LUNG DISEASE – Case Studies

LUNG DISEASE Testimonial # 80many Cases Studies on Many Illnesses

One of the most distressing symptoms that anyone can experience is shortness of breath – dyspnea. Patients describe themselves as 'not getting enough air'. This triggers a series of physiological and behavioral reactions that include increased heart rate, blood pressure and hormonal secretions accompanied by a feeling of general panic. Shortness of breath is a common symptom of many respiratory illnesses. Just as the gut separates and absorbs food from the outside world into the body, the lungs are a passage for the exchange of used air and fresh air. But there's a crucial difference between food and oxygen – we can't store oxygen. We must meet a second-by-second demand for the life-giving element or die within minutes. The body responds immediately to any interference with this exchange. Over 30 million Americans are affected by chronic lung disease. Dozens of illnesses can affect the respiratory system. The study of pulmonary (lung-related) medicine is vast and complicated. It deals with congenital problems like cystic fibrosis, acquired diseases like bronchitis and self- inflicted problems like smoking. The importance of GSH in the respiratory system cannot be overstated. We can't address every known respiratory problem but we will discuss a large number of common and not-so-common ailments, including:

- Asthma Cystic fibrosis
- Bronchitis, acute and chronic Pulmonary fibrosis
- Chronic obstructive pulmonary disease (COPD) Cancer
- Emphysema Pneumonia
- Adult respiratory distress syndrome (ARDS) Toxic exposures
- Tobacco abuse

ANTIOXIDANTS AND THE LUNGS

As you will see in the following pages, inflammation of the lung is common to most pulmonary diseases, whether the disorder is acute – like toxic exposure – or chronic – like cystic fibrosis. The process of infection in asthma, bronchitis or pneumonia all lead to inflammation. Many traditional medications attempt to reduce this inflammation. The body's inflammation response itself generates free radicals, and antioxidants are increasingly used to complement conventional treatments. The researchers P.E. Morris and G.R. Bernard drew attention to this complementary treatment in an article aptly called "Significance of glutathione in lung disease and implications for therapy", in which they reviewed the great weight of evidence that supports such research. There is a fragile balance in the lungs between oxidants and antioxidants. Oxidative stress is high in the lungs for many reasons. For a start, this center of oxygen interchange produces very large numbers of oxyradicals. Secondly, white blood cells are highly active in the lining of the lungs, where they release huge quantities of oxidative products, both because of their high metabolic rates and the way they combat biological and chemical invaders. Finally, antioxidants in the fluid lining of the lungs play a large part in our front-line defense against airborne pollutants, many of which are powerful sources of free radicals. When white blood cells encounter, for example, a bacteria, they release caustic substances like peroxides. This is biochemical warf are, and the white blood cell and the surrounding tissues use GSH to defend themselves. When oxidant levels grow too high or GSH levels too low, the inevitable result is tissue damage. Remember that GSH is the most critical of all naturally-occurring antioxidants and that it effectively supports exogenous antioxidants such as vitamins C and E. Unlike glutathione, exogenous antioxidants are derived from the outside environment and are not native to the body, but together they soak up free radicals. Generally, most tissues and organs must manufacture their own glutathione from dietary or drug-delivered precursors.

However, the lining of the respiratory tree – which usually requires high levels of GSH – can absorb GSH directly. To take advantage of this unusual ability, a topical GSH aerosol has been developed and used successfully to treat a number of diseases, including adult respiratory distress syndrome (ARDS), pulmonary fibrosis and HIV infection. In addition, the topical form of NAC (Mucomist) – a potent GSH precursor – has long been used as a treatment for cystic fibrosis. Oral and intravenous GSH precursors are receiving a lot of attention from researchers, and many papers have been published on the subject. Pulmonologists (lung doctors) are paying increasing attention to lung GSH contentand learning a great deal about future applications. O. Ortolani and his team in Italy placed forty intensive care patients with respiratory difficulties on intravenous GSH. They compared their response to an equal number of patients not given the treatment and found significant reductions in oxidative stress levels. An experiment in preventive medicine was conducted by S. De Flora and his research team at the Institute of Hygiene and Preventive Medicine, University of Genoa. Patients were placed on a course of oral NAC tablets or placebo during the months of the influenza season. Although the number of people infected by the virus was unchanged, subjects receiving NAC experienced significantly fewer and less virulent symptoms.

