

Future of Pleural Disease

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Pleural Disease Research

- Pleural disease research will continue to increase
 - Number of papers increased from 100 in 1965 to 550 in 2015
 - Highest number of papers from United States
 - Japan and Europe also publish a high number of papers
 - In the future there will be a higher percentage of papers from China, Korea and Turkey
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- Bielsa S and Porcel. *Pleura* 2016; 3:1-8

Transudative Pleural Effusion

Occurs when the **systemic** factors influencing the formation of pleural fluid are altered such that pleural fluid accumulates

Fluid may originate in the lung, pleura or peritoneal cavity

Exudative Pleural Effusion

Occurs when the **local** factors influencing the accumulation of pleural fluid are altered such that a pleural effusion develops

Most common cause is increased capillary permeability in the lung leading to increased interstitial fluid

Other mechanisms for exudative pleural effusions include:

- Obstruction of the lymphatics in the pleura
- Increased capillary permeability of the pleura or of structures in the peritoneal cavity

Why Separate Transudates from Exudates

- If patient has a transudative pleural effusion (usually heart failure or cirrhosis), then treat the cause of the effusion
- If patient has an exudative effusion, more investigation is indicated to determine what the local problem is that is causing the pleural effusion



SEPARATING TRANSUDATES AND Exudates

Light's Criteria

An exudate meets one or more of the following criteria while a transudate meets none:

- Pleural fluid/serum protein > 0.5
 - Pleural fluid/serum LDH > 0.6
 - Pleural fluid LDH $>$ two-thirds of upper normal limit for serum
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- Light RW et al. Ann Intern Med 1972; 77:507-514.

Do We Need Biochemical Tests?

For 249 patients, two physicians classified effusion as probable transudate or exudate just before thoracentesis

185 exudates and 64 transudates

Correct	Exudates	Transudates
Clinical	94%	56%
Light's criteria	99.5%	75%

Romero et al: CHEST 2002; 122:1524-1529

How Do We Identity True Transudates When Exudative Criteria Met?

Two Proposed Tests (Transudate)

Gradient = Serum Value – Pleural Fluid Value

Protein Gradient > 3.1 Gm/Dl

Albumin Gradient > 1.2 Gm/Dl

	Exudates	Transudates
Clinical	94%	56%
Light's Criteria	99.5%	75%
Protein Grad	84%	91%
Albumin Grad	88%	86%

Romero et al. Chest 2002; 122:1524-1529

Predictions - 2018

- We will continue to Initially use Light's criteria to determine if transudate or exudate; it has been good for >40 years
- The use of N terminal BNP to identify effusions due to heart failure will increase
- May find a replacement for Light's criteria
- If patient clinically should have a transudative effusion, but Light's criteria are met by a small margin (PR < .65, LDH ratio < 0.9, LDH < upper normal limit for serum), look at gradient between serum and pleural fluid protein
- Gradient above 3.1 g/dl indicates transudate

ANNUAL INCIDENCE OF PLEURAL EFFUSIONS IN THE USA

Congestive heart failure	500,000
Pneumonia	300,000
Malignant disease	200,000
Pulmonary embolism	150,000
Viral illness	100,000
Post CABG	60,000
Cirrhosis with ascites	50,000
Gastrointestinal disease	25,000
Collagen vascular disease	6,000
Tuberculosis	3,000

