LIPID PEROXIDATION IN WORKERS WITH SILICOSIS OR ASBESTOSIS

Thesis

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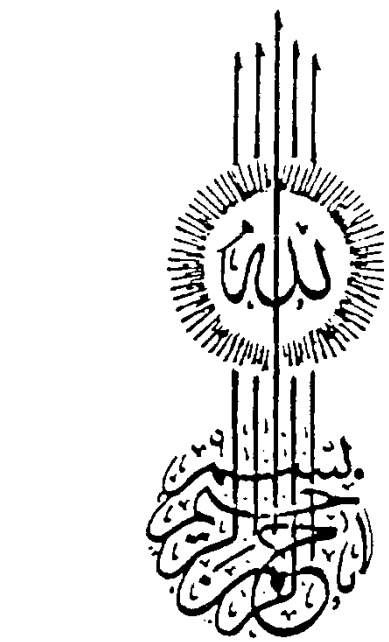

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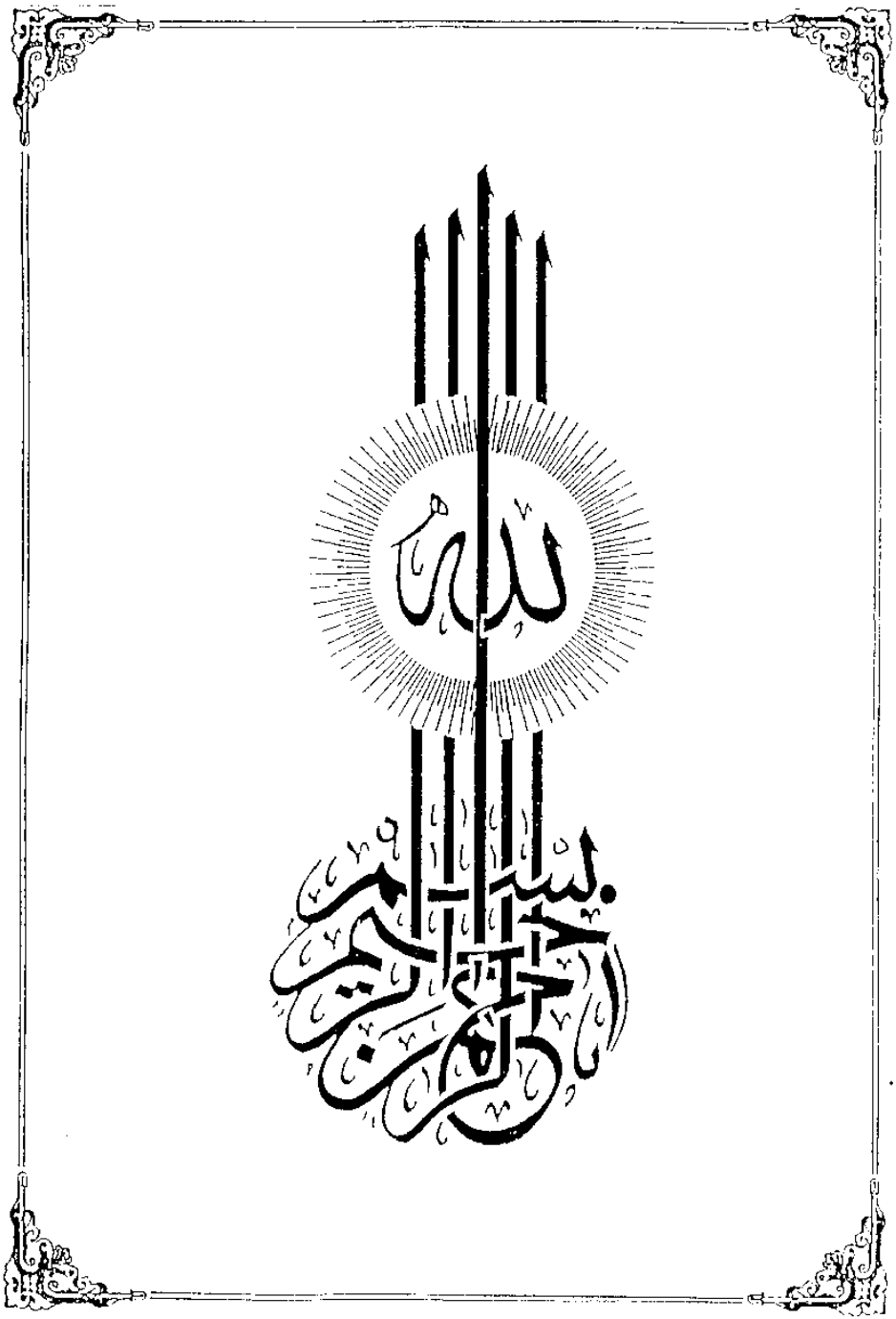

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AHMED SHEREEN Y. HAMMAD

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INTRODUCTION AND AIM OF THE WORK

INTRODUCTION

The exact mechanism of the fibrogenic effect of silica and asbestos dust is still not fully understood.

