Drug-induced pulmonary fibrosis

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ABSTRACT

Pulmonary fibrosis is characterized by the accumulation of excessive connective tissue in the lungs. Its causes include chronic administration of some drugs for example bleomycin, cyclophosphamide, amiodarone, procainamide, penicillamine, gold and nitrofurantoin; exposure to certain environmental factors such as gases, asbestos and silica and bacterial or fungal infections. Some systemic diseases also predispose to the disease for example rheumatoid arthritis and systemic lupus erythematosus. The disease is associated with release of oxygen radicals and some mediators such as tumor necrosis factor-alpha (TNF-alpha), transforming growth factor-beta (TGF-beta), PDGF, IGF-I, ET-I and interleukins 1, 4, 8 and 13. The symptoms of the disease include dyspnea, non-productive cough, fever and damage to the lung cells. It is diagnosed with the aid of chest radiography, high resolution computed tomographic scanning and the result of pulmonary function tests. Drug-induced pulmonary fibrosis may involve release of free oxygen radicals and various cytokines for example IL-Ibeta and TNF-alpha via activation of nuclear transcription factor (NF-beta) as in the case of bleomycin and mitomycin or via release of TGF-beta as in case of tamoxifen or via inhibition of macrophages' and lymphocytes' phospholipases as in the case of amiodarone with the resultant accumulation of phospholipids and reduction of the immune system.

Saudi Med J 2004; Vol. 25 (6): 700-706

The lungs are highly susceptible to a wide array of xenobiotics that enter via inhalation or blood stream. The large surface area of the respiratory passages and alveolar region and the large volume of air delivered to that area provide great opportunity for interaction between inhaled materials and lung tissue. On the other hand, since the lungs receive the entire cardiac output of blood, the tissue may be exposed to xenobiotics that have entered the body via ingestion or injection. Thus, administration of various therapeutic modalities may be associated with respiratory alterations ranging from mild reversible parenchymal destruction to severe chronic pulmonary fibrotic disorder.[1] Pulmonary fibrosis is a pathologic condition that denotes an excessive amount of connective tissue in the lung, as a result of a common response to various insults or injuries. The pulmonary fibrotic disorders occur usually in the pulmonary interstitium and are termed interstitial lung disease (ILD). The pulmonary interstitium comprises the alveolar walls (and lumens), pulmonary microvasculature, interstitial macrophages, fibroblasts, myofibroblasts and matrix components of the lung. Although there is variety of initiating factors, the terminal stages of pulmonary fibrosis are characterized by proliferation and progressive accumulation of connective tissue replacing the normal functional parenchyma.[2] A variety of factors have been associated with pulmonary fibrosis with or without a preceding acute pneumonitis.[3]

Pathogenesis of pulmonary fibrosis. A common sequence of events that results in ILD begins when either a recognized (drugs) or an unidentified agent (as in case of idiopathic pulmonary fibrosis [IPF]) induces alveolitis and vasculitis. Persistence of this inflammatory lesion results in alveolar, capillary or parenchymal cell injury. Abnormal repair leads to proliferation of

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mesenchymal cells, with the production of connective tissue elements. At later stages, the normal lung is replaced by cystic spaces separated by thick bands of fibrous tissue, a condition called honeycomb lung.[2] An early feature in the pathogenesis of fibrosis is epithelial or capillary endothelial injury, which promotes recruitment into the lung, of circulating immune cells such as monocytes, neutrophils, lymphocytes and eosinophils. These effector cells together with resident lung cells such as macrophages, alveolar epithelial cells and endothelial cells release cytokines, which stimulate target cells, typically fibroblasts to replicate and synthesize increased amounts of collagen. Breakdown of extracellular matrix proteins may be also inhibited thereby contributing to the fibrotic process.[4]

Cytokines imbalance. Interferon (IFN-γ) is one of the major Th1 cytokines that possesses profound regulatory activity for collagen deposition during chronic inflammation. It has suppressor effects on the production of extracellular matrix proteins. It inhibits fibroblast expression of type I and III procollagen messenger ribonucleic acid, and up regulates the major matrix degrading metalloproteinases. It also reduces platelet - derived growth factor (PDGF) - induced lung fibroblast growth.[5] Interferon-γ treatment in patients with IPF for one year improved pulmonary functions.[6] The opposing effects of Th1 and Th2 cytokines in fibrotic processes are supported by a number of recent investigations demonstrating that IL-4 is a major Th2 cytokine that promotes the production of fibroblast derived extracellular matrix including type I and III procollagen and fibronectin.[7] IL-13 also has similar biological properties as IL-4 and has been implicated in the development of fibroproliferative disorders.[8]