ASTHMA

Bronchial asthma causes constriction of the bronchioles (airway passages). Figure 34 shows the windpipe and lungs, and cross-sections of normal and narrowed air passages (bronchioles). Asthma is always unpleasant and sometimes even fatal. The intensity of asthma attacks vary, but all are characterized by a feeling of tightness in the chest, shortness of breath, restlessness, coughing and wheezing. Although asthma is reversible and intermittent, it tends to recur and is generally considered a chronic condition. It is one of the most common causes of absenteeism and hospital admission in school-age children, among whom it is most prevalent. It currently affects about 15 million Americans and is on the rise. Asthma is variable in frequency and severity and can be triggered by a very wide variety of stimuli, including allergens (things that provoke an allergic response). These include dust, pollen, dander (tiny particles of animal skin, fur and feather), certain foods and drugs, viral infections, emotional stress, anxiety and even plain old exercise. Muscles within the walls of the bronchioles flex and go into spasm, the walls thicken, air passages become clogged bymucus, and air is trapped in the deepest airways (the alveoli). The wheezing sound is caused by air passing with difficulty through these narrowed passages. In its severest form, breathing become impossible and the patient suffocates. Asthma sufferers should make an effort to identify and avoid the triggers that cause their attacks, whether allergic,infectious, toxic, or emotional. They can also take preventative medications – antihistamines and sodium cromoglycate. These minimize the effects of all allergic response. Once an attack is in progress other drugs are needed to reopen (dilate) the walls of the bronchioles. These are called bronchodilators and are commonly used in inhalers such as salbutemol or albuterol. Inhaled or ingested steroids are also available. They minimize the swelling and inflammation of the bronchial walls. In any case, once an attack has begun, treatment must be immediate and aggressive. The longer an attack lasts, the more the symptoms advance and the longer they take to reverse. There is little time to waste. It has been long thought that low levels of glutathione and glutathione peroxidase levels play a role in the onset and progression of asthma. Numerous studies in asthmatics have identified such abnormalities in their red-blood GSH, white blood cell GSH, serum GSH, platelet GSH and lung-fluid GSH. There is a direct correspondence between low glutathione levels and the severity of the asthma attack. Dietary, environmental, and genetic factors that diminish the potency of the antioxidant systems in the lung increase the

risk of asthma. This relationship between antioxidant levels and asthma is seen in situations of elevated free-radical

activity. Examples are lead poisoning, excessive iron stores and G6PD-deficiency, as well as low levels of vitamin C, vitamin E, and selenium (a component of glutathione peroxidase). A recent presentation to the American Lung Association by pulmonologist Dr. Carol Trenga described an antioxidant cocktail that helped asthmatics who were particularly sensitive to air pollutants. European physicians have long used GSH precursors in the treatment of asthma, particularly as a mucolytic (phlegm thinner) to break down thick secretions. In a double-blind study, inhaled bronchodilators were used with and without NAC. The NAC (GSH-enhanced) group experienced greater improvement in pulmonary function than the control group.

CASE STUDY

Jean-Pierre, a financial analyst, suffered from allergies and asthma his whole life. Summers were particularly bad and he often had to leave his native Montreal for weeks in August to escape the ragweed allergy season. In early summer, he was started on a program of NAC (Nacetylcysteine), L-cysteine, selenium, alpha-lipoic acid, multivitamins and stinging nettle (Urtica dioici). That season, he reported having to use his Ventolin inhaler (salbutemol, a bronchodilators for asthma) only two or three times a week, rather than two or three times a day, and his use of antihistamine drugs was at a minimum. He's even ventured to go camping with his girlfriend.

BRONCHITIS, EMPHYSEMA, AND COPD

Bronchitis is an inflammation or obstruction of the bronchi, the larger airways that eventually branch out to become the bronchioles (the site of asthma). It resembles asthma in some ways, their common symptoms being shortness of breath, a phlegm-producing cough, chest discomfort and occasional wheezing. Bronchitis has two distinct forms – acute or chronic. They differ in important ways. Acute bronchitis is almost always caused by infection, either viral or bacterial. Coughing, chest pains, fever and chills are common complaints. In the healthy individual, it is usually a short-lived illness that clears up once the infection is overcome. If the infection is bacterial or mycoplasmal, antibiotics may be required. Occasionally, some inflammation remains, leading to a post-inflammatory cough that may persist for weeks. Inhaled steroids are often prescribed for this condition. Like emphysema (described below), chronic bronchitis is an ongoing illness requiring frequent medical attention. Although it may be exacerbated by infectious disease, chronic bronchitis is usually caused by long-term exposure to lung irritants – toxins, allergens or repeated bouts of acute bronchitis. The most common cause of chronic bronchitis is cigarette smoke. Lungs exposed to tobacco smoke are subject to several pathological processes. One of the most critical is the dysfunction or loss of cilia lining the airways. Cilia are microscopic hair-like structures that trap and remove dust, mucus and other debris. A single puff of a cigarette can paralyze these hairs, increasing the chances of subsequent lung injury and infection. As chronic bronchitis progresses, the lung's ability to exchange oxygen and carbon dioxide diminishes. In an attempt to compensate for the loss of pulmonary function, energy demands increase, the chest muscles work harder and the heart pumps faster. This in turn can lead to secondary diseases such as pulmonary hypertension, heart failure and emphysema. Emphysema progresses slowly over time and is usually the result of prior lung disease. Chronic cough and shortness of breath are typical symptoms. Although it may occasionally be caused by hereditary factors, environmental exposures, chronic asthma or chronic bronchitis, emphysema most often results from years of heavy smoking. It is the most common cause of death from respiratory disease in North America. Emphysema shares many symptoms with chronic bronchitis. In fact, the two diseases usually overlap to some degree. They are often classed together under the heading COPD (chronic obstructive pulmonary disease). However, they differ anatomically. Emphysema results in irreversible damage to alveoli – tiny sac-like structures

