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PLEURODESIS IN CHRONIC EFFUSIONS

Studies on inflammatory mediators, respiratory function, predictability of
treatment outcome, drug efficiency and survival after treatment.

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ABSTRACT

Metastatic or primary (mesothelioma) malignancy of the pleura often generates major pleural effusion, giving respiratory distress and low quality of life to the patients. Evacuation of fluid by thoracentesis gives only temporary relief, therefore pleurodesis is generally regarded the best way to give palliation. The principle of pleurodesis is to cause a severe inflammation with desquamation of the mesothelial cells, resulting in a fibrosis that obliterates the pleural space. The aims of this thesis were to study various aspects of chemical pleurodesis: the inflammatory response in the pleura and the systemic inflammatory reaction during such treatment and also to investigate if the reaction had predictive value on pleurodesis outcome; the impact of pleurodesis on respiratory function; to compare the efficacy and side effects of two drugs used for pleurodesis; and the long-term survival after pleurodesis in different malignancies.

It was found that the cytokine IL-1 β was present in the pleural fluid before and during chest tube drainage and increased after quinacrine instillation. However high concentrations of IL-1 β values after instillation were related to the need for longer treatment duration.

Successful pleurodesis leads to fibrous adhesions between the lung and costal pleura, which might restrict lung mobility. Ten patients without radiological signs of tumour infiltration and without visible signs of tumour growth in the pleural space at thoracoscopy were investigated after pleurodesis with static and dynamic spirometry, exercise testing with blood gas determination, and radiospirometry. The study showed that pleurodesis in malignant pleurisy has very limited influence on respiratory function.

Quinacrine has been used for pleurodesis with good results in our clinic for decades, and talc, which gradually during recent years become the most commonly used drug for this purpose world-wide. The comparative study between talc and quinacrine in 110 patients showed that both drugs were effective for pleurodesis. Fluid accumulation was stopped within six days in 96% of the talc group and 89% of the quinacrine group. All 89 prospective patients had verified malignant effusion. The markers investigated for the systemic inflammatory reaction were erythrocyte sedimentation rate, C-reactive protein, and leukocyte count from venous blood samples, and fever reaction. Cessation of fluid accumulation was achieved in 82 patients (92%) and all had a prominent transitional elevation of the inflammatory parameters. The unsuccessful attempts (8%) caused negligible or very small elevations, but due to the small number, only the degree of fever after 8 and 48 hours showed a statistically significant difference. Pleurodesis causes a systemic inflammation and there is a tendency to a correlation between the success of pleurodesis and the degree of inflammation caused by the procedure.

Altogether 197 patients with malignant effusion were discharged from our clinic between January 1, 1991 to September 30, 1994 after a successful pleurodesis. The four most common primary tumours were lung, breast, lymphoma and ovarian malignancies. The overall median survival from pleurodesis was 135 days. Patients with breast cancer had the best prognosis (median survival 216 days). In lung cancer patients, this figure was 55 days and in lymphomas 168 days. The longer the time from diagnosis of primary tumour to effusion, the better the prognosis.

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LIST OF ABBREVIATIONS

ARDS	Acute respiratory distress syndrom
BCG	Bacille-Calmette-Guerin
CNS	Central nervous system
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
FPA	Fibrinopeptide A

1 INTRODUCTION

Recurrent and symptomatic pleural effusion is not uncommon in patients with a known malignant disease and may even be the first manifestation of such a disease. Repeated thoracenteses are cumbersome for the patient and the health care system and cause loss of protein and other substances. Thus, there is a need for a method to stop the effusions, and the most often used method is pleurodesis. There are also non-malignant diseases that may cause recurrent and symptomatic pleural effusions, and also in these cases relief can be achieved by pleurodesis (Glazer *et al* 2000, Vargas *et al* 1994). This is a way to fuse the two pleural layers, the visceral which covers the lung, and the parietal, which covers the inside of the chest wall and the diaphragm, thereby making accumulation of fluid impossible.

There are different ways to achieve a pleurodesis. The simplest is to evacuate the fluid and leave a drainage in the pleura space (Izbicki *et al* 1975) for some days; this will actually achieve a pleurodesis in up to half of the cases. Surgical procedure such as decortication is associated with a major surgical trauma and is therefore rarely used in malignant pleurisy but is used commonly in, for instance, treatment of recurring and/or persistent pneumothorax. The most common way to achieve pleurodesis in malignant disease is by installation of an irritant agent into the pleural space that causes inflammation of the pleura.

The ideal agent should cause an effective pleurodesis in all cases without any side effects. However, such an ideal agent has not been found. Since all agents cause inflammation of the pleura, side effects (local and general) are unavoidable, and some side effects may be serious. There is long list of chemical agents of different kinds that have been used for the purpose, reflecting the fact that the agent(s) of choice have not been defined in the literature. Comparative studies are rare. In recent years, talc has become increasingly popular and is recommended by many experts. However, at the Respiratory Division in Karolinska Hospital, Stockholm, we have for decades used quinacrine with excellent results and only minor side effects. We therefore decided to make a prospective randomised study to compare these two agents.

Successful pleurodesis leads to a permanent stop of fluid accumulation and obliteration of the pleural space. The formation of fibrous adhesion between the lung and costal pleura might in theory restrict lung mobility and thereby impair respiratory function. The literature on the impact of pleurodesis on respiratory function is limited. In patients with deficient respiratory function, or bilateral effusion with need for bilateral pleurodesis, the question of the degree of further restriction of respiratory function often arises. We therefore designed a study to evaluate the influence of pleurodesis in malignant pleural effusion on respiratory function.

Pleurodesis treatment works by triggering inflammatory mediators and reactions with the synthesis of several cytokines. Interleukin-1 β (IL-1 β) is one of these important cytokines involved in acute inflammatory reactions. The release of IL-1 β causes fever, activation of neutrophils, of T- and B-lymphocytes, as well as induction of other cytokines and many acute phase reactants. IL-1 β also regulates endothelial activities such as expression of adhesion molecules, the expression of procoagulants and

induction of plasminogen activator inhibitor (PAI-1) (Dinarello 1988, Dinarello 1992). The presence of IL-1 β in untreated malignant effusion has earlier been demonstrated (Shimokata et al 1991). We therefore investigated this substance in pleural fluid and the effects of pleurodesis on it.

Several studies have investigated the inflammatory response at pleurodesis but these studies are mostly focused at local level, i.e., in the pleural space both in animal experiments and in humans. These studies have revealed leukocyte as the dominating cell at the acute phase. There is little in the literature about the systemic inflammatory reaction with pleurodesis. There is no proof that the intensity of inflammation is correlated to the outcome of pleurodesis. We thus decided to study the basic inflammatory markers that physicians in everyday practice are confronted with, such as ESR, CRP, fever and leukocyte count.

Pleurodesis is a palliative intervention. An alternative to pleurodesis is intermittent or continuous drainage of the pleural fluid which is only recommended to patients with very limited life expectancy. However, the role of pleurodesis for symptom relief is well established, but not the effect on survival time in different malignant diseases. The retrospective study on patients treated with pleurodesis showed that patient age is more or less irrelevant for survival and what matters is the tumour histocytology and the time from primary disease to effusion.

1.1 GENERAL BACKGROUND

1.1.1 Anatomy of the pleura

The pleural space is a serous cavity surrounding each lung except at the hili where blood and lymphatic vessels, the mainstem bronchi, and nerves pass from the mediastinum to the lungs. The visceral and parietal pleurae are originally the same serous membrane, which merges at the hilum. The inside of the chest wall is covered by the parietal pleura. The visceral pleura covers the lung and separates the lung lobes, forming the interlobar fissures. The interlobar fissures make it possible for a lobe to expand or collapse unaffected by the other lobe(s) (Wang 1998). The parietal pleura is separated from the visceral pleura by the pleural cavity. During the embryonic process, the pleural membranes are developed before the lungs (Patten *et al* 1974). The mediastinum separates the two pleural cavities from each other in man.