Extracellular matrix remodeling and fibrosis. Transforming growth factor-beta (TGF-ß) has the most potent stimulatory effect on extracellular matrix deposition of any cytokines.[4] Transforming growth factor-beta is the key cytokine during development of pulmonary fibrosis. It was found by immunohistochemical studies to be localized in bronchial epithelial cells, epithelial cells of honeycomb cysts and hyperplastic type II pneumocyte in lungs of IPF patients and animal models of bleomycin induced pulmonary fibrosis.[9] Multiple sources of TGF-ß appear to be activated during the development of pulmonary fibrosis with macrophages and epithelial cells being the primary sources. Transforming growth factor-beta is chemotactic for fibroblasts and polymorphonuclear cells.[10]

The role of apoptosis in pulmonary fibrosis. The potentially important effect of TGF-ß is the induction of programmed cell death (apoptosis) in epithelial cells. This can be achieved through induction of P53 (an apoptosis inducible protein on the surface of cells with damaged DNA), which causes increased expression and clustering of Fas receptors (cell death receptors) and activation of caspases (endonucleases) with subsequent cellular apoptosis.[10] This was evidenced by the finding of increased expression of P53 in lungs of patients with IPF and animal models of bleomycin induced pulmonary fibrosis.[10]

Oxidants or antioxidants imbalance. Altered antioxidant status with pulmonary glutathione deficiency may be factors influencing lung injury and subsequent fibrosis in IPF patients and animal models of bleomycin induced pulmonary fibrosis.[4,11] The epithelial lining fluid contains a number of antioxidants such as ascorbic acid, glutathione, metal binding proteins such as ceruloplasmin and transferrin and antioxidant enzymes such as superoxide dismutase and catalase.[12] Oxidants or antioxidants imbalance in the lower respiratory tract has been proposed as a mechanism for the lung injury in a number of inflammatory conditions including IPF and bleomycin induced pulmonary fibrosis. An increased oxidant burden in the lungs of patients with IPF was thought to arise from accumulation of inflammatory cells including activated alveolar macrophages and neutrophils, which show an exaggerated release of free radicals. Oxidants may also be released by target cells.[12,13] In the presence of iron and oxygen, bleomycin is a powerful oxidizing agent and oxidants generated may induce DNA breaks leading to cellular apoptosis. Also, bleomycin causes activation of cytokines particularly TGF-ß leading to induction of apoptosis.[10]

Diagnosis of pulmonary fibrosis. Clinical manifestations. The clinical consequences of wide spread lung fibrosis is diminished lung compliance, which presents as restrictive lung disease. Patients usually describe a gradual or an insidious onset of exertional dyspnea and non-productive cough. Fever may be present. Chest examination reveals fine late inspiratory crackles at the lung bases. Digital clubbing is seen in 25-50% of cases especially in patients with IPF. The history, particularly occupational and medication history may provide an evidence of a specific cause.[3]

Chest radiography. Lung fibrosis can be diagnosed using chest radiography; however, it is non-specific.[3] A significant advance in diagnosis is the use of high resolution computed tomography. If it is combined with clinical data, it can lead to specific diagnosis in 60-80% of cases.[14] In addition, complete pulmonary function tests should be performed.[15]

Drug-induced pulmonary fibrosis. Many drugs have been reported to induce pulmonary fibrosis, which usually occurs in a small fraction of patients who receive such drugs. Drug-induced pulmonary

fibrosis can be classified into a) cytotoxic antineoplastic drugs induced and b) non-cytotoxic drugs induced.

Cytotoxic drugs-induced pulmonary fibrosis. Pulmonary disorders induced by cancer chemotherapeutic agents vary in severity from mild to life threatening. Based on their presentation, they can be divided into early onset and late onset.[16] Early onset chemotherapy induced pulmonary injury is in the form of hypersensitivity type inflammatory interstitial pneumonitis, which may be induced by methotrexate or carmustine (BCNU). Chemotherapy induced acute pneumonitis generally resolves if the offending agent is discontinued.[16] Late onset chemotherapy induced pulmonary disease occurs in the majority of chemotherapy induced lung injury presenting more than 2 months after therapy has been started, with the most common manifestation being pulmonary fibrosis.