where the actual exchange of oxygen and carbon dioxide occurs. Alveoli are counted in the millions, like bubbles in a bubble bath. Emphysema causes them to burst one by one. They then coalesce into fewer, larger sacs. As a result, their total surface area dwindles, decreasing the amount of air that can be exchanged by each breath. It is well known that most lung diseases are characterized by weak antioxidant activity and impaired glutathione-related enzyme systems. Taking advantage of this information, a group of French researchers tested to see whether GSH screening could predict a predisposition to pulmonary diseases. They tested subjects for the absence of a gene (GSTM1) responsible for a specific GSH enzyme. About 47% of the French population lacks this gene. They found that heavy smokers with moderate chronic bronchitis were missing this gene 66% of the time and that smokers with severe chronic bronchitis were deficient in 71 % of cases. They concluded that factors diminishing GSH function – in this case a hereditary factor – put individuals at higher risk for respiratory problems. Other studies determined that COPD patients were very sensitive to low GSH levels after even light exercise, demonstrating the precarious balance of glutathione in these patients and the great importance of maintaining adequate stores of GSH. N.C. Hansen and his team at Odense University in Denmark conducted a double-blind study of the general well-being of patients with mild chronic bronchitis. They administered oral NAC during the winter months to these patients, and placebo to a similar group. Of the two groups, the GSHenhanced group did much better on a GHQ (general health questionnaire). Several other research teams have studied the use of oral NAC as a preventative measure. Although it didn't significantly reduce the number of chronic bronchitis attacks, their severity – measured by symptoms and days off work – was greatly reduced. In a large open study of over two thousand patients, K.P. Volkl, B. Schneider from Hanover Medical School in Germany showed that the use of NAC led to clear improvements in symptoms and pulmonary function. The four-week study included patients with acute and chronic bronchitis, bronchial asthma and emphysema. All groups had similar improvement in their disease.

SMOKING AND GSH

There is no longer any doubt that cigarette smoking is a major risk factor for chronic bronchitis, emphysema, COPD, cancer and cardiovascular disease. One of the ways in which cigarette smoke damages the body is by profoundly raising the extent of oxidative stress in the lungs. A single puff of cigarette smoke contains billions of free radicals and can literally "burn up" antioxidants. But this isn't the worst of it. A still greater source of oxidative stress results from the lung inflammation resulting from smoking. The total oxidative damage caused by smoke corresponds directly to the degree of lung injury, respiratory compromise, morbidity and mortality found in individual patients. Pharmacologists are investing the use of inhaled GSH to prevent the occurrence or progression of emphysema in smokers. As a GSH precursor, NAC is receiving equal attention. Double blind studies in smokers using NAC demonstrate the enhanced ability of their lungs to clear away thick secretions in their airways. R.B. Balansky at the Institute of Hygiene and Preventive Medicine in Italy exposed rats to high levels of cigarette smoke. This led to decreased body weight, intense pathological damage of the terminal airways, inflammation of the bronchial and bronchiolar linings, alveolar damage, emphysema, white blood cell abnormalities and pre-cancerous lesions. Rats given daily NAC at the same time suffered significantly less damage, demonstrating the protective role of GSH against lung damage and the onset of cancer. Smokers are also more prone to the development of infectious bronchitis and pneumonia. Chronic bronchitis in smokers results in increased bacterial colonization. Treatment with NAC has decreased both the frequency of infectious episodes and the virulence of the bacteria.