The thin sheet of pleura can be seen by light microscopy to consist of five layers. Starting from the surface, these layers are: 1) the mesothelial cell layer, 2) the submesothelial connective tissue layer, 3) the superficial elastic layer, 4) the loose connective tissue layer, containing fat tissues, blood vessels, nerves and lymphatics, and 5) the deep fibroelastic layer, which is adherent to the parenchyma or to the chest wall (Albertine *et al* 1982, Hayek 1960, Mariassy *et al* 1983, Nagaishi C 1972).

The mesothelial cells are extremely flattened with a diameter of 16.4 to 41.9 μm and a thickness of about 1 to $> 4 \mu\text{m}$ (Albertine *et al* 1982, Wang NS 1974). The pleura is thicker at the caudal part of the lung where the mesothelial cells are actually cuboidal (Wang N-S 1974). In electron microscopy it can be seen that the mesothelial cell has a bush-like, wavy and aggregated surface of microvilli with a length of about 3 μm and diameter of 0.1 μm .

The function of the pleurae is similar to that of peritoneum and of the pericardium and its cavity. The sheets of pleura are elastic and lubricated by fluid, thereby decreasing friction (Andrews *et al* 1973) and allowing the movements and necessary changes of the size of the lungs. The function is evidently to protect the lung from infection and other damage.

1.1.1.1 Blood circulation

The parietal pleura gets its blood supply from the subclavian, bronchial, intercostal and internal mammary arteries where as the venous drainage is through the bronchial veins into the superior vena cava. Blood supply to the diaphragmatic pleura is from branches of the internal mammary artery, the thoracic and abdominal aorta and the celiac artery, venous drainage is into the inferior vena cava and brachiocephalic trunci. The visceral pleura blood supply is from branches of the bronchial arteries forming a large and loose network of capillaries. The venous drainage is mainly through the pulmonary veins except at the hilum, which is drained into the bronchial veins (Bernaudin *et al* 1985, Sahn 1988).

1.1.1.2 Lymphatic circulation

The pleural space has two different lymphatic systems: The parietal pleura lymphatics and the visceral pleura lymphatics. The lymphatics of the parietal pleura are the true lymphatics of the pleural space and those of the visceral are the superficial lymphatic system of the lung (Bernaudin *et al* 1985).

The visceral pleura lymphatic circulation has no direct communication with the pleural space (Pistolesi *et al* 1989). The lymph drainage of the visceral pleura is through the deep and superficial lymphatic plexus to the hilar lymph nodes (Weidner *et al* 1971).

The parietal lymphatic vessels collect lymph from the pleural space through valved lymphatic vessels to the right lymph duct and to the thoracic duct (Courtice *et al* 1954). The lymphatic system of the parietal pleura is the only way for pleural fluid proteins, cells, and particulate matter to exit from the pleural space. These contents empty through Cohn's pores or so-called stomata, which are found mainly in the lower part of the costal pleura. These stomata intermittently open and close during breathing, and it is also the breathing movements that force the lymph to continue into the lymphatic vessels, where the valves prevent the lymph from going in the wrong direction. Cells from malignant tumours in the pleura generally do not invade the lungs, but may spread to the visceral pleura and invade the lung *per continuitatem*.

1.1.1.3 Innervation

The visceral pleura has no sensory innervation. The costal pleura and the peripheral part of the diaphragmal pleura are innervated from the intercostal nerves whereas the

central part of the diaphragmal pleura is supported from the phrenic nerve (Seaton *et al* 1989a). Pleuritic pain often gives referred pain sensations. Pain from the central part of the diaphragmal pleura is felt in the shoulder and from the peripheral diaphragmal pleura in the upper abdomen.

1.1.2 Physiology of the pleural space

The pleural space has a negative pressure relative to the atmosphere due to the effect of opposite forces: the outward pulling force of the thoracic cage and the inward recoiling force of the lung. These forces make breathing movements very energy effective, i.e. very little energy is consumed in the healthy person at rest when breathing. The pulmonary and systemic circulation, the lymphatic drainage, the low colloid osmotic pressure, and the movement of the chest cage and the heart cooperate to keep a minimal amount of serous liquid in the pleural cavity. Animal model studies have shown that under physiologic condition, the capacity of the lymphatic fluid removal normally greatly exceeds the fluid formation (Broaddus *et al* 1988).

1.1.2.1 Pleural fluid

Under physiological conditions the amount of fluid in the pleura is small, less than 1 ml in man, but in a few cases up to 20ml can be found (Yamada *et al* 1933). The fluid forms a layer of about 10 µm thickness and acts as a lubricant between the visceral and parietal pleurae (Agostoni *et al* 1969, Butler *et al* 1995). Its content of protein is about 1-2 g /100 ml and has about 1400 to 4500 cell per 1 µL, consisting mostly of macrophages, a few lymphocytes, and some red cells (Yamada *et al* 1933, Miserocchi *et al* 1971). It is estimated that the amount of fluid turnover in a normal pleural space is about 300 mL/day (Andrews *et al* 1994).

The colloid osmotic pressure is lower in the pleura than in the plasma due to a lower content of proteins. This gradient regulates the fluid filtration in and mainly out of the pleural space. Liquid and small particles less than 4 nm pass freely between the mesothelial cells (Zocchi *et al* 1992). Cells and smaller particles like bacteria, directly or indirectly after phagocytosis, are effectively removed through the stomas of the lymphatic system of the parietal pleura. The concentration of sodium in the liquid is less than in the serum, an effect of the Donnan equilibrium (Zocchi *et al* 1991), whereas the chloride concentration is not greater than in the serum, as would have been expected taking consideration to Donnan equilibrium (Sahn *et al* 1979, Zocchi *et al* 1991). The concentration of glucose in the fluid is basically the same as that of the serum, since glucose is a small molecule that easily passes into the pleura (Sahn *et al* 1979).

1.2 DISEASES OF THE PLEURA

1.2.1 General overview

The pleura can be involved in various disease processes, such as benign or malignant tumours, localised or diffuse thickening of the pleurae, and/or fluid accumulation in the

cavity. The pleura has a great capacity to heal. Minor changes or damage to the pleura can be repaired without causing clinical symptoms or radiologic changes (Peng *et al* 1994). Even larger pleural changes that occur in diseases such as pneumonia, pulmonary infarction, heart failure, and early empyema, can regress without mechanical intrapleural intervention (Light RW 1990), leaving no traces.

Pleural fluid

A small amount of fluid accumulation can be observed in the posterior costophrenic sulcus on chest radiography. Larger amounts of free-floating fluid are easiest to detect on decubital radiography, where also a rough estimate of the amount can be made.

The aetiology of unilateral effusions includes tuberculosis, pneumonia, empyema, pancreatitis, subphrenic abscess, pleural tumour and/or metastases, lymphoma, congestive heart failure and thoracic trauma. Previously, tuberculosis was the major cause of fluid accumulation in the pleural cavity, but apart from congestive heart failure the most common cause in the industrialised parts of the world is now malignancy. The most common causes of bilateral effusions are congestive heart failure, connective tissue diseases, and diseases associated with hypoproteinemia as in cases of renal and/or hepatic disease.

The most prominent symptom of excessive accumulation of fluid in the pleural space is dyspnea. Cough, probably due to compression of lungs and bronchi, can also occur. Chest pain is due to tumour involvement or irritation of parietal pleura or damage to the rib. The degree of symptom depends on the quantity of the accumulated fluid, the patient's underlying pulmonary function, and how fast the fluid accumulates. A very slow filling of the pleura will cause the patient to adapt gradually to the new situation and consequently will not feel very dyspnoic. About 25 percent of patients with malignant pleural effusion are asymptomatic at the time of diagnosis (Chernow *et al* 1977).