1) Antibiotics. a) Bleomycin is an antibiotic isolated from the fungus *Streptomyces verticillus* with anti-tumor activity. It is commonly used as a part of the cytostatic treatment of several tumor types. Bleomycin exerts its antitumor effect by inducing tumor cell death and inhibition of tumor angiogenesis.[17] Its cytotoxicity occurs by induction of free radicals. Bleomycin forms a complex with Fe(II), which is subsequently oxidized to Fe(III), resulting in reduction of oxygen to free radicals. These free radicals cause DNA breaks leading to cell death.[18] Bleomycin can be deactivated by the enzyme bleomycin hydrolase, which is found predominantly in the liver, spleen, bone marrow and intestine.[19] Due to the lack of this enzyme in the lungs and skin, bleomycin induced toxicity occurs predominantly in these organs.[20] The most hazardous and dose limiting side effect of bleomycin is its induction of pulmonary toxicity. Several distinct pulmonary syndromes have been associated with the use of bleomycin such as bronchiolitis obliterans with organizing pneumonia (BOOP), eosinophilic hypersensitivity and most commonly interstitial pneumonitis, which may progress to fibrosis. Overall, approximately 4% of patients treated with bleomycin develop fibrosis.[10]

The mechanism and pathogenesis of bleomycin induced pneumonitis (BIP) has been intensively studied in animals, but data from human studies are scarce. In animals, the first event noted is endothelial damage of the lung vasculature accompanied by edema. This is followed by influx of inflammatory cells such as neutrophils, macrophages and lymphocytes in the lung parenchyma and subsequently by fibroblasts leading to pulmonary fibrosis.[21] The mechanism of BIP includes the production of reactive oxygen intermediates (free radicals), induction of apoptosis and induction of cytokines[10] such as IL-1ß and TNF-α [22] released from alveolar macrophages. The free radicals that contribute to the endothelial damage are produced by bleomycin directly after oxidation of the bleomycin-Fe(II) complex and by activated mononuclear leucocytes.[18,23] After the damage of endothelial cells and the subsequent infiltration of inflammatory cells in the interstitium, fibroblasts are activated with deposition of collagen. The fibroblasts are activated by bleomycin directly[24] and indirectly through cytokines induction especially TNF-α and TGF-ß, which is one of the central mediators in the process of collagen production by fibroblasts.[25] There is an evidence from an experimental study that the activation of nuclear transcription factor (NF-ß), through generation of reactive oxygen intermediates, plays a central role in bleomycin induced lung injury and fibrosis in mice. The activation of nuclear factor leads to increased expression of genes for IL-1, IL-6 and TNF-α. [26]

Often BIP starts gradually during treatment, but it was reported to occur up to 6 months after discontinuation of therapy.[27] Patients present initially with a non-productive cough, exertional dyspnea and sometimes fever, with progressive pneumonitis, dyspnea at rest, tachypnea and cyanosis may occur. Because bleomycin is assumed to induce its toxicity partially by induction of free radicals, the administration of high inspired oxygen could be hazardous. Animal studies have shown this relation, for instance, in hamsters treated with bleomycin and 70% oxygen for 72 hours, the mortality was 90% compared with 15% in those animals that received bleomycin only.[28] The mortality of patients with BIP has been reported to be approximately up to 3% of all patients treated with bleomycin.[29]

b) Peplomycin is an analogue of bleomycin. Chemically it is identical in structure to bleomycin except for a phenylethylamine propylamine at the terminal amine position of bleomycin, it also causes pulmonary fibrosis.[30]

c) Mitomycin (also commonly known as mitomycin-C) is an antineoplastic antibiotic isolated from the bacteria *Caespitosus.* It is an alkylating agent, which requires activation by reduction of its quinone group and loss of the methoxy group. Its mechanism of action is thought to be an inhibition of DNA synthesis and degradation of preformed DNA.[31] The incidence of pulmonary reactions in patients receiving mitomycin in combination with vinca alkaloids may be as high as 39%. The prevalence of mitomycin induced fibrosis is lower (5%),[32] and the development of pneumonitis usually occurs 3-12 months after completion of therapy. In addition, use of mitomycin as a part of multiple-drug regimens containing bleomycin, cyclophosphamide and doxorubicin appear to show increased lung toxicity.[16] Pneumonitis or fibrosis induced by mitomycin is histologically

indistinguishable from that caused by other cytotoxic drugs except for increased degree of interstitial mononuclear cell infiltrates.

