physiologic changes consistent with synthesis of lung connective tissue. To investigate the time course and control of this process, we measured lysyl oxidase activity. Crosslink analysis of elastin and collagen. In our previous studies of postpneumonectomy lung growth, we noted a suggestion of a secondary rise during the second postoperative week. Amino acid analysis of NaBH₄ reduced elastin extracted in hot alkali in five day post-PN lungs revealed a distribution of crosslink components consistent with biosynthesis of new crosslinks.

We have recently shown that inspired oxygen influences the size of the lung following PN, hyperoxia abolishing and hypoxia accentuating the post-PN increase in lung volume (Am Rev Respir Dis 109:732, 1974). Thirty percent oxygen depressed the first day

### References


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**Session 6: Basic Science**

### Lung Lysyl Oxidase and Elastin Synthesis during Compensatory Lung Growth*


Lysyl oxidase is an enzyme responsible for the initial deamination of lysine and hydroxylysine leading to formation of compounds which produce the characteristic crosslinks of elastin and collagen. In our previous studies of postpneumonectomy lung growth, we noted physiologic changes consistent with synthesis of lung connective tissue. To investigate the time course and control of this process, we measured lysyl oxidase activity (LO) in the right lungs of adult hamsters that had undergone prior left pneumonectomy (PN). We found that LO was similar in central and peripheral lung tissue, so that all subsequent analyses were performed on whole lung homogenates. Lysyl oxidase activity rose within two hours of surgery, reached a peak that was 201 ± 20 percent of control values at one day and fell to control values five days after pneumonectomy. There was a suggestion of a secondary rise during the second postoperative week. Amino acid analysis of NaBH₄ reduced elastin extracted in hot alkali in five day post-PN lungs revealed a distribution of crosslink components consistent with biosynthesis of new crosslinks.

We have recently shown that inspired oxygen influences the size of the lung following PN, hyperoxia abolishing and hypoxia accentuating the post-PN increase in lung volume (Am Rev Respir Dis 109:732, 1974). Thirty percent oxygen depressed the first day.

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post-PN rise in LO to 146 percent of control values, while 13 percent oxygen accentuated the normal day one increase in LO to 334 percent of control (Table). Lysyl oxidase activity also rose in control animals exposed to hypoxia, suggesting that elastin synthesis may also be important to hypoxia induced lung growth.

Thus, in addition to new collagen synthesis reported during the second week following PN (Fed Proc 33: 2248, 1974), there appears to be an early adaptation of an enzyme in the lung essential for elastin and collagen maturation. These data also suggest that oxygen plays an important role in controlling connective tissue biosynthesis in the lung.

Prolyl Hydroxylase Activity of Human Lung*

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Hydroxyproline, which accounts for about one-sixth of the total amino acid residues in collagen, appears to stabilize the molecule in its triple helix configuration, a structure which gives collagen resistance to most proteolytic enzymes. The hydroxyproline in collagen is formed intracellularly by hydroxylation of proline already peptide bound in nascent collagen molecules. The hydroxylation enzyme, prolyl hydroxylase (PH), acts specifically upon proline residues in the sequence X-Pro-Gly.

PH has been identified in animals, plants and microorganisms. Purified PH from whole chick embryos and newborn rat skin has been characterized and used to prepare anti-PH antibody. By immunoassay, tissues demonstrate much higher PH content than by assay of functioning enzyme. The non-functional immunoreactive material has a lower molecular weight than the active enzyme suggesting that active PH is assembled from immunoreactive subunits.¹

The PH activity of many animal tissues has been determined including human serum and some human tissues. Increased PH activity has been observed regularly in tissues actively synthesizing collagen. Fetal and neonatal animal tissues have higher activity than mature animal tissues.² Activity rises in a variety of human diseased tissues such as psoriatic skin³ and rheumatoid synovia.⁴ In experimental silicosis, the PH activity of lung increases. This change precedes an increase in lung collagen content and the histologic appearance of pulmonary fibrosis.⁵ The PH activity of human lung has not been reported.

To measure the PH activity of human lung, we obtained fresh lung tissue from 21 patients undergoing thoracotomy for lung biopsy, lobectomy or pneumonectomy and from five fetuses delivered by hysterotomy at 9-15 weeks of gestation because of life-threatening maternal illness. PH activity was measured as described by Fleckman, Jeffrey and Eisen.⁶ The results were related to the tissue histology and the tissue content of DNA and hydroxyproline. The histologic patterns of the tissue in the adults were as follows: normal—seven patients; fibrosing alveolitis—four patients; sarcoidosis—two patients; and miscellaneous chronic inflammatory conditions—six patients. In most patients, there was gradual progression of disease (Fig 1); however, one patient with sarcoidosis and one with bronchiolitis obliterans were having rapidly advancing disabling changes at the

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