1.2.1.1 Pathophysiology of pleural fluid

Accumulation of fluid in the pleural space may theoretically be due to both increased fluid formation and decreased capacity of the lymphatics to remove fluid, and probably in most cases both mechanisms are involved (Light *et al* 1997). As mentioned, the parietal pleural lymphatics have the function of resorption of fluid and proteins. Interference with the lymphatic system at any point between the parietal pleura and the mediastinal lymph nodes can result in pleural effusion. Malignant fluid accumulation is probably due mainly to decreased fluid clearance rather than increased formation of fluid (Leckie *et al* 1965). The very large reserve capacity of the lymphatic mechanism could be one of the reasons why metastases to the pleurae do not necessarily lead to effusion.

In tuberculous pleurisy an exudative early phase with little signs of inflammation is seen, whereas cessation of exudation is related to inflammation, with thickening of the pleural wall, fibrin formation and generation of adhesions. The adhesions are soon organised with formation of connective tissue and blood vessels. This series of events

has been demonstrated to take place within two weeks in experimental pleurisy induced by BCG (Widström *et al* 1982).

In malignant pleural effusion the pleural surface generally shows little signs of inflammation.

Our clinical impression is that fluid production seems to be related to tumour histopathology, tumour quantity, and presence of an intact pleural surface. Fibrotic surfaces seem to have a reduced tendency to produce fluid. Malignant pleural fluid may be serous, serosanguineous or bloody, and the fluid is usually an exudate. Bloody exudation gives a rather high probability of malignant aetiology (Mårtensson *et al* 1985). The occurrence of erythrocytes in the malignant effusions may be due to direct tumour invasion of blood vessels, occlusion of venules, or release by the cancer cells of vasoactive substances increasing capillary permeability (Meyer 1966). The increased fluid production could also be due to such substances, one of which might be VEGF (Vascular Endothelial Growth Factor), a very potent vasodilator (Dvorak *et al* 1991).

The normal pleural fluid has a very high activity of fibrinolysis (Agrenius *et al* 1989, Agrenius *et al* 1991). Chemical pleurodesis causes inflammation and destruction of the mesothelial surfaces. On instillation of the substance, the mesothelial cells produce interleukin-8 (IL-8) which in turn causes inflow of neutrophils and accumulation of macrophages, which in their turn generate continuous inflammation and proliferation of fibroblasts and fibrin precipitation, resulting in a pleural fibrosis (Van den Heuvel *et al* 1998, Miller 1999).

Thus, pleurodesis causes adhesions, vascularisation and fibrosis, similar to the findings in tuberculous pleurisy. To achieve this, presumably the fibrinolytic activity of the pleura must first be diminished. To clarify if this is actually the case, our group investigated the fibrinolytic and coagulation activity in the pleura during pleurodesis. During pleurodesis treatment the fibrinolytic activity showed a decrease. Coagulation activity measured as thrombin activity increased. Thus, inflammation causes formation of fibrous tissue, which in turn diminishes the exudation (Agrenius *et al* 1989, Agrenius *et al* 1991).

The inflammatory process caused by pleurodesis also causes systemic effects. Thus, there is usually a rise of body temperature within 24 hours after instillation of the agent. This temperature rise can be seen as an indicator of the induced inflammation in the pleural space.

1.2.2 Malignant pleural effusion

1.2.2.1 Incidence

The incidence of malignant effusion increases with ageing. In a study from Central Bohemia, the overall incidence of pleural effusion was 0.32 per cent in the general population (Marel *et al* 1993). Almost half were due to congestive heart failure, but malignancy caused 31%, i.e. the incidence of malignant pleural effusion was about 0.1 per cent. This seems a little high for Swedish material, in the catchment area of the

Karolinska Hospital we should then see around 800 cases a year, whereas at the respiratory division we in fact see about 100 cases a year, but probably many are never referred.

In some patients pleural effusion is the first manifestation of disease, otherwise effusions develop during the course of disease progression. Between 90 and 95 per cent of all malignant effusions are caused by metastases and the rest, 5-10 per cent, are caused by a primary mesothelial tumour, i.e. by a mesothelioma.

Malignant effusions have no specific visible characteristics, they may be serous, serosanguineous, sanguineous/hemorrhagic or chylous, mostly seen in non-Hodgkins lymphoma which can obstruct the thoracic duct. Malignant effusions are usually an exsudate but can be a transudate depending on the stage/spread of disease.

1.2.2.2 Anti-cancer treatment associated effusions

Few cases of malignant effusions can resolute spontaneously and some may disappear after systemic chemotherapy or steroids as in myelodysplastic syndromes (Hicsonmez *et al* 1998). Radiotherapy of some malignant diseases can by itself cause pleural effusion, through radiation pleuritis or lymphatic vessels obstruction caused by fibrosis induced by irradiation (Rodriguez-Garcia *et al* 1991, Morrone *et al* 1993), that can lead to lymphatic leakage (Van Renterghen *et al* 1995). Ueda *et al* (2000) observed that about 30% of all patients that had undergone bone marrow transplantation developed pleural effusion.

1.2.2.3 Primary tumours

Involvement of the pleural space is either through direct growth, as in most of the cases of bronchial carcinoma, or through lymphatic or haematogenous pathways. Almost all types of malignancy can spread to the pleural space but the most common primary tumours are bronchial in men and mammary in women. Pleural effusion occurs in 7 - 15% of all patients with bronchial carcinoma (Sahn 1985). Other common primaries are ovarian and stomach cancers and lymphomas. These carcinomas account for about 80% of all malignant effusions (Sahn 1998). Pleural involvement is more frequent in non-Hodgkin's lymphomas than in Hodgkin's lymphoma (Blank *et al* 1980), but the incidence increases in Hodgkin's lymphoma as disease progresses (Wong *et al* 1963). Johnston WW (1985) reported that 10% of malignant pleural effusions with positive cytologic examination were due to non-Hodgkin's lymphomas. Sarcoma is rarely associated with malignant effusion (Meyer 1966). Pleural malignancy of unknown origin accounts for a number of cases, mostly of adenomatous origin.

Of the types of lung cancer, adenocarcinoma is the cell type that most commonly spreads to the pleura, probably because of its nature of peripheral location (Hsu 1987). Metastases from mammary carcinoma occur either through invasion of the chest wall, resulting in ipsilateral effusion, or via haematogenous spread, when both pleurae may be victims (Fentiman *et al* 1981).

Paramalignant effusions are usually caused by lymphatic obstruction (Chernow *et al* 1977).

1.2.2.4 Chylothorax

Chylothorax, i.e. pleural effusions consisting of chyles, the special lymph that is formed in the gastrointestinal tract, is due to obstruction of, or damage to, the ductus thoracicus through which the chylus passes. This is often associated with lymphomas (Light 1995) but also other malignancies with metastases to the mediastinum may cause compression and/or invasion of the thoracic duct and non-malignant chylothorax may result from trauma such as thoracic surgery (Le Coultre *et al* 1991), or movement of chylous ascites to the pleural space.

1.2.2.5 Prognosis

The presence of malignant effusion in patients with bronchial carcinomas indicates inoperability, and effusion caused by non-intrathoracic malignancies indicates disease extension and limited survival (Decker *et al* 1978, Sahn 1988). Both groups have a deteriorated quality of life, which, if pleurodesis can be performed, will improve, even if their life expectancy is low because of the nature of the underlying disease. The median overall survival time in one series of 120 treated patients was nine months (Martinez-Moragon 1998) and in another series it was seven months (Schulze 2001). As could be expected, the survival after pleurodesis is dependent on the underlying disease: about four months for lung cancer, seven for mammary cancer and nine for ovarian carcinoma (Sanchez-Armengol 1993).