2) Alkylating agents. a) Busulfan is a bifunctional alkylating agent. It interacts with cellular thiol groups and nucleic acid producing crosslinks primarily between DNA and proteins and a small amount of DNA interstrand cross linking. Busulfan is indicated for use in the palliative treatment of chronic myelogenous leukemia (CML). Interstitial pulmonary fibrosis is a rare but clinically significant adverse effect necessitating immediate discontinuation of busulfan. Bronchopulmonary dysplasia with pulmonary fibrosis is potentially fatal and can develop within 8 months to 10 years after therapy initiation. Reported cases have involved average therapy duration of 4 years. There have been isolated cases of pulmonary toxicity occurring only after 4-8 weeks of busulfan treatment.[33,34] The basic pathological process of this syndrome appears to be a chemically induced alveolitis with proliferation of granular pneumocytes, followed by fibrosis of alveolar walls. Microscopically, the lesion is an organizing fibrinous edema with atypical cells derived from type II granular pneumocytes.[35] Thorax radiotherapy prior to or following busulfan administration may enhance development of interstitial pneumonitis.[36]

b) Cyclophosphamide has been associated with an interstitial pneumonitis, alveolar injury and pulmonary fibrosis. The frequency of these unwanted effects is <1%. It usually presents with dry cough, exercise dyspnea and fever.[37] Cyclophosphamide-induced pneumonitis has been reported as occurring from 3 weeks to 3 years after treatment has begun. The mortality rate is nearly 50%.[38] If patients were being treated with high doses of cyclophosphamide and pulmonary radiotherapy, the frequency of pneumonitis or pulmonary fibrosis is approximately 33%. Although not completely proven, cyclophosphamide could be a sensitizing agent for the injury induced by radiotherapy. The discontinuation of cyclophosphamide is usually followed by clinical recovery in approximately 50% of patients and in some cases, reversal of lung injury.[37]

c) Chlorambucil administration has been rarely associated with occurrence of acute pneumonitis, interstitial pneumonia and pulmonary fibrosis.[39]

d) Melphalan - the incidence of melphalan induced pulmonary injury appears to be very low. Interstitial pneumonitis and pulmonary fibrosis are described, which are gradually reversible upon discontinuation of the drug.[40]

e) Nitrosoureas - all the nitrosoureas have been implicated in the development of pulmonary fibrosis. Thus, monitoring of pulmonary function is indicated during prolonged therapy due to its fatal cases that have been reported. However, BCNU is the most frequently used and has the highest frequency of producing pulmonary fibrosis.[1] Carmustine partially inhibits glutathione reductase, the enzyme required to regenerate glutathione, thus reducing tissue stores. The reduced glutathione reserves might lead to pulmonary injuries through alteration of the oxidant or antioxidant balance.[41] Carmustine has been implicated in 3 pulmonary syndromes: (a) an early-onset fibrosis and alveolitis occurring in 1% of the patients receiving low doses and 30% of the patients receiving high doses of carmustine, (b) a late onset fibrosis (up to 17 years after therapy) and (c) a contributing agent to the bone marrow transplantation-induced pulmonary fibrosis. Up to 40% of the patients who receive this combination will, within 2 years, develop a pulmonary fibrosis syndrome.[1]

3) Antimetabolites. a) Methotrexate induces pulmonary toxicity in approximately 7% of patients who receive the drug. The occurrence of pulmonary complications may be acute, chronic or delayed a few weeks after discontinuation of the drug. Higher doses used in treatment of malignancy and lower doses used as a part of an anti-inflammatory regimen have been associated with pulmonary toxicity but probably less frequent in the latter case. Pulmonary reactions have occurred after IV or intrathecal administration of methotrexate. Methotrexate can cause pulmonary fibrosis, although the predominant syndrome is more of a hypersensitivity pneumonitis. Methotrexate can be associated with an acute fibrotic syndrome with features of hypersensitivity pneumonitis.[16] Risk factors that appear to be associated with methotrexate-induced pulmonary toxicity include frequency of administration, multidrug regimen, corticosteroid tapering and previous adrenalectomy.[1] The etiology of methotrexate induced pneumonitis is unknown. Postulated actions leading to injury include direct toxic effect of methotrexate on the lung and hypersensitivity reaction to methotrexate.[42]

b) Edatrexate is an antineoplastic analog of methotrexate. Pulmonary toxicity characterized by pneumonitis with symptoms of fever, cough and dyspnea and radiologic evidence of diffuse interstitial changes have been reported after several courses of edatrexate therapy in some patients.[43] Another 2 antimetabolites that are associated with pneumonitis and fibrosis are azathioprine[41] and fludarabine.[16]

4) Plant alkaloids. a) Vinca alkaloids are cell cycle specific antimitotic antineoplastic agents. They block cells in mitosis by binding to tubulin and inhibiting microtubule formation in the mitotic spindle.[44] There are numerous reports concerning respiratory distress syndrome "acute shortness of breath and severe bronchospasm" following administration of vinca alkaloids, vincristine, vinblastine and vindesine. These reactions are most

frequently encountered when the vinca alkaloid is used in combination with mitomycin C. It has been suggested that vinca alkaloids not only potentiate an acute toxicity but may contribute to the chronic toxicity of mitomycin C.[44]