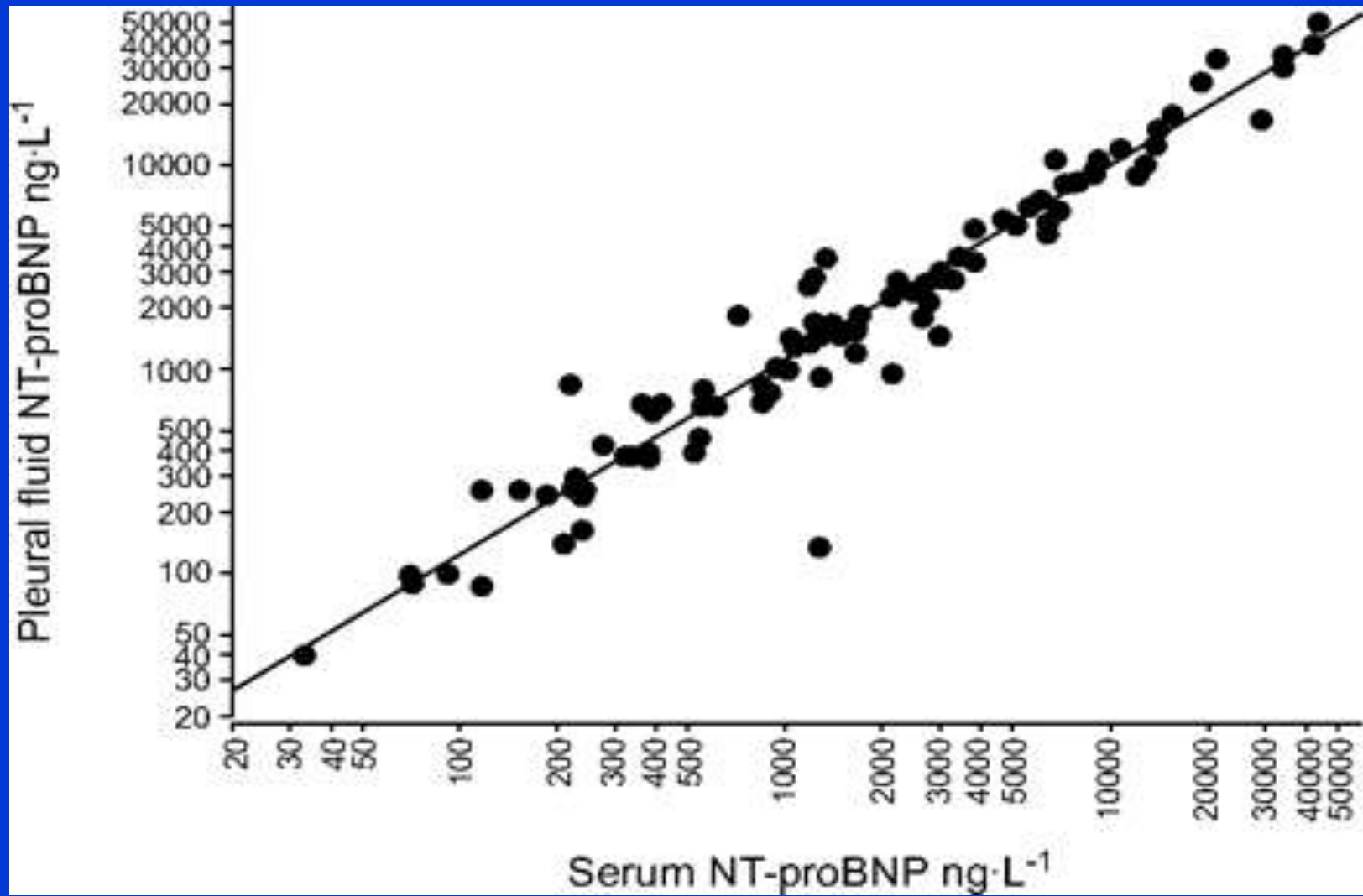


BNP and NT-pro BNP

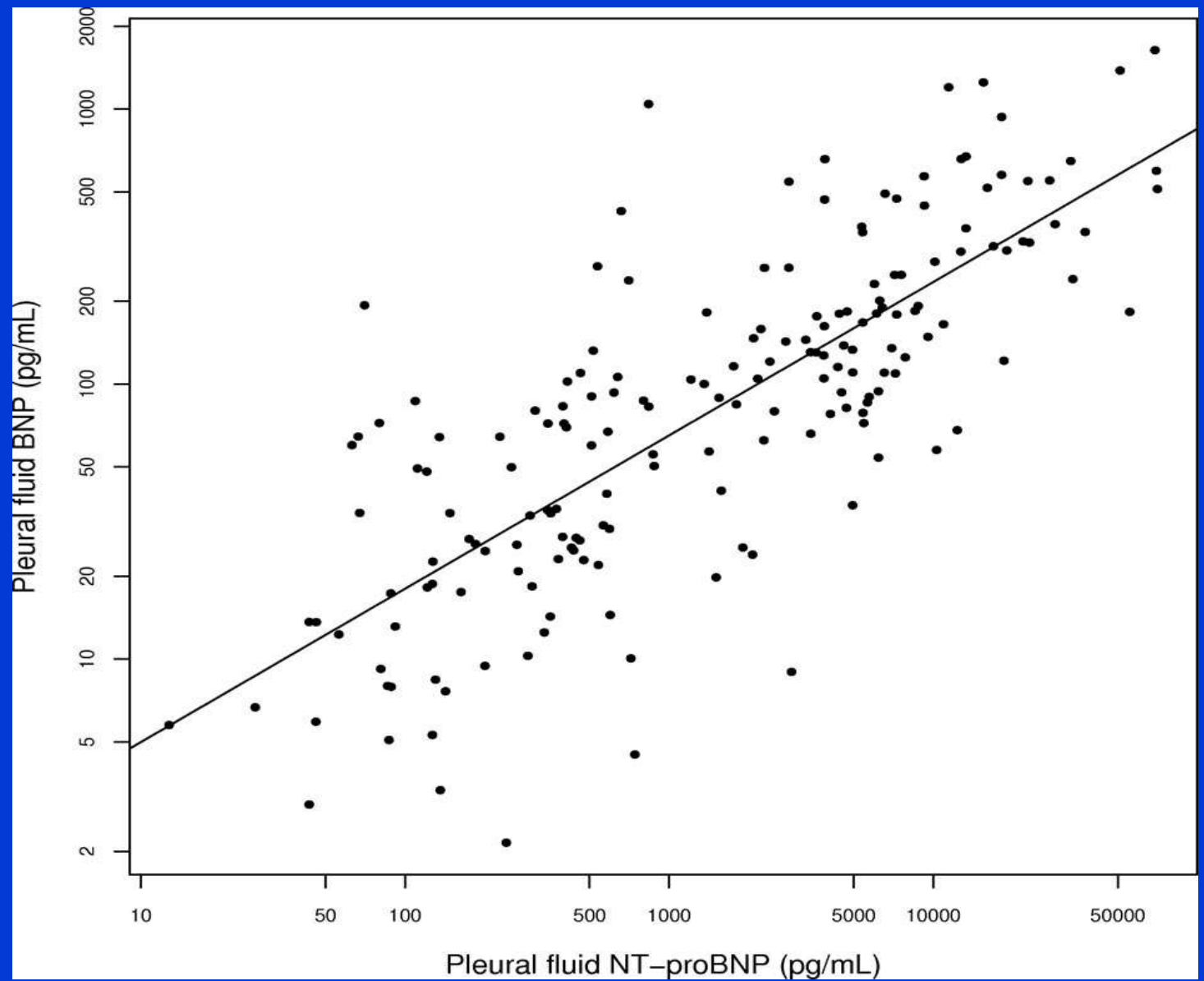
- Biologically active pro-brain natriuretic peptide (BNP) and the larger aminoterminal part NT-pro-BNP are released in equimolar amounts in the circulation when the cardiac ventricles are subjected to increased pressure or volume loads.

N Terminal Probrain Natriuretic Peptide (NT-proBNP)

- Pleural fluid NT-proBNP levels are useful in identifying effusions due to CHF
 - CHF (N = 44) 6931
 - CIRRHOSIS (N = 10) 551
 - MALIGNANCY (N = 25) 347
 - TUBERCULOSIS (N = 20) 101
 - PARAPNEUMONIC (N=13) 515
- NT-pro BNP >1500 diagnostic of CHF
- Serum values closely correlated with pleural fluid values
 - Porcel JM et al: Am J Med 2004; 116:417-20.



Kolditz M, et al. Eur Respir J. 2006; 28:7



Porcel J et al. Chest 2009; 136:671

Comparison of NT-BNP with pleural fluid gradients for albumin and protein

- Twenty patients with CHF whose pleural fluid met exudative criteria by Light's criteria.
 - Measured NT-proBNP and pleural fluid gradients for albumin and protein
 - 18/20 had NT-proBNP above 1300
 - 16/20 had NT-proBNP above 1500
 - 14/20 had BNP above 115
 - 10/20 had protein gradients above 3.1
 - 9/12 had albumin gradients above 1.2
-
- Porcel JM et al. Chest 2009; 136:671

The Future for BNP and NT-proBNP

- Can you use the levels of BNP in the serum or pleural fluid to establish the diagnosis of CHF?
 - Levels of BNP are much lower and are not closely correlated with levels of NT-proBNP in either serum or pleural fluid
 - NT-proBNP much superior to BNP in identifying CHF effusions
 - NT-proBNP better than protein gradient in borderline exudates
 - Porcel JM et al. *Chest* 2009; 136:671
- Why are the levels in the serum and the pleural fluid so closely correlated?
- With treatment do the levels in the pleural fluid and the serum decrease at the same rate?
- What are the pleural fluid BNP levels when the patient has CHF plus another disease?