ADULT RESPIRATORY DISTRESS SYNDROME (ARDS)

ARDS is acute, life-threatening respiratory failure following pulmonary injury. It leads to profound dyspnea (shortness of breath), pulmonary edema (fluid accumulation in the lungs) and hypoxemia (oxygen starvation). This all-too-common medical emergency is caused by a number of different acute processes that directly or indirectly damage the lung. They include bacterial or viral pneumonias, inhalation of stomach contents or other toxins, direct trauma to the chest, sepsis (overwhelming generalized infection), profound circulatory shock, drowning and many other medical conditions. Even with appropriate therapy the survival rate is only about 50%. Long-term complications include the eventual development of pulmonary fibrosis. ARDS is a very complicated inflammatory process of which edema is only one facet. In the past, physicians treated this disorder aggressively with corticosteroids, because of their well-known anti-inflammatory properties. Unfortunately, randomized trials have shown that steroids are relatively ineffective against this disease. A hunt is on for useful treatments. For several reasons, ARDS patients experience high levels of oxidative stress and subsequent depletion of antioxidants and glutathione. One cause may be the release of free radicals at the injury site by endotoxins. Endotoxins are produced by certain bacteria, though only released when the bacteria die. However, most of this oxidative stress probably comes from inflammation. Some white blood cells (neutrophils) are very active at sites of inflammation, producing very large amounts of reactive oxygen species, such as free oxygen radicals, hydrogen peroxide, 'hot' oxygen, and others. Recognizing the severe oxidant-antioxidant imbalance and GSH depletion that comes with this condition, many researchers have pt NAC under the spotlight. G.R. Bernard and his team at Vanderbilt University tested the usefulness of intravenous NAC for the lungs. Both in the lab and in clinical trials they found increased oxygen delivery, improved lung compliance (elasticity) and an improvement in the condition of pulmonary edema patients. Trials with another GSH precursor – OTZ (Procysteine) – led to similar results and reduced the duration of lung injury. In a larger double-blind study, P.M. Suter's group at the University of Geneva used intravenous NAC on intensive care patients. Compared to a control group, the NAC patients showed significant improvement in oxygenation and required less time on mechanical ventilators (life support).

PULMONARY FIBROSIS

Pulmonary fibrosis is also called fibrosing alveolitis or interstitial fibrosis, among other things. It is a non-specific condition in which the lungs respond to damage by the production of scar tissue (fibrosis). This leads to stiffness of the lungs and difficulties clearing secretions. It also interferes with gas exchange. Its causes include numerous bacterial, viral or fungal infections and inhaled toxins, dusts (organic and inorganic) and chemicals. Occasionally stomach contents can be inhaled to the detriment of the lungs. Other diseases are involved less often, such as certain autoimmune disorders (mistaken immune response to healthy processes), sarcoidosis (a multi-system inflammatory disorder), or collagen-vascular diseases (rheumatoid arthritis, lupus, polyarteritis nodosa, scleroderma and dermatomytosis). This disease is often an unwanted result of radiation therapy or chemotherapy. The standard treatments have limited success. Oxidative stress plays an important role in the causes and conditions of many types of pulmonary fibrosis. J. Behr and his group of pulmonologists from the University of Munich studied this phenomenon both in laboratory cultures and in pulmonary fibrosis patients. Because pulmonary fibrosis is an inflammatory disorder, their treatment includes therapy to suppress the immune inflammatory response. With the help of NAC, patients' pulmonary function tests improved and the number of oxidative breakdown products fell. By using aerosolized NAC, Z. Borok from the NIH (National Institute of Health) revered the oxidant-antioxidant imbalance in pulmonary fibrosis patients. Both NAC and aerosol GSH have shown success in this situation. Clearly, both oral and inhaled NAC can successfully raise pulmonary GSH levels. In patients with pulmonary fibrosis,

fibroblasts – cells in part responsible for the fibrous scar tissue – grow excessively in both number and activity. When tissue cultures were made of these cells, it was found that the presence of GSH down-regulated their growth. This implies that GSH may slow the progress of pulmonary fibrosis.

CASE STUDY

With a background in law from her native France, Nona became actively involved with business and philanthropological pursuits in Canada. She was a 41 year-old mother of three suffering from Hodgkin's disease and requiring both chemotherapy and radiotherapy. Although these treatments cured her of Hodgkin's disease, the treatments left her lungs scarred – the condition of pulmonary fibrosis. Her interests had to be dropped as her breathing deteriorated. She ended up staying at home, using home oxygen and many medications. Despite all interventions, her pulmonary function tests (PFT's) continued to fall. After six weeks of Immunocal 20 grams/day she went back to her pulmonary doctor, claiming she could breath again. Thinking there might be a placebo effect; the physician repeated her pulmonary function tests, which showed her back at about 90% of normal values. To eliminate other possibilities, the Immunocal was withdrawn. She subsequently deteriorated again. Three weeks after reinstating the Immunocal, her PFT's went back up to 95% of normal values. She promised herself never to stop again.