Lipid peroxidation has been defined as one of the molecular biological mechanisms involved in the pathogenesis of the toxic effects of metals and organic solvents *(De Eruin, 1976)*.

Cellular membrane destruction has come to be recognised as a critical component of the cytotoxicity of silica dusts *(Gabor and Anca 1975: Zsoldos. et al., 1983)*.

Interaction of the siliceous dust with specific lipoidal elements and the final peroxidative decomposition of structural lipids is thought to account for this membrane damage *(Stalder, 1970)*.

In direct analogy, the existing evidence limits the cytotoxic action of asbestos dusts to lipoperoxidative injury of cell membrane *(Arkhipova, 1983)*.

The above mentioned information are mostly gained through experimental studies.

Aim of the Work

The aim of this study is to investigate whether silicosis or asbestosis is associated with lipid peroxidation in humans or not.

REVIEW OF LITERATURE

LIPID PEROXIDATION

In the last decade abody of evidence has accumulated assigning a place of primary importance to autocatalytic lipo-peroxidation as a molecular biological mechanism involved in the deleterious effects of a variety of harmful agents *(De Eruin, 1976).*

Lipid peroxidation has been identified as a damaging reaction that occurs during the modern human life time in response to environmental oxidants, toxicants and diseases *(Slater, 1972).* Also, it can be identified as the process of autoxidation of polyunsaturated fatty acids in response to toxic substances *(NuKai and Goldstein, 1976).*

When the results of action of these foreign agents which initiate lipid peroxidation overwhelm the protective mechanisms in the cells a peroxidative decomposition and disintegration of the microsomal membrane and other cell contents occur with the release of its enzymatic contents in the plasma, this is called "hole in the membrane theory" *(Recknagel and Hrus-Zkewycz, 1976).*

Mechanism of Lipid Peroxidation:

The exact mechanism by which lipid peroxidation occurs in biological systems is still a subject of investigation. However in order to give an idea about the possible course of its occurance, the course of peroxidation in pure lipids, will be discussed.

Peroxidation of Pure Lipids:

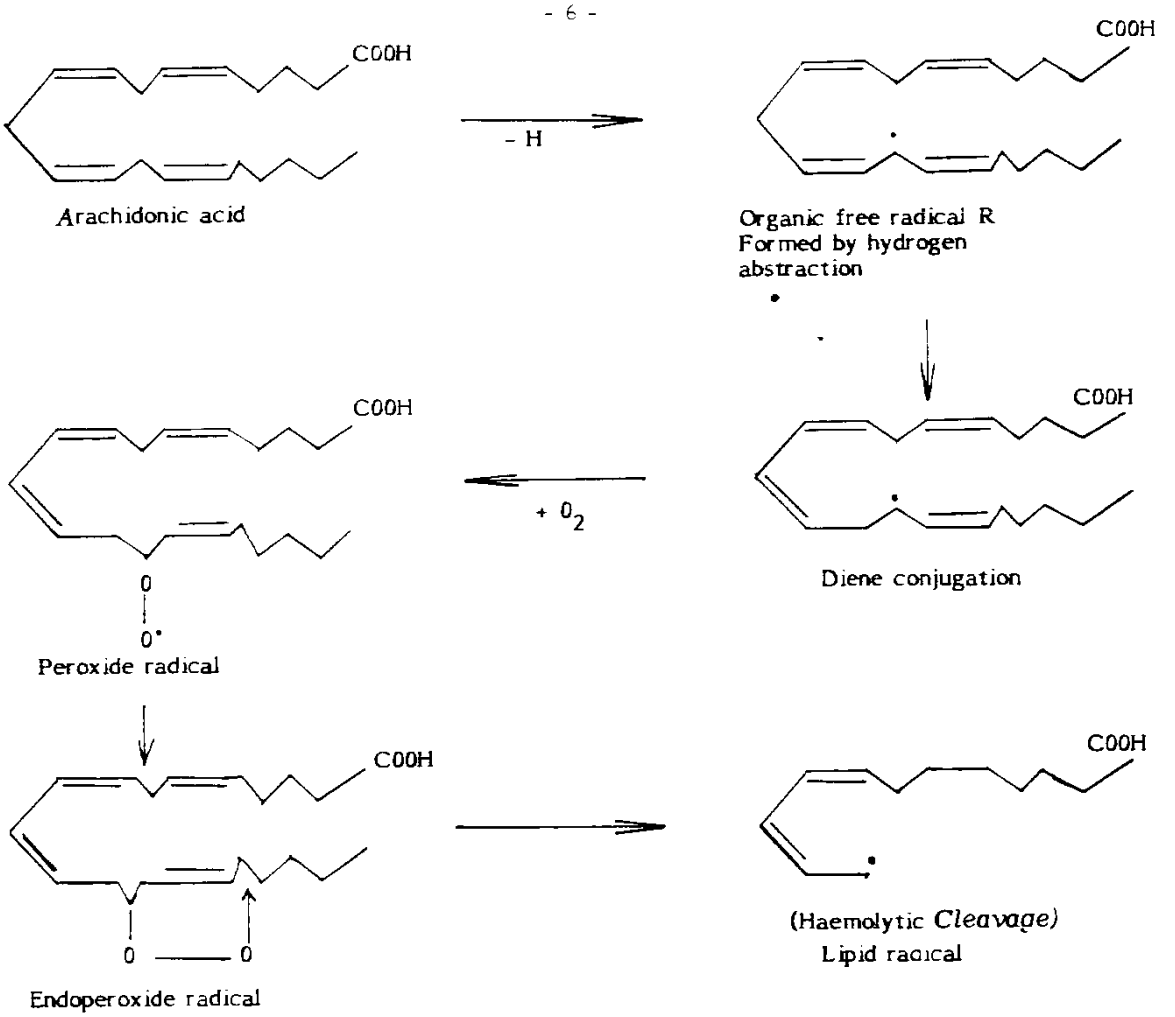
This is extensively reviewed by *Holman, 1954; Dahle et al., 1962; Swern, 1962; Uri, 1961; Wills and Rotblat, 1964*. As an example peroxidation of arachidonic acid will be demonstrated (Fig. 1).