Non-cytotoxic drugs that may induce pulmonary fibrosis. Diffuse interstitial pulmonary disease (alveolitis or fibrosis) may result from a variety of non-cytotoxic agents including the following:

1) Hormonal therapy - tamoxifen therapy given to postmastectomy patients receiving radiation increases the risk of radiation-induced pulmonary fibrosis. Tamoxifen is involved in the induction of TGF-ß secretion, which has been implicated in the pathogenesis of radiation-induced fibrosis.[45] Bicalutamide is a pure non-steroidal antiandrogen used in the treatment of prostate cancer. Interstitial pneumonitis, eosinophilic lung disease, dyspnea, cough, pharyngitis and rare cases of pulmonary fibrosis have been reported with bicalutamide use.[46] Nilutamide is a non-steroidal antiandrogen, which has demonstrated efficacy in the treatment of metastatic prostatic carcinoma. There is a strong evidence that nilutamide is responsible for interstitial pneumonitis with or without interstitial fibrosis in some individuals. The incidence of this adverse reaction is higher in patients receiving both nilutamide and leuprolide (LHRH analogue) combination or buserelin.[47]

2) Drugs used for treatment of cardiovascular diseases: a) Amiodarone is an iodinated benzofuran derivative with a chemical structure similar to thyroxine.[48] Pulmonary toxicity induced by amiodarone has been described as pulmonary alveolitis, pulmonary infiltrates, pneumonitis, lipoid pneumonia and pulmonary fibrosis. Asthmatic symptoms have been reported in patients with or without bronchial asthma. Amiodarone induced pulmonary fibrosis is an infrequent adverse reaction, observed in only 1-4.5% of patients. It is definitely dose related and the onset ranges between a few weeks and several years after the initiation of treatment.[49]

The mechanism of the adverse reaction is still a matter of research. There are 2 main hypotheses: (i) favoring a toxic and (ii) the immunologically mediated reaction. It is well documented that amiodarone induces the accumulation of phospholipids in macrophages, lymphocytes and other cell types by inhibiting phospholipase A_1, A_2 and C. The above alterations affect cellular immunity, which offers a possible explanation for amiodarone induced interstitial lung tissue damage. There is also some evidence that the injury may be due, in part, to damage caused by toxic oxygen metabolites. The binding of amiodarone or one of its metabolites to pulmonary proteins could elicit an immune reaction towards the drug behaving as a hapten. Otherwise, toxic injuries of pulmonary tissue could produce neo-antigens that can be able to trigger an autoimmune response.[41,49] More recently, in an in vitro study, it was found that amiodarone (AM) and its metabolite N-desethyl-amiodarone (DEA) caused disruption of mitochondrial membrane and adenosine triphosphate (ATP) depletion and subsequent cell death of isolated hamster alveolar and bronchiolar epithelial cells. It was suggested that amiodarone and DEA induce perturbations of mitochondrial functions, which may initiate pulmonary toxicity.[50] b) Mexiletine is a class IB anti-arrhythmic drug with pharmacological properties similar to lidocaine. Pulmonary fibrosis was reported in a 75-year-old male following 3 months of mexiletine therapy. Three other cases have been reported. Mexiletine causes an alveolitis or fibrosis with reticulonodular infiltrates on chest radiographs.[51] c) Procainamide is a class IA anti-arrhythmic drug. It is commonly used to treat supraventricular and ventricular arrhythmias. A case of reversible pleural fibrosis due to procainamide was reported in a 65-year-old male. The patient had been receiving procainamide for 5 years prior to symptoms of arthralgia and progressively increasing pleuritic type chest pain. Discontinuation of procainamide after one year of follow up; the examination revealed resolution of restrictive and diffusion defects.[52] d) Bumetanide is a loop diuretic similar in structure to frusemide, used for treatment of edema. Pulmonary fibrosis, granulocytic alveolitis and chronic inflammation developed after 4 months of therapy with bumetanide in a patient who had received thiazides for 20 years and then was switched to bumetanide. The patient also experienced migratory arthralgia, dyspnea and chest heaviness.[53]

3) Antibacterials - Nitrofurantoin is a synthetic nitrofuran antimicrobial. It has been used for several decades in the treatment of acute urinary tract infection and in chronic suppression therapy for asymptomatic bacteriuria. Nitrofurantoin was one of the first drugs to be implicated as a cause of pulmonary disease. Although acute respiratory distress syndrome and alveolar hemorrhage have been reported, most cases of nitrofurantoin toxicity fall into one of 2 distinct categories: an acute form, which typically fits the pattern of hypersensitivity lung disease and a chronic alveolitis fibrosis syndrome.[54] Chronic nitrofurantoin toxicity often occurs in elderly patients undergoing chronic oral suppressive therapy for bacteriuria. As in the acute form, dyspnea, cough and cyanosis are seen. Fatigue, weight loss and other constitutional symptoms are often observed. The mechanism of pulmonary toxicity is unknown but there is some evidence that toxic oxygen metabolites play a role in inducing lung injury.