CYSTIC FIBROSIS

Cystic fibrosis affects many organ systems, but particularly the lungs. It is also called mucoviscidosis because it secretes a sticky mucus which neither lubricates nor flows freely in the nose, throat, airways and intestines. Cystic fibrosis is one of the most common inherited diseases in North America and affects some 30,000 people. Survivors live to an age of about 28 years, depending on the extent of pulmonary involvement. Cystic fibrosis is most often classified as a disorder of the exocrine glands, and primarily affects the pancreas in fibrocystic pancreatic disease, the sweat glands, and pulmonary mucus production in mucoviscidosis. The problem stems from an inherited defect in the gene responsible for secreting certain fluids from these glands. The disease often becomes apparent early in life. As babies, cystic fibrosis patients have extremely frequent digestive difficulties. Their pancreas do not provide enough digestive juice. This leads to malabsorption (poor ability to use nutrients) and malnutrition. Their skin loses large amounts of salt and they may sweat profusely. The lungs secrete a very thick (viscous) mucus that can obstruct airways, causing coughing, wheezing, and recurrent lung infections. Comprehensive and intensive therapy with health workers specialized in nursing, nutrition, physical therapy ad respiratory therapy is essential for this problem. Dr. Larry Lands, director of the cystic fibrosis clinic at McGill University in Montreal, aptly points out that inflammation is central to cystic fibrosis, that inflammation always precedes lung infection, and that lung infection almost inevitably follows severe inflammation. Continued inflammation depletes antioxidants and GSH even more and a vicious circle ensues. The decrease of GSH in cystic fibrosis is noticeable in the fluid lining of the lungs (epithelial lining fluid), and also in blood serum, red blood cells and elsewhere. This points to whole-body depletion as a result of ongoing oxidative stress. Cystic fibrosis patients are at even further risk of antioxidant depletion because of pancreatic involvement leading to digestive difficulties and poor absorption of essential nutrients. Many researchers are investigating the use of supplemental antioxidants in this disease, including Lands' team investigating Immunocal, the whey-based GSH precursor. NAC as long been utilized in an aerosol form to break down mucus accumulation in cystic fibrosis patients. It can be used

in the same way for asthma, bronchitis, COPD, emphysema, pneumonia and other situations where thick secretions impair pulmonary function.

CASE STUDY

Eight year-old Zach, a cystic fibrosis patient, loved baseball. He was smaller than the rest of the kids, but it was shortness of breath and recurrent respiratory problems, not height, that kept him off the team. He took more care of his nutritional needs and was good about taking his additional vitamin and antioxidant supplementation. His parents learned how to provide him with home aerosol treatments by mask. He has been using both oral and nebulized (by mask) Mucomyst (N-acetylcysteine). Although primarily used as a “bench-warmer,” Zach is back on the team.

CONCLUSION

An impressive amount of research has made clear the critical importance of antioxidants and GSH in all these pulmonary diseases. Unlike most other tissues, the lungs can use GSH as-is – through direct contact – rather than having to first absorb its precursors and then manufacture it, s is the case elsewhere in the body. There are many ways to elevate pulmonary GSH, including oral, intravenous and inhaled therapies. In the next few years we will see increased use of these products to raise glutathione levels in acute, chronic and critical care patients.

REFERENCES TO LUNG DISEASE

BALANSKY RM, DE FLORA S. Chemoprevention by N-acetylcysteine of urethane-induced clastogenicity and lung tumors in mice. *Int. J. Cancer 77:302-305, 1998*

BALANSKY RB, D’AGOSTININ F, ZANNACCHI P, DE FLORA S. Protection of N-acetylcysteine of the histopathological and cytogenetical damaged produced by exposure of rats to cigarette smoke. *Cancer Lett. 64:123-131, 1992*

BARANOVA H, PERRIOT J, ALBUISSON E, ET AL. Peculiarities of the GSTM1 o/o genotype in French heavy smokers with various types of chronic bronchitis. *Human Genetics 99: 822-826, 1997*

BEHR J, DEGENKOLB B, MAIER K, ET AL. Increased oxidation of extracellular glutathione by bronchoalveolar inflammatory cells in diffuse fibrosing alveolitis. *Eur. Respir. J. 8: 1286-1292, 1995*

BEHR J, MAIER K, DEGENKOLB B, ET AL. Antioxidative and clinical effects of high-dose N-acetylcysteine in fibrosing alveolitis. Adjunctive therapy to a maintenance immunosuppression. *American J. Respir. Crit. Care Med. 156: 1897-1901, 1997*

BERNARD GR. Potential of N-acetylcysteine as treatment for the adult respiratory distress syndrome. *Eur. Respir. J. Suppl. II: 496S-498S, 1990*

BERNARD GR. N-acetylcysteine in experimental and clinical acute lung injury. *American J. Med. 91(3c): 54S-59S, 1991*

BERNARD GR, WHEELER AP, ARONS MM, ET AL. A trial of antioxidants N-acetylcysteine and Procysteine in ARDS. The antioxidant in ARDS Study Group. *Chest 112: 164-172, 1997*