1.2.2.6 Diagnostic approach

There are three major ways to diagnose a pleural malignancy: fluid cytology, closed needle pleural biopsy, and thoracoscopic biopsy. These diagnostic approaches give different success rates.

1.2.2.7 Cytology

The yield of pleural fluid cytology is around 40-87 % (Collins *et al* 1987, Grunze 1964). The yield increases as disease progresses (Salzer *et al* 1975). This means that some patients with established malignancy could have cytology negative pleural effusions at an early stage of effusion and later become positive. The sensitivity for diagnosis is not dependent on the quantity of pleural fluid volume analysed (Sallach *et al* 2002).

1.2.2.8 Closed needle biopsy

This is a diagnostic intervention with a minimal invasive technique using a biopsy needle, performed without direct visualisation (Winkelmann *et al* 1981, Prakash *et al* 1985) or with image guidance (Screaton *et al* 2000, Metintas *et al* 1995). It was introduced by DeFrancis in 1955 and later improved by Abrams (Abrams 1958). This technique is most successful where the disease process in the pleura is generalised, such as in tuberculosis pleurisy, and less successful where the pleural involvement often is patchy, as in pleural malignancy (Tomlinson *et al* 1987).

1.2.2.9 Thoracoscopic biopsy

This is the best diagnostic intervention for pleural diseases (Menzies *et al* 1991, Oldenberg *et al* 1979). It is usually performed by a non-surgeon (medical thoracoscopy) under local anaesthesia and conscious sedation. It allows visualisation of the pleural space and guided biopsy samples. The diagnostic yield for malignant pleural disease has a very high specificity and sensitivity (Boutin *et al* 1980, Blanc *et al* 2002). However, a limitation is extended and/or complete adhesion of the pleura, which does not allow the induction of pneumothorax.

1.2.3 Treatment

1.2.3.1 Specific therapy

A few patients with malignant pleural effusions have tumours that are responsive to systemic cytostatics and/or endocrine treatment, thereby resolving effusions and achieving relief from associated symptoms. Examples are small cell lung carcinoma, mammary carcinoma, and lymphomas. The ligation of the thoracic duct (O'Callaghan *et al* 1995) is theoretically possible in cases of recurrent chylothorax but these patients with malignant diagnosis are usually not in medical condition to undergo such surgical intervention. Mediastinal radiation therapy is also an option for recurrent chylothorax (Roy *et al* 1967). Conservative treatment with fat-free nutrition is not recommendable for these patient groups. Most patients with carcinoma of the breast and effusions respond to hormonal therapy (Levine *et al* 1986). However, cessation of fluid production is not always achieved in these patients. Chemical pleurodesis should therefore be considered in addition to the specific treatment. Local administration of neoplastic drugs into the pleural space is not sufficiently effective. External radiation is not used in the treatment of malignant effusions because of the large area (hemithorax) involved. The adverse effects such as pneumonitis are greater than the benefits.

1.2.3.2 Surgical pleurectomy

Surgical pleurectomy can also be used in controlling metastatic malignant effusion. This surgical intervention is associated with certain morbidity and mortality and is rarely used nowadays but might be considered in selected cases.

1.2.3.3 Thoracocentesis

Generally, thoracocenteses only lead to temporary relief of symptoms. The total lung capacity (TLC) increases with about 30% of the amount of fluid removed and the forced vital capacity (FVC) increases with about 50% of TLC (Judson *et al* 1995). Patients with extensive tumour growth that might cause atelectasis of a large part of the lung, infiltration of the lung parenchyma, or extensive growth into the mediastinum, will usually not benefit from thoracocentesis, or to only a minor degree. In these cases, pleurodesis should not be considered. In some cases, where the general condition and expected survival of the patients is poor, thoracocentesis could be the only choice of palliation, even if it has to be performed repeatedly. Indeed, the patients could live at home with an in-dwelling catheter and even learn to empty their pleural space themselves (Leff *et al* 1986, Pien *et al* 2001).

1.2.3.4 Pleuroperitoneal shunt

In selected patients, a shunt can be placed in the pleura and, via a subcutaneous channel where a hand-driven pump is placed, the fluid can be transported to the peritoneal cavity and be resorbed there. Limited experience of this method exists but it can evidently be a useful alternative in some cases (Murphy *et al* 1989, Tsang 1990, Petrou *et al* 1995).

1.2.3.5 Chemical pleurodesis

If the condition of patients and their expected survival is good, the best palliation is to achieve a permanent stop of fluid accumulation in the pleural space with chemical pleurodesis. In some cases, thoracentesis alone and especially together with a suction tube can activate the inflammatory process. However, in most cases a chemical pleurodesis will be needed.

If the mesothelial cells are covered by extensive tumour growth, the instilled agents have a limited contact with the metabolically active mesothelial cell and the success of pleurodesis is reduced (Sahn 2000). Another factor for a good result is that the lungs are sufficiently expanded before pleurodesis, i.e. before the lungs become “trapped” by fibrin and/or tumour cells, making expansion difficult or impossible. The earlier a pleurodesis is performed the better it is, because recurrent thoracenteses lead to a risk of fibrin and/or malignant cells covering the pleural surface, thereby restricting expansion of the lung (Hillerdal 1995) making pleurodesis less effective.

Other factors shown to increase the risk of failure are a low pleural fluid pH and a low glucose content (Martines-Moragon 1998). This should not, however, be used for assessing patient eligibility for pleurodesis.

There is a long list of agents that have been used locally in the pleura to achieve chemical pleurodesis. Some examples are:

Antineoplastic drugs: Thiotepea (Anderson *et al* 1968), nitrogen mustard (Anderson *et al* 1974), mitoxantrone (Groth *et al* 1991), vincristine (Vidyasagar 1999), and bleomycin (Martines-Moragon 1997+98, Norum *et al* 1994).

Antibiotics or other substances that are toxic to the mesothelial cells, such as mepacrine (Stiksa *et al* 1979, Hillerdal), tetracycline (Gravelyn *et al* 1987, Martines-Moragon 1997+98), Doxycycline (Månsson 1988), radioactive phosphorus (Izbicki *et al* 1975), gold (Ariel *et al* 1966), corynebacterium parvum (Millar *et al* 1979), talc either as poudrage (Bethune 1935, Vargas *et al* 1994), or as a slurry (Kennedy *et al* 1994).

Various studies of the different agents have shown different success rates and different toxicity profiles. Some comparative studies have been made: tetracycline vs. Bleomycin (Martinez-Moragon *et al* 1997), mepacrine vs bleomycin (Koldsland *et al* 1993), talc slurry versus talc poudrage in pigs (Cohen *et al* 1996), bleomycin vs doxycycline (Patz *et al* 1998), tetracycline vs *Corynebacterium parvum* (Hillerdal *et al* 1986).

The agent(s) of choice have thus not been defined in the literature. Two agents are of special interest for this work: quinacrine (mepacrine), which has been used for some decades in Sweden and with which there is considerable experience; and talc, which is now probably the most commonly recommended agent in most centres world-wide.

1.2.3.6 Quinacrine

Quinacrine was used originally as an anti-malarial agent during and after World War II, then given for longer periods and in much higher doses than those used for pleurodesis. In this setting, serious central nervous complications occurred (Engel 1947). Cellular studies suggested that the substance could also act as a cytostatic, and therefore it was suggested to be used intrapleurally and has been used as a pleurodesis agent since the 1960s (Gellhorn *et al* 1961, Ultman 1963, Dollinger 1967, Hickman 1970). The early reports showed only minor and unimportant side effects, despite the substance being installed in the pleura for 3 to 5 consecutive days (Ultman 1963).