4) Anti-inflammatory drugs such as a) Penicillamine is a degradation product of penicillin

and acts as a chelator of heavy metals. It has been very successful for treatment of rheumatoid arthritis. The pulmonary manifestations of penicillamine toxicity include ILD, bronchiolitis obliterans, and alveolar hemorrhage occurring as a part of pulmonary renal syndrome. Penicillamine associated interstitial lung disease in the form of chronic alveolitis or fibrosis has been reported only in patients being treated for rheumatoid arthritis. The patients' condition was improved after discontinuation of penicillamine therapy.[55] b) Other drugs - with regard to other drugs, isolated reports implicated gold compounds,[56] mesalamine[57] and nabumetone[58] in induction of pulmonary fibrosis.

5) Miscellaneous drugs - induced pulmonary toxicity. Various drugs have also been implicated in induction of pulmonary fibrosis. These included phenytoin,[59] bromocriptine[60] and cabergoline.[61]

References

1. Cooper JA Jr. Drug induced lung disease. ***Adv Intern Med*** 1997; 42: 231-268.
2. Kuwano K, Hagimoto N, Hara N. Molecular mechanisms of pulmonary fibrosis and current treatment. ***Curr Mol Med*** 2001; 1: 551-573.
3. Reynolds HY. Diagnostic and management strategies for diffuse interstitial lung disease. ***Chest*** 1998; 113: 202.
4. Coker RK, Laurent GJ. Pulmonary fibrosis: Cytokines in the balance. ***Eur Respir J*** 1998; 11: 1218 -1221.
5. Strieter RM. Mechanisms of pulmonary fibrosis: Conference summary. ***Chest*** 2001; 120: 77S- 85S.
6. Ziesche R, Hofbaur E, Wittman K, Petkov V, Block LH. A preliminary study of long term treatment with interferon g-1b and low dose prednisolone in patients with idiopathic pulmonary fibrosis. ***N Engl J Med*** 1999; 341: 1264-1269.
7. Postlethwaite AE, Holness MA, Katai H, Raghow R. Human fibroblasts synthesize elevated levels of extracellular matrix proteins in response to interleukin-4. ***J Clin Invest*** 1992; 90: 1479-1485.
8. Oriente A, Fedarco NS, Pacocha SE, Huang SK, Lichtenstein LM, Essaayan DM. Interleukin-13 modulates collagen homeostasis in human skin and keloid fibroblasts. ***J Pharmacol Exp Ther*** 2000; 292: 988-994.
9. Branton MH, Kopp JB. Tansforming growth factor-ß and fibrosis. ***Microbes Infect*** 1999; 1: 1349-1365.
10. Cooper JA Jr. Pulmonary fibrosis: pathways are slowly coming into light. ***Am J Respir Cell Mol Biol*** 2000; 22: 520-523.
11. Meyer A, Buhl R, Magnussen H. The effect of oral N-acetylcysteine on lung glutathione levels in idiopathic pulmonary fibrosis. ***Eur Respir J*** 1994; 7: 431-436.
12. MacNee W, Rahman I. Oxidants/antioxidants in idiopathic pulmonary fibrosis. ***Thorax*** 1995; 50: S53-S58.
13. Strausz J, Muller-Quernheim J, Steppling H, Ferlinze R. Oxygen radical production by alveolar inflammatory cells in idiopathic pulmonary fibrosis. ***Am Rev Respir Dis*** 1990; 141: 124-128.
14. Raghu G, Mageto YN, Lockhart D, Schmidt RA, Wood DE, Godwin JD. The accuracy of the clinical diagnosis of new onset idiopathic pulmonary fibrosis and other interstitial lung diseases: A prospective study. ***Chest*** 1999; 116: 1168-1174.
15. Xaubt A, Agusti C, Luburich P, Roca J, Monton C, Ayuso MC et al. Pulmonary function tests and CT scan in the management of idiopathic pulmonary fibrosis. ***Am J Respir Crit Care Med*** 1998; 158: 431-436.
16. Abid SH, Malhotra V, Perry MC. Radiation-induced and chemotherapy induced pulmonary injury. ***Current Opin Oncol*** 2001; 13: 242-248.