BIBI H, SCHLESINGER M, TABACHNIK E, ET AL. Erythrocyte glutathione peroxidase activity in asthmatic children. Ann. *Alergy 61: 339-340, 1988*

BOROK Z, BUHL R, GRIMES GJ, ET AL. Effect of glutathione aerosol on oxidant-antioxidant imbalance in idiopathic pulmonary fibrosis. *Lancet 338: 215-216, 1991*

BRIGHAM K. Oxidant stress and adult respiratory distress syndrome. *Eur. Respir. J. Suppl. 11: 482S-484S, 1990*

BROWN RK, KELLY FJ. Evidence for increased oxidative damage in patients with cystic fibrosis. *Pediatr. Res. 36: 487-493, 1994*

BUHL R, MEYER A, VOGELMEIER C. Oxidant-protease interaction in the lung. Prospects for antioxidant therapy. *Chest 110 (6 Suppl): 267S2727S, 1996*

BUHL R, VOGELMEIER C. Therapy of lung diseases with anti-oxidants. *Pneumologie 48: 50-56, 1994*

BUHL R, VOGELMEIER C, CRITINDEN, ET AL. Augmentation of glutathione in the fluid lining the epithelium of the lower respiratory tract by directly administering glutathione aerosol. *Proc. Natl. Acad. Sci. USA87: 4063-4067, 1990*

BUNNEL E, PACHT ER. Oxidized glutathione is increased in the alveolar fluid of patients with the adult respiratory distress syndrome. *American Rev. Respir. Dis. 148: 1174-1178, 1993*

CANTIN A, CRYSTAL RG. Oxidants, antioxidants and the pathogenesis of emphysema. *Eur. J. Dis. Suppl. 139: 7-17, 1985*

CANTIN A, HUBBARD RC, CRYSTAL RG. Glutathione deficiency in the epithelial lining fluid of the lower respiratory tract in idiopathic pulmonary fibrosis. *American Rev. Respir. Dis. 139: 370-372, 1989*

CANTIN A, LARIVEE P, BEGIN RO. Extracellular glutathione suppresses human lung fibroblast proliferation. *American J. Respir. Cell. Mol. Biol. 3: 79-85, 1990*

CATO A, GOLDSTEIN I, MILLMAN. A double-blind parallel study of acetylcysteine-isoproterenol and salineisoproterenol in patients with chronic obstructive lung disease. *J. Int. Med. Res. 5: 175-183, 1977*

CONAWAY CC, JIAO D, KELLOFF GJ, ET AL. Chemopreventive potential of fumaric acid, N-acetylcysteine, N-(4-hydroxyphenyl) retinamide and beta-carotene for tobacco-nitrosamine-induced lung tumors in A/J mice. *Cancer Lett. 124: 85-93, 1998*

COTGREAVE IA, MOLDEUS P. Lung protection by thiol-containing antioxidants. *Bull. Eur. Physiopathol. Respir. 23: 272-277, 1987*

D'AGOSTINI F, BAGNASCO M, GIUNCIUGLIO D, ET AL. Inhibition by oral N-acetylcysteine of doxorubicin-induced clastogenicity and alopecia, and prevention of primary tumors and lung metastasis in mice. *Int. J. Oncol. 13: 217-224, 1998*

DAVREUX CJ, SORIC I, NATHENS AB, ET AL. N-acetyl cysteine attenuates acute lung injury in the rat. *Shock 8: 432-438, 1997*

DE FLORA S, GRASSI C, CARATI L. Attenuation of influenza-like symptomatology and improvement of cell-mediated immunity with long-term Nacetylcysteine treatment. *Eur. Respir. J. 19: 1535-1541, 1997*

DEMLING R, IKEGAMI K, LALONDE C. Increased lipid peroxidation and decreased antioxidant activity correspond with death after smoke exposure in the rat. *J. Burn Care Rehabil. 16(2 Pt 1): 104-110, 1995*

DEMLING R, LALONDE C, PICARD L, BLANCHARD J. Changes in lung and systemic oxidant and antioxidant activity after smoke inhalation. *Shock 1: 101-107, 1994*

EISERICH JP, VAN DER VLIET, ET AL. Dietary antioxidants and cigarette smoke-induced biomolecular damage: a complex interaction. *American J. Clin. Nutr. 62(6 Suppl): 1490S-1500S, 1995*

GOLDSTEIN RH, FINE A. Potential therapeutic initiatives for fibrogenic lung diseases. *Chest 108: 848-855, 1995*

GREENE LS. Asthma and oxidant stress: nutritional, environmental and genetic risk factors. *J. American Coll. Nutr. 14: 317-324, 1995*