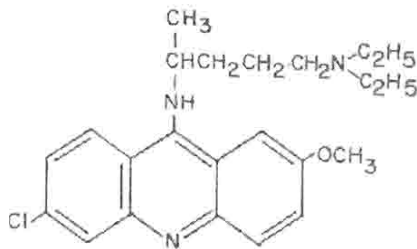


Figure 1. Structural formula of quinacrine.

However, because of the experience from anti-malarial treatment, serious warnings were published when it was suggested to use the drug for pleurodesis (Engel 1966). In fact, a number of CNS side effects were reported, such as hallucinations (Borja *et al* 1973) and convulsions (Borda *et al* 1967), and the substance therefore never became very popular in large parts of Europe or in the USA. In most reviews ever since, quinacrine has been dismissed with a few lines stating that it was too toxic to be used (Andrews *et al* 1994). Nevertheless, a few centres in Europe had already started using this substance, and since their experience was different, i.e. few side effects and those that occurred were easily treated, they have continued to use it. Siksa reported 121 cases with 87% success.

One of these centres is the Respiratory Division of the Karolinska Hospital, with more than three decades of experience. The results are good, well above 80% successful pleurodesis and, as mentioned, only rare side effects.

1.2.3.7 Talc

Talc ($Mg_3Si_4O_{10}[OH]_2$) was first used in man to produce pleural symphysis in 1935 (Bethune 1935) and since then has a long history of use in Europe, especially in France and the Netherlands where it has even been used for pleurodesis in treatment of pneumothorax (Janssen *et al* 1994). The results have been satisfactory. For a long period the drug of choice in the United States was Tetracycline, despite the rather poor results published in some papers. The main advantage with this substance is the low price and comparatively low incidence of serious side effects. However, this substance is no longer provided for intrapleural use and therefore a new substance had to be found. This substance seemed to be talc, which is increasingly recommended (Kennedy 1994, Walker-Renard *et al* 1994).

Very good results have been reported from use of talc. Of 327 evaluable patients treated with talc poudrage the success rate was 90.2% and the side effects were few: 9.8% fever, 2.5% empyema (Viallat 1996). Very good success rates have also been reported by others (Boniface 1989, Milanez 1995, Aelony 1998, de Campos 2001, Engeler 1992).

Talc has also been used for treatment of pneumothorax with good results (Milanez *et al.* 1994, Tschopp 2002).

A serious side effect is an ARDS syndrome which seems to occur even after low doses, even if it is more common with higher doses. Recently, the size of the particles has also been shown to be of importance: the larger the talc, the less systemic spread and the fewer side effects (Ferrer 2002; Fraticelli 2002). Various talc preparations vary markedly in size (Ferrer 2001). In Europe, mainly French talc is used from a mine in southern France, while in the US the talc comes from American mines.

Serious side effects, sometimes life-threatening, have been reported for other agents as well (DiBardino *et al* 2002).

1.2.3.8 Rationale for comparing talc and quinacrine

In the late 1990s, it seemed that talc would become the main agent used for chemical pleurodesis all over the world. As mentioned, quinacrine was still used in Sweden and other European centres, since we were never satisfied with the results of doxycycline. It was therefore logical and necessary to compare these two agents as regards efficiency and side effects and such a study was also performed (**paper III**).

1.3 THE PRESENT STUDY

1.3.1 The aims of the present study

This series of studies elucidates different aspects of pleurodesis.

1.3.1.1 Paper I

To determine the role of interleukin-1 β in pleural fluid during pleurodesis since IL-1 β could explain many of the events seen during pleurodesis treatment.

Is IL-1 β involved in fever reaction?

Is IL-1 β involved in the increase of pleural inflammation and decrease of fibrinolytic activity?

1.3.1.2 Paper II

To evaluate the effect of pleurodesis on respiratory function.

Successful pleurodesis is achieved by the formation of fibrous adhesion between the lung and the parietal pleura, which in theory might restrict lung mobility.

Does pleurodesis compromise respiratory function?

Does pleurodesis lead to a better quality of life?

1.3.1.3 Paper III

A prospective randomized study comparing the effects of talc and quinacrine.

Which of these agents has the best efficacy?

Do they differ in regard to adverse effects?

1.3.1.4 Paper IV

To describe the systemic inflammatory reaction following intrapleural sclerosing agent instillation and to investigate if the reaction had any predictive value on pleurodesis outcome.

Can markers used daily, such as erythrocyte sedimentation rate, C-reactive protein, leukocyte count from venous blood samples and fever reaction, predict treatment outcome?

1.3.1.5 Paper V

Long-term survival of patients with malignant pleural effusion after chemical pleurodesis.

Which groups of patients with malignant effusion are most suitable for pleurodesis?

Should all malignant pleural effusions, irrespective of primary site, be treated with pleurodesis?

2 MATERIAL AND METHODS

2.1 PATIENTS AND METHODS

A procedure common to all five studies was the procedure of pleurodesis, which is the routine at the Division of Respiratory Medicine, Karolinska University Hospital. The procedure involved thoracentesis, with removal of pleural fluid (mean 860 ml, range 500-1800 ml) and insufflation of approximately 500 ml of room air. Chest radiography on decubital position with the affected side up was performed to assess the relation between the chest wall and the lung. Thoracoscopy was then performed in local anaesthesia with conscious sedation. The remaining fluid was evacuated to allow inspection and direct biopsy tissues were obtained. Finally, a chest tube drainage (6.7 mm x 50 cm, Sherwood Medical, Tullamore, Ireland.) was inserted and connected to suction starting from -5 cm H₂O and gradually increasing to -15 cm H₂O. Chest radiography was performed on the following days and, when the lung had expanded sufficiently, the sclerosing agent, dispersed in saline, was instilled through the drainage tube. The tube was clamped for two hours, after which suction was resumed. The tube was removed when the fluid production was less than 50 ml/24 hours. The procedure lasted 4-10 days.

2.1.1 Paper I

Pleural fluid samples were collected for analysis on five occasions, at initial thoracentesis, just after the insertion of drainage tube at thoracoscopy, 24 hours after insertion of tube, 24 and 48 hours post instillation of quinacrine.

2.1.2 Paper II

This was a retrospective study in which ten patients who were previously treated (1-102 months) with pleurodesis, and who were in good general health with the underlying malignancy under control were included. Patients were investigated with spirometry, exercise test, blood gases and radiosprometry.

2.1.3 Paper III

Performance status according to WHO was evaluated before thoracentesis irrespective of origin to recurrent effusion. When the lung was sufficiently expanded, patients were randomised to either talc or quinacrine. Daily fluid production was measured and adverse effects were registered and treated. Follow-up was on four occasions during a six-month period from the date of pleurodesis.

2.1.4 Paper IV

This study was selectively made on recurrent malignant effusion from patients in paper III. Body temperature was measured with an ear thermoscan (Braun, Germany) at the fourth, eighth, hour after instillation of the drug, and then every twelfth hour. Venous blood samples for analysis of Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP), and leukocyte count were acquired every 24th hour until the drainage tube had been removed.

2.1.5 Paper V

A retrospective review of hospital records of all patients discharged from the hospital after successful chemical pleurodesis from January 1, 1991 to September 30, 1994. Where time of death was unknown, the Swedish National Death registry was consulted to obtain the date of death. Patients were grouped into different diagnosis categories. Survival was calculated using the method of Kaplan and Meier.

3 RESULTS

3.1 PAPER I

During pleurodesis treatment of malignant pleural effusions an inflammatory reaction is evoked by insertion of a tube drainage and instillation of an irritant. There is a rise in fever in the patient within 24 hours after quinacrine instillation. The pleural fluid accumulation decreases. As has been shown earlier, the treatment leads to decreased fibrinolytic activity and increased fibrin formation in the pleural space, which seems to be important in stopping pleural exudation. These events could be influenced by IL-1 β and the aim of this study was to evaluate a possible connection.

