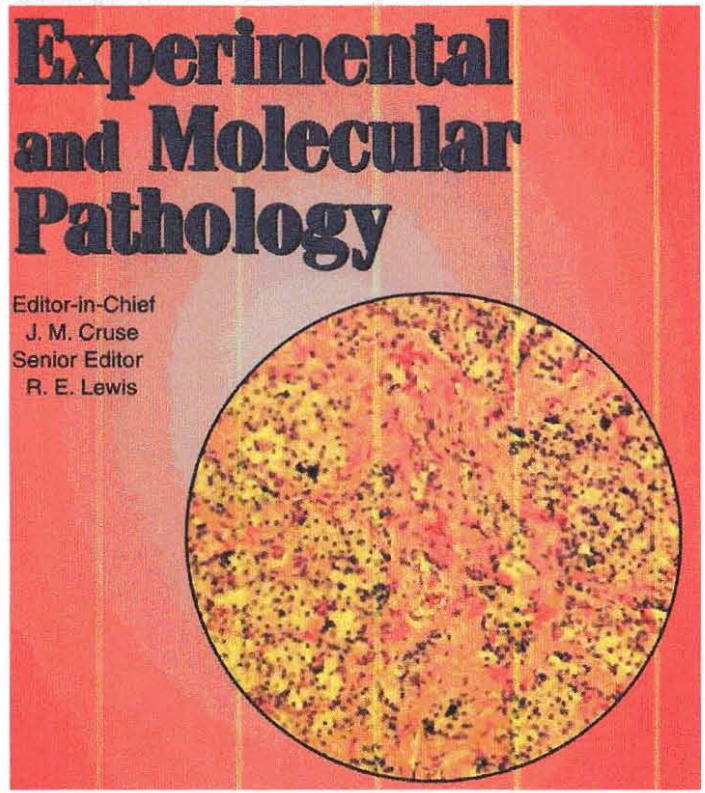
The mutation p.E292V of transporter protein ABCA3 was found in a case with severe interstitial pulmonary fibrosis and retarded cerebral dystrophy in an 8 day old infant. The thyroid showed dense fibrous trabeculae. Four other complete examples of the syndrome were reported.



ESPECIAL THANKS TO EDITH LOUISE POTTER, M.D., PH.D. (1901-1993) FOR HER WORK FROM 1936 TO 1966 AS REFERENCE PATHOLOGIST FOR THE CITY OF CHICAGO PERINATAL MORTALITY STUDY UNDER THE DIRECTION OF HERMAN N. BUNDESEN, M.D., SC.D. (1882-1960). THE DATA ACCUMULATED IS ALL THE MORE REMARKABLE CONSIDERING THE DOMINANT YEARS INVOLVED FROM 600 TO 830 PERINATAL AUTOPSIES PER YEAR. DR. POTTER PRECEDED THE AUTHOR AS PATHOLOGIST-IN-CHIEF AT THE CHICAGO LYING-IN HOSPITAL, UNIVERSITY OF CHICAGO.

(*The FASEB Journal.* 2011;25:114.4)

114.4

Thyroid and adrenal factors in hyaline membrane disease

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Bilateral cervical vagotomy (BCV) in newborn rabbits is a known model for hyaline membrane disease (HMD) of premature human newborns. The survival curve of animals kept in air is triphasic, a semi-log plot, a steep slope to 9h, then -0.136 to 67 hours, and -0.476 terminally [Exp.Mol.Pathol. 2010, 89, 36]. Mean gross lung change, by pleural surface measurement, was 3.95±0.89% in phase A ($p<0.001$) and 35.82±9.34 and 37.0±12.74 (n.s.), in phases B-C. Pre-BCV thyroxine at 1, 10, 100 mg/kg at 3 h modifies the outcome in various ways: [1] maximal survivals were 0.76, 0.66, and 0.76 of control, [2] extent of lung change phase A increased to means of 8.33, 20.77, and 25.7% respectively with no significant change occurred in phase B or C.. By contrast 1 unit/kg thyrotropin produced phase A lung injury similar to BCV-air controls but more than doubled the effect in phases B (73%) and C(72%). Archival human autopsy data, (450 cases, 154 HMD and 296 without), reveals consistent undergrowth of the thyroid and the adrenals in HMD. When normalized against the maximal gland weights in the 37-39 week non-HMD group (N= 81), both adrenals and thyroids in HMD cases had mean weights at 0.562 of the standard controls; at 34-36 weeks the ratio for thyroids was 0.434, for adrenals, 0.595. Lower values for HMD were seen over the gestational span from 25-39 weeks, with near linear progression; the non-HMD values accelerated from 31 to 35 weeks. John A Hartford Fdn.