GRESSIER B, LEBEGUE S, GOSSET P, ET AL. Protective role of glutathione on alpha ! proteinases inhibitor inactivation by the myeloperoxidase system. Hypothetic study for the therapeutic strategy in the management of smoker's emphysema. *Fundam. Clin. Pharmacol. 8: 518-524, 1994*

HANSEN NC, SKRIVER A, BRORSEN-RIIS L, ET AL. Orally administered N-acetylcysteine may improve general well-being in patients with mild chronic bronchitis. *Respir. Med. 88: 531-515, 1994*

HASSELMARK L, MALMGREN R, UNGE G, ZETTERSTROM O. Lowered platelet glutathione peroxidase activity in patients with intrinsic asthma. *Allergy 45: 523-527, 1990*

HULL J, VERVAART P, GRIMWOOD K, PHELAN P. Pulmonary oxidative stress response in young children with cystic fibrosis. *Thorax 52: 557- 560, 1997*

HUNNINGHAKE GW, KALICA AR. Approaches to the treatment of pulmonary fibrosis. *American J. Respir. Crit. Care Med. 151(3 Pt 1): 915-918, 195*

IKEGAMI K, LALONDE C, YOUNG YK, ET AL. Comparison of plasma reduced glutathione and oxidized glutathione with lung and liver tissue oxidant and antioxidant activity during acute inflammation. *Shock 1: 307-312, 1994*

KADRABOVA J, MAD'ARIC A, KOVACIKOVA Z, ET AL. Selenium status is decreased in patients with intrinsic asthma. *Biol. Tr. Elem. Res. 52: 241-248, 1996*

KELLY FJ, COTGROVE M, MUDWAY IS. Respiratory lining tract fluid antioxidants: the first line of defense against serious gaseous pollutants. *Cent. Eur. J. Public Health 4 Suppl: 11-14, 1996*

LANDS LC, GREY VL, GRENIER. Total plasma antioxidant capacity in cystic fibrosis. *Pediatr. Pulmonol. 29: 81- 87, 2000*

LAURENT T, MARKERT M, FEIHL F, ET AL. Oxidant-antioxidant balance in granulocytes during ARDS. Effect of Nacetylcysteine. *Chest 109: 163-166, 1996*

LOTHIAN B, GREY V, KIMOFF RJ, LANDS LC. Treatment of obstructive airway disease with a cysteine donor protein supplement: A case report. *Chest: 117:914-916, 2000*

MACNEE W. Chronic obstructive pulmonary disease from science to the clinic: the role of glutathione in oxidantantioxidant balance. *Monaldi. Arch. Chest Dis. 52: 479-485, 1997*

MACNEE W, BRIDGEMAN MM, MARSDEN M, ET AL. The effects of N-acetylcysteine and glutathione on smokeinduced changes in lung phagocytes and epithelial cells. *American J. Med. 91(3C): 60S-66S, 1991*

MEYER A, BUHL R, KAMPF S, MAGNUSSEN H. Intravenous N-acetylcysteine and lung glutathione of patients with pulmonary fibrosis and normals. *American J. Respir. Crit. Care Med. 152: 1055-1060, 1955*

MEYER A, BUHL R, MAGNUSSEN H. The effect of oral N-acetylcysteine on lung glutathione levels in idiopathic pulmonary fibrosis. *Eur. Respir. J. 7:431-436, 1994*

MISSO NL, POWERS KA, GILLON RL, ET AL. Reduced platelet glutathione peroxidase activity and serum selenium concentration in atopic asthmatic patients. *Clin. Exp. Alergy 26: 838-847, 1996*

MORRIS PE, BERNARD GR. Significance of glutathione in lung disease and implications for therapy. *American J.Med. Sci. 307: 119-127, 1994*

NOVAK Z, NEMETH I, GYURKOVITS K, ET AL. Examination of the role of oxygen free radicals in bronchial asthma in childhood. *Clin. Chim. Acta. 201: 247-251, 1991*

OLIVIERI D, MARISCO SA, DEL DONNO M. Improvement of mucociliary transport in smokers by mucolytics. *Eur. J. Respir. Dis. Suppl. 139: 142- 145, 1985*

ORTOLANI O, GRATINO F, LEONE D, ET AL. Usefulness of the prevention of oxygen radical damage in the critical patient using the parental administration of reduced glutathione in high doses. *Bol. Soc. Ital. Biol. Sper. 68: 239-244, 1992*

PACHT ER, TIMERMAN AP, LYKENS MG, MEROLA AJ. Deficiency of alveolar fluid glutathione in patients with sepsis and the adult respiratory distress syndrome. *Chest 100: 1397-1403, 1991*

PARR GD, HUITSON A. Oral Fabrol (oral N-acetylcysteine) in chronic bronchitis. *Br. J. Dis. Chest 81: 341-348, 1987*