17. Shirner M, Hoffman J, Menard A. Anti-angiogenic chemotherapeutic agents: characterization in comparison to their tumour growth inhibition in human renal cell carcinoma models. ***Clin Cancer Res*** 1998; 4: 1331-1336.
18. Burger RM, Pesach J, Horwitc SB. Activated bleomycin: A transient complex of drug, iron and oxygen that degrades DNA. ***J Biol Chem*** 1981; 256: 11636-11644.
19. Umezawa H, Takeuchi T, Hosi S, Sona T, Ishizuka M. Studies on the mechanism of antitumour effect of bleomycin in squamous cell carcinoma. ***J Antibiot*** 1972; 25: 409-420.
20. Onuma T, Holland JF, Masuda H, Waligunda JA, Goldberg GA. Micro-biological assay of bleomycin: inactivation, tissue distribution and clearance. ***Cancer*** 1974; 33: 1230-1238.
21. Adamson IY, Bowden DH. The pathogenesis of bleomycin induced pulmonary fibrosis in mice. ***Am J Pathol*** 1974; 77: 185-197.
22. Scheule RK, Perkins RC, Hamilton R, Holian A. Bleomycin stimulation of cytokine secretion by the human alveolar macrophage. ***Am J Physiol*** 1992; 262: L386-L391.
23. Moseley PL, Shasby DM, Brady M, Hunninghake GW. Lung parenchymal injury induced by bleomycin. ***Am Rev Respir Dis*** 1984; 130: 1082-1086.
24. Moseley PL, Hemken C, Hunninghake GW. Augmentation of fibroblast proliferation by bleomycin. ***J Clin Invest*** 1986; 78: 1150-1154.
25. Giri SN, Hyde DM, Hollinger MA. Effect of antibody to transforming growth factor-ß on bleomycin induced accumulation of lung collagen in mice. ***Thorax*** 1993; 48: 959-966.
26. Gurujeyalakshmi G, Wang Y, Giri SN. Taurine and niacin block lung injury and fibrosis by down-regulating bleomycin-induced activation of transcription nuclear factor (NF-ß) in mice. ***J Pharmacol Exp Therap*** 2000; 293: 82-90.
27. White DA, Stover DE. Severe bleomycin induced pneumonitis: clinical features and response to corticosteroids. ***Chest*** 1984; 86: 723-728.
28. Tryka AF, Skornik WA, Godleski JJ, Brain JD. Potentiation of bleomycin induced lung injury by exposure to 70% oxygen. Morphologic assessment. ***Am Rev Respir Dis*** 1982; 126: 1074-1076.
29. Simpson AB, Paul J, Graham J, Kaye SB. Fatal bleomycin pulmonary toxicity in the west of Scotland 1991-95: a review of patients with germ cell tumours. ***Br J Cancer*** 1998; 78: 1061-1066.
30. Takita T, Ogino T. Peplomycin and liplomycin, new analogues of bleomycin. ***Biomed Pharmacother*** 1987; 41: 219-226.
31. Doll DC, Weiss RB, Issell BF. Mitomycin: ten years after approval for marketing. ***J Clin Oncol*** 1985; 3: 276-286.
32. Watanabe I, Yokobayashi T, Nakajima T, Mizutani H, Ohashi Y. Peplomycin induced pneumonitis resulting in death. ***J Maxillofac Surg*** 1984; 12: 114-117.
33. Hankins DG, Sanders S, Macdonald FM, Drage CW. Pulmonary toxicity recurring after a six week course of busulfan therapy and after subsequent therapy with uracil mustard. ***Chest*** 1978; 73: 415-416.
34. Case records of the Massachusetts General Hospital, weekly clinico pathologic excercises. Case 25-1997. A 60 year old man with pulmonary infiltrates after bone marrow transplantation. ***N Engl J Med*** 1997; 337: 480-489.
35. Rosenow E. Drug induced pulmonary disease. ***Dis Mon*** 1994; 150: 253-310
36. Ginsberg SJ, Comis RL. The pulmonary toxicity of antineoplastic agents. ***Semin Oncol*** 1982; 9: 34-51.
37. Segura A, Yuste A, Cercos A, Lopez-Tendero P, Girones R, Perez-Fidalgo JA et al. Pulmonary fibrosis induced by cyclophosphamide. ***Ann Pharmacother*** 2001; 35: 894-897.

