solely to the receptor, studies were undertaken utilizing fluoride ion (F⁻) and GMP-PNP (a synthetic guanyl nucleotide). Both of these reagents stimulate adenylate cyclase via a mechanism independent of the beta receptor. Again the addition of TDI to samples stimulated with either fluoride or GMP-PNP produce identical responses, 44 and 43 percent inhibition respectively.

These results are in disagreement with those previously reported by Davis et al., who demonstrated reduction in isoproterenol-stimulated lymphocyte adenylate cyclase activity. However, this inhibition did not increase with increasing concentration of TDI. Davis suggested TDI possessed partial beta agonist activity at $1 \times 10^{-8}$M, a concentration which was not effective in inhibiting isoproterenol-stimulated activity.

In the present investigation, TDI did not exert any agonist activity between $10^{-2}$ to $10^{-7}$ molar concentrations. All of these observations are consistent with a nonspecific inhibitory effect by TDI. The location of this inhibitory action cannot be determined with the results of the present investigation alone, although one may speculate about the following possibilities: 1) a nonspecific (toxic) effect on the membrane due to protein denaturation resulting from covalent binding of the isocyanate groups to membrane protein (possibly including the receptor); 2) inhibition of adenylate cyclase activity due to covalent modification; 3) modification of the guanyl nucleotide regulatory site(s); 4) combination of the above.

In summary, TDI exerts a nonspecific effect on the beta adrenergic-adenylate cyclase system of frog erythrocyte membrane preparations stimulated by isoproterenol in vitro. Further studies are planned to investigate in vivo responses after inhalation of TDI vapors mimicking true occupational exposure.

ACKNOWLEDGMENT: We wish to thank Ms. Jamie Campbell for excellent technical assistance and Ms. J. Fogle for typing.

REFERENCES


DISCUSSION

Dr. Simon: Do you have any estimate of the concentrations of TDI that are in the secretions or effector-cells? Are these relatively high concentrations obtained in the actual exposure of patients?

Dr. McKay: Probably not. Occupational exposure effects are seen at extremely low concentrations.

Dr. Crystal: By the use of the term nonspecific do you mean that TDI inhibits distal to the beta receptor?

Dr. McKay: TDI is probably causing some membrane protein damage which is resulting in a loss of adenylcylase activity. We cannot exactly say that it affects solely the beta receptor; it’s a general nonspecific effect.

Dr. Salvaggio: By nonspecific, we mean that this occurs in TDI sensitive and nonsensitive individuals, that anybody’s lymphocytes will show this effect, and that the effect is not only induced by beta agonists but also by prostaglandin, so there are at least two receptors.

Pulmonary Asbestosis and Idiopathic Pulmonary Fibrosis: Pathogenetic Parallels*

J. Cadek, M.D.; G. Hunninghake, M.D.; C. Schoenberger, M.D.; G. Fells; and R. Crystal, M.D.

Interstitial lung disease associated with asbestos exposure appears to share several important pathogenetic mechanisms with idiopathic pulmonary fibrosis (IPF). Pathologically, both are associated with extensive disorganization of interstitial collagen ("fibrosis") as well as alterations of cellular architecture. In addition, recent studies (Bignon et al, Am Rev Respir Dis 1978; 117:56) suggest that asbestosis, like IPF, is characterized by the chronic accumulation of neutrophils within the alveolar structures. Schoenberger et al (Am Rev Respir Dis 1980; 121:257), demonstrated that asbestosis stimulates alveolar macrophages to recruit circulating neutrophils via the release of a cell-derived, neutrophil-specific chemotactic factor. A parallel macrophage-mediated accumulation of neutrophils in the IPF lung results in the presence of an active, specific collagenase within the lower respiratory tract (N Engl J Med 1979; 301:737).

In order to assess the likelihood that these parallel

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pathogenetic mechanisms extend through the generation of active collagenase within the lower respiratory tract in asbestosis, individuals with asbestos exposure were subjected to bronchoalveolar lavage. The concentrated lavage fluid was then analyzed for the presence of neutrophils and active, specific collagenase. The lower respiratory tract of asbestos-exposed individuals contained an increased proportion of neutrophils (mean ± SEM-8 ± 38). In addition, active collagenase was also present within the lower respiratory tract fluid (collagenase activity: 0.32 ± 0.1 ng collagen digested/hr-mg lavage fluid albumin) of these patients. The lower respiratory tract collagenase present in asbestos exposure cleaved type I collagen (produced by human lung fibroblasts) into specific TCA and TC fragments but did not digest type III collagen; this is a substrate profile characteristic of neutrophil-specific collagenase.