IL-1 β was found in the untreated malignant pleurisy, and levels remained unchanged after thoracoscopy and tube drainage. After quinacrine instillation, IL-1 β levels increased and pleural fluid production decreased. There was a correlation between levels of IL-1 β , pleural fluid production and drainage time, indicating that IL-1 β had a promoting rather than an inhibitory effect on fluid production. Another observation was that patients, earlier treated with anti-cancer chemotherapy, seemed to exhibit a lower rise in IL-1 β and a shorter drainage time. However, the pleurodesis treatment was equally successful in all patients whether they had previously received anti-cancer treatment or not. In this study, there were no correlations between IL-1 β levels and degree of fever, pleural leucocyte content, activation of coagulation (increase of levels of FPA) or inhibition of fibrinolysis (decrease in levels of D-Dimer).

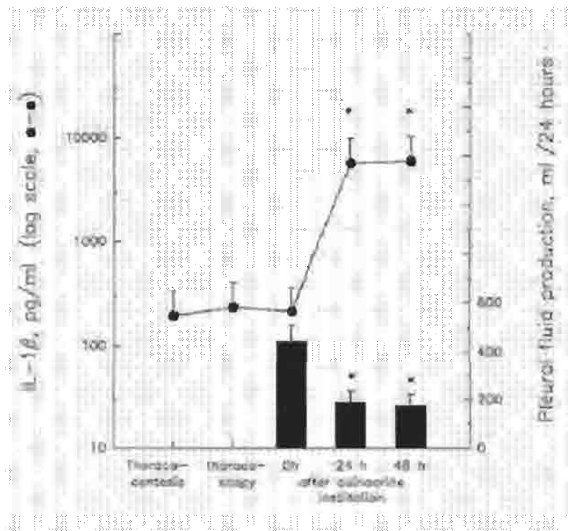


Fig. 2. IL-1 β levels (●: log scale) in pleural fluid from patients treated for malignant pleurisy. Pleural samples collected at thoracocentesis, at thoracoscopy, and from the drainage tube before (0 h) and 24 and 48 h after quinacrine instillation. Mean values \pm SEM. Comparisons have been made with values on the first thoracocentesis. The statistical calculations concern 12 patients in whom samples were obtained on all five occasions. In 1 patient no data were available because no fluid was produced at 48 h. The volume of pleural fluid (■) decreased, i.e., in a comparison with levels at 0 h, in evidence of a significant decrease in fluid production. * $p < 0.001$.

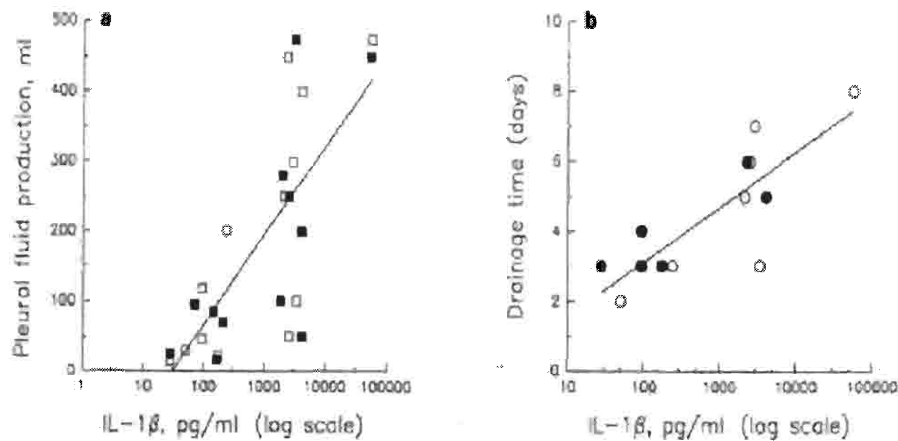


Fig. 3. a Relation between pleural fluid production and the levels of IL-1 β in the pleural fluid. There is a significant correlation, Spearman, $r = 0.77$ ($p < 0.002$ two-sided test). \square = 0–24 h; \blacksquare = 24–48 h. **b** Relation between the tube drainage time after quinacrine instillation and the levels of IL-1 β in pleural fluid. There is a significant correlation, Spearman, $r = 0.70$ ($p < 0.01$ two-sided test). \bullet = Anti-cancer chemotherapy; \circ = no chemotherapy.

3.2 PAPER II

Successful pleurodesis leads to permanent cessation of fluid accumulation as a result of the formation of fibrous adhesion between the lung and costal pleura, which in theory, might restrict lung mobility. In patients with a poor lung function, or with a need for bilateral pleurodesis, the apprehension of further impairment of lung function often arises. The aim of this study was to evaluate the effects of pleurodesis on lung function. Therefore 10 patients without radiological signs of tumour infiltration and without visible signs of tumour growth in the pleura at thoracoscopy were investigated with static and dynamic spirometry, exercise testing with blood gas determination and with radiospirometry.

Spirometry values were low but within reference limits. Blood gas determination showed no signs of alveolar hypoventilation. Radiospirometry showed a slight attenuation of activity in the treated lung but a similar turnover of gas in the treated versus the untreated side. The study showed that pleurodesis in malignant pleurisy has only a minor impact on respiratory function.

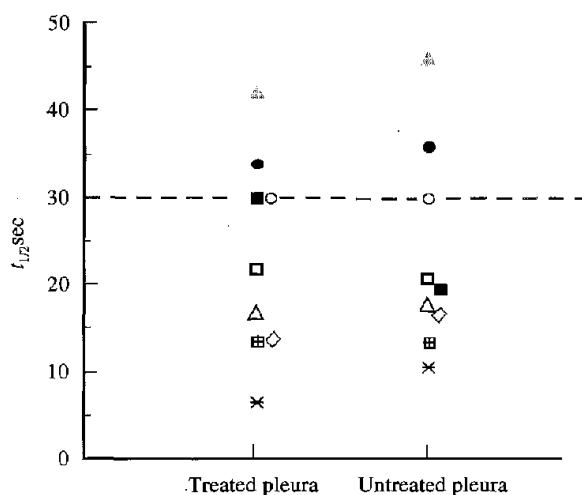


Figure 4. Washout time ($t_{1/2}$) for xenon in 9 patients after successful one-sided pleurodesis. Each patient is represented by identical symbols for the treated/untreated pleura. The dotted line represents the highest normal value.

3.3 PAPER III

A total of 110 patients, 43 women and 67 men, were included and randomised to either quinacrine/mepacrine or talc pleurodesis. Thoracoscopy was performed in local anaesthesia in all patients. The chest roentgenograms were evaluated at 2 weeks and then 2, 4, and 6 months after pleurodesis.

There were 54 patients in the quinacrine/mepacrine group and 56 in the talc group. All had a malignancy except 21 patients (18 per cent) in which the pleural malignant aetiology was suspected but not confirmed.

Primary success rate, as measured by a production of 50 ml of exudate or less over 24 hours within the first six days, was good (96 per cent in the talc group versus 89 per cent in the mepacrine group, difference statistically not significant). Patients receiving mepacrine needed significantly more often a repeated treatment than patients treated with talc (20% as compared with 4%, $p < 0.05$). On the other hand, patients treated with talc had a tendency to need more narcotic analgesic (46 per cent) than those treated with quinacrine (35 per cent), but this was not statistically significant.

In summary, the results of this study indicate that both drugs gave good result, talc being the most efficient and is at present the drug of choice for pleurodesis.