38. Stentoft J. Progressive pulmonary fibrosis complicating cyclophosphamide therapy. ***Acta Med Scand*** 1987; 221: 403-407.
39. Crestani B, Jaccard A, Israel-Biet D, Coudere LJ, Frija J, Clauvel JP. Chlorambucil associated pneumonitis. ***Chest*** 1994; 105: 634-636.
40. Goucher G, Rowland V, Hawkins J. Melphalan induced pulmonary interstitial fibrosis. ***Chest*** 1980; 77: 805-816.
41. Israel-Biet D, Labrune S, Huchon GJ. Drug induced lung disease: 1990 review. ***Eure Respir J*** 1991; 4: 465-478.
42. Sostman HD. Methotrexate induced pneumonitis. ***Medicine*** 1976; 62: 608.
43. Vandenberg TA, Pritchard KI, Eisenhauer EA, Trudeau ME, Norris BD, Lopez P et al. Phase II study of weekly edatrexate as first line chemotherapy for metastatic breast cancer: a National Cancer Institute of Canada Clinical Trials Group study. ***J Clin Oncol*** 1993; 11: 1241-1244.
44. Konits PH, Aisner J, Sutherland JC, Wiernik PH. Possible pulmonary toxicity secondary to vinblastine. ***Cancer*** 1982; 50: 2771-2774.
45. Bentzen SM, Skoczylas JZ, Overgaard M, Overgaard J. Radiotherapy related lung fibrosis enhanced by Tamoxifen. ***J Natl Cancer Inst*** 1996; 88: 918-922.
46. MacCaffery JA, Scher HI. Interstitial pneumonitis following bicalutamide treatment for prostate cancer. ***J Urol*** 1998; 160: 131.
47. Seigneur J, Trechot PE, Hubert J, Lamy P. Pulmonary complications of hormone treatment in prostate carcinoma. ***Chest*** 1988; 93: 1106.
48. Kowey PR, Marinchak RA, Rials SJ, Filart RA. Intravenous amiodarone. ***J Am Coll Cardiol*** 1997; 29: 1190-1198.
49. Lee KL, Tai YT. Long term low dose amiodarone therapy in the management of ventricular and supraventricular tachyarrhythmias: efficacy and safety. ***Clin Cardiol*** 1997; 20: 372-377.
50. Bolt MW, Card JW, Brian JF, Massey TE. Disruption of mitochondrial function and cellular ATP levels by amiodraone and N-desethylamiodarone in initiation of amiodarone induced pulmonary cytotoxicity. ***J Pharmacol Exp Therap*** 2001; 298: 1280-1289.
51. Bero CJ, Rihn TL. Possible association of pulmonary fibrosis with mexiletine. ***DICP*** 1991; 25: 1329-1331.
52. Woosley RL, Drayer DE, Reidenbrg MM, Nies AS, Carr K, Oates JA. Effect of acetylator phenotype on the rate at which procainamide induces antinuclear antibodies and the lupus syndrome. ***N Engl J Med*** 1978; 298: 1157-1159.
53. Barnett R, Israel HL, Scott R, Fish JE, Peters SP. Pulmonary fibrosis in a patient treated with bumetanide: clinical improvement associated with transition from a granulocytic to lymphocytic alveolitis. ***Respir Med*** 1990; 84: 71-75.
54. D'Arcy PF. Drug interactions and reactions update: Nitrofurantoin. ***Drug Intell Clin Pharm*** 1985; 19: 540-547.
55. Aronchick JM, Gefter WB. Drug induced pulmonary disease: an update. ***J Thorac Imaging*** 1991; 6: 19-29.
56. Evans RB, Ettensohn DB, Fawaz–Estrup F, Lally EV, Kaplan SR. Gold lung: recent developments in pathogenesis, diagnosis and therapy. ***Semin Arthritis Rheum*** 1987; 16: 196-205.
57. Sossai P, Cappellato MG, Stefani S. Can a drug induced pulmonary hypersensitivity reaction be dose dependent? A case with mesalamine. ***Mt Sinai J Med*** 2001; 68: 380-395.
58. Morice A, Atherton A, Gleeson F, Stewart S. Pulmonary fibrosis associated with nabumetone. ***Postgrad Med J*** 1991; 67: 1021-1022.
59. Polman AJ, van der Werf TS, Teibosch AT, Zijlstra JG. Early onset phenytoin toxicity mimicking a reno-pulmonary syndrome. ***Eur Respir J*** 1998; 11: 501-503.
60. McElvaney NG, Wilcox PG, Churg A, Fleetham JA. Pleuropulmonary disease during bromocriptine treatment of Parkinson's disease. ***Arch Intern Med*** 1988; 148: 2231-2236.
61. Frans E, Dom R, Demedts M. Pleuropulmonary changes during treatment of Parkinson's disease with a long acting ergot derivative, cabergoline. ***Eur Respir J*** 1992; 5: 263-265.