PATTERSON CE, RHOADES RA. Protective role of sulfhydryl reagents in oxidant lung injury. *Exp. Lung Res. 14 Suppl: 1005-1019, 1988*

PEARSON DJ, SUAREZ-MENDEZ VJ, DAY JP, MILLER PF. Selenium status in relation to reduced glutathione peroxidase activity in aspirin- sensitive asthma. *Clin Exp. Allergy 21: 203-208, 1991*

PORTAL BC, RICHARD MJ, FAURE HS, ET AL. Altered antioxidant status and increased lipid peroxidation in children with cystic fibrosis. American J. Clin. Nutr. 61: 843-847, 1995

POWELL CV, NASH AA, POWERS HJ, PRIMHAK RA. Antioxidant status in asthma. *Pediatr. Pulmonol. 18: 34-38, 1994*

RAHMAN I, MACNEE W. Role of oxidants/antioxidants in smoking-induced lung diseases. *Free Radic. Biol. Med. 21: 6669-681, 1996*

RASMUSSEN JB, GLENNOW C. Reduction in days of illness after long-term treatment with N-acetylcysteine controlled-release tablets in patients with chronic bronchitis. *Eur. Respirol. J. 4:351-355, 1988*

RIISE GC, LARSSON S, LARSSON P, ET AL. The intrabronchial microbial flora in chronic bronchitis patients: a target for N-acetylcysteine therapy*? Eur. Respir. J. 7: 94-101, 1994*

ROGERS DF, JEFFERY PK. Inhibition by oral N-acetylcysteine of cigarette smoke-induced “bronchitis” in the rat. Exp. *Lung Res. 10: 267-283, 1986*

ROUM JH, BUHL R, MCELVANEY, ET AL. Systemic deficiency of glutathione in cystic fibrosis. *J. Appl. Physiol. 75: 2419-2424, 1993*

SALA R, MORIGGI E, CORVASCE G, MORELLI D. Protection by N-acetylcysteine against pulmonary endothelial cell damage induced by oxidant injury. *Eur. Respir. J. 6: 440-446, 1993*

SIMON LM, SUTTORP N. Lung cell oxidant injury: decrease in oxidant mediated cytotoxicity by N-acetylcysteine. *Eur. J. Dis. Suppl. 139: 132-135, 1985*

SUTER PM, DOMENIGHETTI G, SCHALLER, ET AL. N-acetylcysteine enhances recovery from acute lung injury in man. A randomized, double- blind, placebo-controlled clinical study. *Chest 105: 190-194, 1994*

TANSWELL AK, FREEMAN BA. Antioxidant therapy in critical care medicine. *New Horiz. 3: 330-341, 1995*

TATTERSALL AB, BRIDGMAN KM, HUITSON A. Irish general practice study of acetylcysteine (Fabrol) in chronic bronchitis. *J. Int. Med. Res. 12: 96-101, 1984*

TERAMOTO S, FUKUCHI Y, UEJIMA Y, ET AL. Superoxide anion formation and glutathione metabolism of blood in patients with idiopathic pulmonary fibrosis. *Biochem. Mol. Med. 55: 66-70, 1995*

VAN ZANDWIJK N. N-acetylcysteine (NAC) and glutathione: antioxidant and chemopreventative properties, with special reference to lung cancer*. J. Cell. Biochem. Suppl. 22: 24-32, 1995*

VAN ZANDWIJK N. N-acetylcysteine for lung cancer protection. *Chest 107: 1437-1441, 1995*

VINA J, SERVERA E, ASENI M, ET AL. Exercise causes blood glutathione oxidation in chronic obstructive pulmonary disease: prevention by O2 therapy*. J. Appl. Physiol. 81: 2198-2202, 1996*

VOLKL KP, SCHNEIDER B. Therapy of respiratory tract diseases with N-acetylcysteine. An open therapeuticobservation study of 2,512 patients. *Fortschr. Med. 110: 346-350, 1992*

WAGNER PD, MATH IEU-COSTELLO O, BEBOUT BE, ET AL. Protection against pulmonary O2 toxicity by Nacetylcysteine. *Eur. Respir. J. 2:116- 126, 1989*

WHITE CW, REPINE JE. Pulmonary antioxidant defense mechanisms. *Exp. Lung Res. 8: 81-96, 1985*

WINKLHOFER-ROOB BM. Oxygen free radicals and antioxidants in cystic fibrosis: the concept of an oxidantantioxidant imbalance. *Acta. Paediatr. Suppl. 83: 49-57, 1994*

WITSCHI H, ESPIRITU I, YU M, WILLITS NH. The effects of phenethyl isothianate, N-acetylcysteine and green tea on tobacco smoke-induced lung tumors in strain. A/J mice. *Carcinogenesis 19: 1789-1794, 1998*