Table 1. Success rate in the two treatment groups at end of pleurodesis procedure

	Quinacrine (n = 54)	Talc (n = 56)	95% CI for differences between treatment groups
Success at 1 st instillation	37 (68.5%)	52 (92.9%)	-0.384; -0.103
Success at 2 nd instillation	12 (22.2%)	2 (3.6%)	0.065; 0.307
Failures	5 (9.3%)	2 (3.6%)	-0.034; 0.148
Overall primary success	49 (90.7%)	54 (96.5%)	-0.148; 0.034

3.4 PAPER IV

Eighty-nine prospective patients with verified malignant pleural effusion that received pleurodesis with either talc (48 patients) or quinacrine (41 patients) were included in this study. The study was aimed to describe the systemic inflammatory reaction following the use of an intrapleural sclerosing agent and to investigate if the reaction had any predictive value on the pleurodesis outcome. The markers investigated were erythrocyte sedimentation rate, C-reactive protein, and leukocyte count from venous blood samples, and fever reaction.

Symphysis was achieved in 82 patients (92%) and all had a prominent transitional elevation of the inflammatory parameters. The unsuccessful attempts (8%) caused negligible or very small elevations, but due to the small number only the degree of fever after 8 and 48 hours post intrapleural instillation showed a statistically significant difference.

It was observed that patients with high baseline values of these inflammatory markers were amongst those with unsuccessful pleurodesis. This may be assumed as an expression of advanced and refractory disease, hence treatment failure.

Talc evoked a higher inflammatory response than quinacrine, which might explain one of the reasons why the talc-treated patients much less often need a second intrapleural instillation but, on the other hand, more often needed pain-killers.

In conclusion, pleurodesis causes a systemic inflammation and there is a tendency to a correlation between the success of pleurodesis and the degree of inflammation. Talc causes a significantly higher inflammatory reaction compared with quinacrine, (Figure 6).

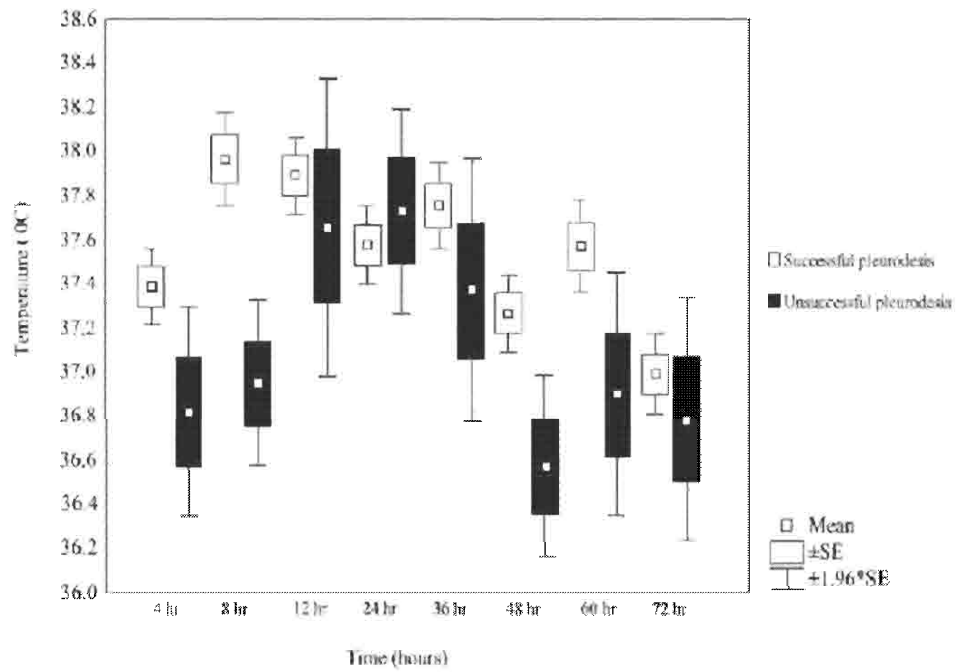


Fig 5. Time course of intrapleural drug instillation on fever reaction (centigrade) in successful and unsuccessful symphysis. The main effect of time* outcome interaction was statistically non-significant, $p = 0.30$.

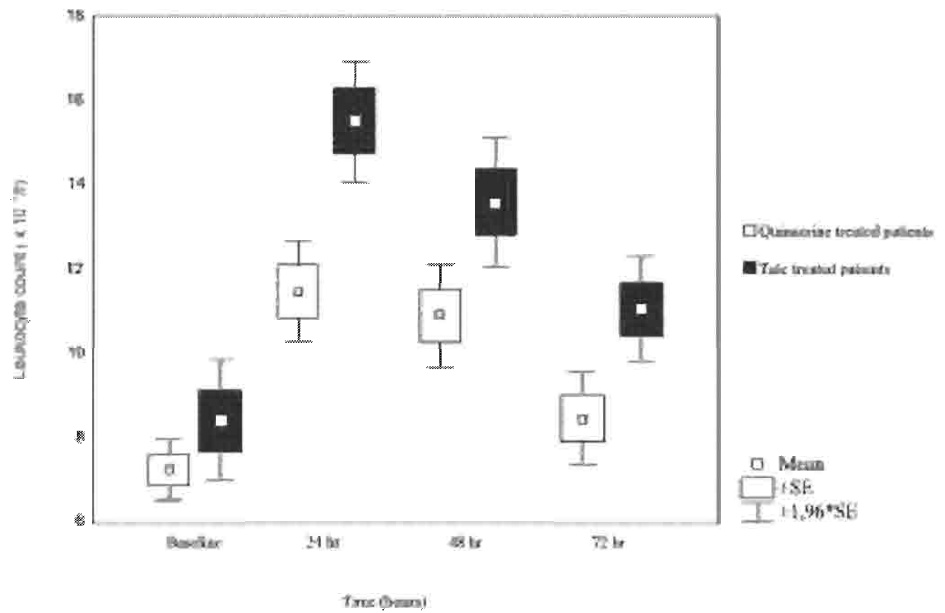


Fig 6. Leukocyte count in the quinacrine and in the talc treated patients, $p = 0.001$.

3.5 PAPER V

The aim of this retrospective study was to investigate results and survival after pleurodesis in patients with different primary tumours. Patients included in the study were those with malignant effusion who were discharged from our clinic during the period from January 1, 1991 to September 30, 1994 after a successful chemical pleurodesis, a total of 197 patients. The four most common primary tumours were lung, breast, lymphoma and ovarian malignancies.

The median survival from pleurodesis in the entire study population was 135 days (Figure 7). Breast cancer had the best prognosis with a median survival of 216 days. In lung cancer patients, the median survival was 55 days whereas in patients with lymphomas median survival was 168 days. The longer the time from diagnosis of primary tumour to effusion, the better the prognosis (Table II).

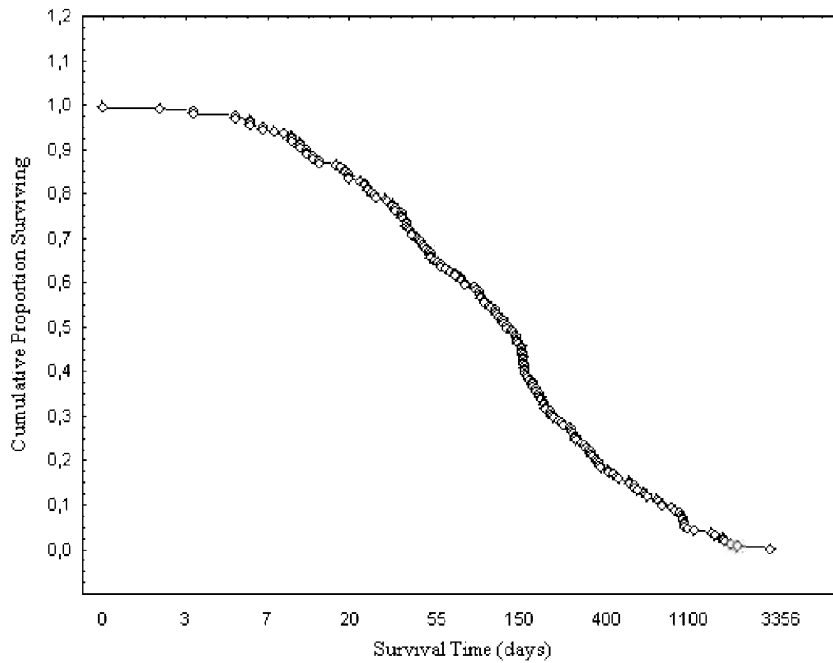


Figure 7. Survival of the entire study population.