These findings suggest that the parallels between IPF and pulmonary asbestosis may extend to a role for neutrophil collagenase in the pathogenesis of these fibrotic lung diseases.

**DISCUSSION**

Dr. Petty: How did you obtain tissue?

Dr. Gadek: We had some problems with the size of the sample obtained by transbronchial biopsy—so we insisted on an open lung biopsy.

Dr. Zwillich: Is there anything different about any of the patients, their biochemistry, pulmonary function?

Dr. Gadek: Pulmonary function tests for the most part were similar. There was a correlation with the number of neutrophils, so we think that the presence of collagenase may indicate active disease.

Dr. Renzetti: It is a little difficult to believe that collagenase acts unihed all those years. Is it possible that there are other protease inhibitors other than collagenase inhibitor?

Dr. Gadek: We began the study because of the alterations in the ultrastructure of the connective tissue. In addition to alteration in quantity of collagen, there was considerable distortion and fraying of the collagen bundles. Collagenase is probably working at the same time as there is new collagen production but in the presence of collagenase this is a relatively inefficient attempt at repair.

Dr. Filley: I have been struck by how many neutrophils there are in pneumonoccal pneumonia and how the lung is never damaged. Is there something special about those neutrophils?

Dr. Gadek: I don't think the neutrophil is clever enough to specify its effect; and it has a limited repertoire. I think it is the persistence of the neutrophils that is important.

Dr. Brody: Where do most of the neutrophils reside? Is it possible that the neutrophils are due to chronic small airways disease?

Dr. Gadek: There was no evidence on bronchoscopy of large airway disease, but this does not obviate the possibility there were neutrophils in the terminal airways.

**Deposition Pattern and Clearance Pathways of Inhaled Chrysotile Asbestos**

Arnold R. Brody, Ph.D., and Lila H. Hill, B.S.

It has been known for many years that asbestos inhalation leads to a characteristic diffuse interstitial pulmonary fibrosis. Chrysotile, the most commonly used form of asbestos, clearly is cytotoxic and has been implicated as an etiologic factor in asbestosis and neoplasia in man and experimental animals. Very little is known concerning the early events of particle translocation and cell injury which lead to the characteristic diseases. There seems to be no information available on actual sites of deposition in the most distal anatomic regions of the pulmonary parenchyma. We have attempted to determine how the initial deposition pattern and subsequent translocation of inhaled chrysotile asbestos correspond with the earliest development of the characteristic lesions of asbestosis.

**MATERIALS AND METHODS**

White rats were exposed (nose-only) to aerosolized asbestos in carefully monitored steel chambers to a respirable mass concentration of 4.0 mg per m³ of air. Animals were sacrificed immediately after the one-hour exposure and at various times thereafter.

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Table 1—Mean Score (±SD) of Degree of Asbestos Deposition and Retention*

<table>
<thead>
<tr>
<th>1 Hr. Exposure</th>
<th>1 Hr. Exposure</th>
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<tbody>
<tr>
<td>Alveolar Duct</td>
<td>0 Hr. Recovery</td>
</tr>
<tr>
<td>Bifurcation No. (N=13 tissue blocks)</td>
<td>5 Hr. Recovery (N=8 tissue blocks)</td>
</tr>
<tr>
<td>1</td>
<td>2.44 ± .70</td>
</tr>
<tr>
<td>(N=48)</td>
<td>1.80 ± .90</td>
</tr>
<tr>
<td>2</td>
<td>1.65 ± .90</td>
</tr>
<tr>
<td>(N=41)</td>
<td>.93 ± .78</td>
</tr>
<tr>
<td>3</td>
<td>1.42 ± .60</td>
</tr>
<tr>
<td>(N=19)</td>
<td>.56 ± .63</td>
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</tbody>
</table>

*Score of 0=no asbestos present; 1=1 to 3 fibers observed; 2=4 to 6 fibers; 3=more than 6 fibers present on the alveolar duct surface. The mean value decreases with increasing distance from the terminal bronchiol and after a five hour recovery in room air.

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