It is known that hydrogen atoms on methylene carbons separating double bonds in polyenoic fatty acids are particularly susceptible to free radical attack *(Holman, 1954; Porter, 1980)*, sequently abstraction of this hydrogen atom (by an initiated free radical) convert arachidonic acid into a lipid radical R". The lipid radical formed can be converted to diene conjugation through resonance shift of the free radical electron (this diene conjugation can be measured spectrophotometrically at the 233 nm wave length). This step is reversible *(Dahle et al., 1962)*.

Either before or after this resonance shift, molecular oxygen attaches itself, because of its diradical character, to the lipid radical, this results in the formation of cyclic endoperoxides. This reaction occurs extremelly rapid *(McMillon and Gaivert, 1965)* because of the fact that molecular oxygen is paramagnatic, it bears unpaired electron *(Gerschman, 1958).*

Haemolytic cleavage of the oxygen - oxygen bond and subsequent intramolecular charge shift leads to the irreversible cleavage of the molecule into malonaldehyde, pentyl radical and lipid radical. If alpha-linolenic acid is the starting point instead of arachidonic acid, ethane will be obtained instead of pentan. The resulting radicals attack the methylene hydrogen of a neighbouring unsaturated fatty acid. Thus once peroxide formation begins, new free radicals appear via these cleavage reaction, setting of new chains of peroxide formation.

This autocatalytic process leads to rapid decomposition of polyenoic fatty acids with formation malondialdehyde or organoleptic aldehydes *(Dahle et al., 1962).*



Peroxidation of arachidonic acid

(Fig. 1)

Sequalae of Lipid Peroxidation:

There is abundant evidence that peroxidative decomposition of structural lipids in cellular and subcellular membranes is catastrophic for living systems *(Alfin-Slater et al., 1963)*.

As an example peroxidative decomposition of the red cell membrane lipids has been correlated with increased permeability and haemolysis of red cells in Vit. E deficiency *(Tappel and Collier, 1960, Tappel, 1962)*. Lipid peroxidation results in mitochondrial and lysosomal disintegration *(Tappel and Zalkin, 1959)*. Also consequence of lipid peroxidation, activities of the enzymes which depend in their function on the integrity of microsomal phospholipid membrane are lost. So membrane damage, cell lysis and death of the cell occur *(Pryor W.A., 1978)*.

Role of lipid peroxidation in the development of the damaging effect in response to toxicants and diseases:

1. Radiation effects:

Several lines of investigation have indicated that lipid peroxidation reactions could be of significance in the initial phases of radiation damage. These include studies on the oxidation of pure lipids and foods by ionizing radiations *(Hannan and Shephered, 1954; Buonits Kaya, 1961)*, studies on radiation induced inactivation of biological antioxidants *(Ottolenghi and Bernhein, 1960)*, and studies on the radiomimetic action of lipid peroxides on biological systems *(Horgan et al., 1957)*.

In x-ray exposed animals, a temporary rise of free radicals occurs in the liver and spleen *(Slater, 1972; Prior, 1976)*. This level in the hepatic microsomal fraction is proportional to the dose applied *(Barber, 1963)*.

Ionising radiation by virtue of free radical attack on unsaturated fatty acids initiate auto-