Table II. Median survival time (days) after pleurodesis for tumours of different origin. Time from primary diagnosis to diagnosis of effusion for breast cancer is specified

Tumour types and time of effusion	n	Survival from time of pleurodesis median (range, min - max)
Lung cancer:	58	55.5 (3 - 486)
3.1.1		
Breast cancer:	53	216 (1 – 2045)
effusion as 1 st symptom	3	311 (20 - 1306)
7 - 12 months	3	205 (151- 711)
13 - 60 months	22	136 (1 - 2045)
> 60 months	25	421 (2 - 1167)
Lymphoma:	12	167.5(5 – 2216)
Ovarian cancer:	10	163.5(12 – 3308)
Kidney cancer:	6	90,5(6 – 1691)
Mesothelioma:	6	191.5 (11 - 1850)
Unknown primary sites:	39	151 (6 - 1612)

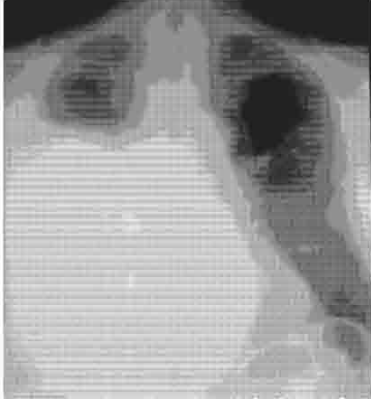


Figure 8. Chest x-ray showing a large right-sided malignant pleural effusion at time of admission.



Figure 9. Film after thoracentesis prior to thoracoscopy.



Figure 10. Chest film after thoracoscopy, chest tube inserted in the right-sided pleural space, lung fully expanded and quinacrine instilled



Figure 11. Pleurodesis achieved, chest tube removed. Patient ready to be discharged from hospital.

4 DISCUSSION

At thoracoscopy of chronic pleurisy, inspection reveals classic macroscopic inflammatory changes such as swelling/thickening, hyperaemia, redness and fibrin of variable degree depending on duration of effusions. On local instillation of irritants for pleurodesis, a strong inflammatory reaction is triggered resulting to cessation of fluid accumulation in the majority of patients (Thorsrud 1965, Stiksa *et al* 1979). In experimental pleurisy caused by BCG there was a prominent fibrin deposition and adhesions as a result of the inflammatory reactions evoked (Widström *et al* 1982). This is additional evidence to confirm the relation between fibrin formation and cessation of fluid accumulation. Unlike in cases of pneumothorax with a risk of developing tension pneumothorax, the chest tube removal should be done immediately after the completion of pleurodesis to limit the risk of pleural space infection. The tube can either be removed at the end of inspiration or end of expiration (Bell *et al* 2001).

Systemic chemotherapy is known to have anti-inflammatory effects but we have earlier shown that, in general, recent systemic chemotherapy treatment should not negatively influence the outcome of pleurodesis (**paper I**). Pleurodesis can be offered to the individual patient who develops effusion when undergoing systemic treatment because the earlier the pleurodesis intervention the greater the possibility to stop of fluid accumulation.

Due to the symphysis caused by pleurodesis, a successful pleurodesis might restrict lung mobility and thereby respiratory function. The literature on this subject is limited and no previous studies on the influence of pleurodesis on respiratory function in malignant effusions have been published. Some observations (Hardman *et al* 1994, Boersma *et al* 1995) have shown that local and/ or locoregional radiotherapy to the chest wall impairs respiratory function. Patients in need of this type of radiotherapy are mostly those with breast carcinoma and lymphoma both diagnoses contribute a high percentage of patients with pleural effusions and were also represented among the included patients (**paper II**). Although the patients included in this study had minimal tumour burden, their respiratory function did not show strikingly abnormal values. In this study, quinacrine was the sclerosant used, but we assume that the result would be similar if talc was the pleural sclerosant.

Talc and quinacrine are among the long list of agents used for pleurodesis, but in the recent decade talc has been more widely used both as slurry through a chest tube or as insufflation at thoracoscopy (Yim *et al* 1996). Studies have shown that both methods gave similar success rates (Hartman *et al* 1993, Kennedy *et al* 1994). In the literature, the administered dose of talc varies from 2-5 g but occasionally up to 10 g. Even at a low dose of 2 g, serious adverse effects have been reported and at autopsy talc crystals were found in almost every organ (Campos *et al* 1997), but no adverse effects were seen in this study (**paper III**) with a dosage of 5 g. Although a small percentage of patients in the talc group needed a second instillation, they got the same initial dosage of 5 g, but some clinicians recommend that a slightly higher dose be tried on

account of a dose-response relationship being found in animal models (Light *et al* 1995).

Quinacrine has been the routine drug used in the Division for more than two decades with very good success rates and serious adverse effects have been rare. The most serious adverse effect experienced during this long period of time concerned 3-5 patients who developed temporary confusion and hallucination and had to be treated with neuroleptics from the day of instillation to the next day.

Pleurodesis has only a minor impact on respiratory function. Because of this limited impact on respiration, patients with bilateral chronic effusions can be offered treatment that obliterates both pleural spaces, provided that pleurodesis is not given simultaneously.

The intensity of inflammatory reaction following intrapleural instillation of drug is an important factor for achieving successful obliteration of the pleural space with fibrosis tissue formation. The elevation of the basic inflammatory markers studied (**paper IV**) was transitional. Previous studies on pleural fluid glucose level and pleural pH have shown contradictory results. The small group with unsuccessful pleurodesis had a less intense systemic inflammatory reaction. The most common complication with pleurodesis is pleural infection, which can be controlled with pleural lavage and/or in combination with antibiotics.

The two most important factors that have impact on survival after pleurodesis are the type of tumour and the time interval from primary diagnosis to manifestation of effusion, the shorter the interval the less good the prognosis. Patients with breast cancer and lymphoma have the best prognosis after pleurodesis (**paper V**) but this does not mean that only these tumour types should be offered pleurodesis.

Pleurodesis enables patients to have less discomfort at the terminal stage of life either at home care or in hospice clinics, even if survival time after pleurodesis is short. Intermittent drainage is only suitable for patients whose health condition does not permit pleurodesis.

5 CONCLUSIONS

- I. Malignant pleural effusions contain interleukin-1 β . The concentration increases considerably at instillation of quinacrine and a relation was found between the level of pleural IL-1 β after quinacrine instillation and drainage time thus, the higher the amount the longer the drainage time.
- II. This study showed that successful pleurodesis does not compromise respiratory function.
- III. Talc and quinacrine are effective for pleurodesis, with 96 and 89 % success rates, respectively, and minor adverse effects. However talc seems to be a better agent because the onset of sclerosing is quicker and there is a significantly reduced need for repeated instillation.
- IV. Pleurodesis evokes inflammation locally in the pleural space, causing symphysis of the pleural sheets and also a systemic inflammation. There is a tendency to a correlation between the success of pleurodesis and the degree of systemic inflammation.
- V. Pleurodesis should be offered to all malignant effusions with reasonable life expectancy but the group of patients that benefit more from pleurodesis are those with a long interval between diagnosis of the primary tumour and manifestation of effusions.

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