Pleural Fluid ADA

- Two isozymes
 - ADA-1 produced by lymphocytes and monocytes
 - ADA-2 produced only by monocytes and elevated with tuberculosis
- Patients with TB almost always have levels **above 40 U/L**
- High levels also seen with empyema and rheumatoid pleuritis
- Specificity increased if combined with PF lymph/poly ratio greater than 3
- Non-tuberculous lymphocytic effusions usually have levels **< 40 U/L**
 - 10/506 patients (2%) had elevated ADA levels

Meta-analysis for ADA

- Reviewed 63 studies with 2796 patients with TB pleuritis and 5297 patients with pleural effusions due to other diseases
- Mean sensitivity was 0.92 (95% confidence 0.90 – 0.93)
- Mean specificity 0.90 (95% confidence interval 0.89 – 0.91)
- Positive likelihood ratio 9.03 (95% CI 7.19 - 11.35)
- Negative likelihood ratio 0.10 (95% CI 0.07- 0.14)
 - Liang QL et al. Respir Med 2008; 102:744



Needle Biopsy Of Pleura

- Blind needle biopsy of pleura most common way to diagnose TB pleuritis over past 60 years
 - Easier to diagnose TB with pleural fluid tests at the present time
- Also can diagnose pleural malignancy but inferior to cytology
 - Cytology much better in most series
- Rarely is needle biopsy indicated where thoracoscopy is readily available

In the Future Will Do More Image Guided Pleural Biopsies

- If pleural is thickened or contains nodules, one good way to get tissue is with a CT or ultrasound-guided needle biopsy
- Less invasive than thoracoscopy but cannot do procedure to produce pleurodesis
- One study 170 patients with cytologically negative suspected malignant pleural effusions
 - Randomized to CT scan with cutting needle or medical thoracoscopy
 - CT –guided cutting needle made the diagnosis in 42/48 (87.5%) of patients with TB or pleural malignancy
 - Medical thoracoscopy made the diagnosis in 48/51 (86%) of patients with TB or pleural malignancy
 - Metintas M et al. Chest 2010;137:1362-1368

Thoracoscopy Will Remain a Mainstay For The Diagnosis Of Pleural Disease

- Very efficient (>90%) at establishing the diagnosis of malignancy including mesothelioma
- Also good (>95%) at establishing the diagnosis of tuberculosis
- Rarely establishes the diagnosis of other benign causes of pleural effusion
- Concomitantly procedure can be done to create a pleurodesis
 - Pleural abrasion, a tetracycline derivative or 2% silver nitrate



Parapneumonic Effusions and Empyema – The Future

- It is likely that in the future we will culture pleural tissue rather than pleural fluid to identify the etiology of parapneumonic effusions – analogous to TB pleuritis
- More sophisticated methods such as PCR will be used to identify the organism responsible
- Viral infections will be demonstrated to be responsible for many effusions that are present called “idiopathic”

MIST II

- Multicenter double blind randomized study of 210 patients comparing:
 - tPA 10 mg
 - DNAase 5 mg
 - tPA 10 mg plus DNAase 5 mg
 - Saline
- Each given twice daily for three days
- % reduction of absolute abnormality on hemi-thorax between 1 and 7 days
 - tPA 10 mg $17.2 \pm 24.3\%$
 - DNAase 4 mg $14.7 \pm 16.3\%$
 - tPA 10 mg plus DNAase 4 mg $29.5 \pm 23.3\%^*$
 - Saline $17.2 \pm 19.6\%$
 - $P = 0.002$
- Hospital stay was shorter in combination group
- Higher number of DNase patients - surgery
 - Rahman NM et al. N Engl J Med 2011; 365:518-526.

Parapneumonic Effusions and Empyema

- The use of the combination of a fibrinolytic (e.g.TPA) and DNase will become more widespread and will result in less surgery
- 107 patients from eight centers treated with tPA/DNase
 - 84 % received drugs more than 24 hours after failing to respond to antibiotics and tube thoracostomy
- Pleural opacity cleared from 35% to 14% within 72 hours
- 92.3% did not require surgery
- No deaths from pleural infection

Questions about the combination of tPA and DNase

1. Can the two compounds be mixed or do they need to be administered individually? They can be mixed. Majid A, Kheir F, Ann Am Thorac Soc 2016;13:1512-8.
2. Do you need to give all six doses? Probably not but this has not been studied.
3. Can you give the compounds once a day? Yes - Mehta HJ, et al Respiration 2016;91:101-6.
4. Can you give the compounds for more than three days? Yes - McClune JR et al. Canadian Respiratory Journal 2016;2016:1-6.
5. What are the optimal doses for tPA and Dnase? Unknown
6. The mechanism for the effectiveness of Dnase will be defined.

Pleural Effusion Secondary To Malignancy

- Most common cause of subacute or chronic exudative effusion in geriatric patient
- Pleural effusion indicates systemic dissemination - surgery cannot cure
- Bad prognosis - median survival 90-120 d
- Treat effusion if patient **dyspneic** and **dyspnea** relieved by therapeutic thoracentesis
- If patient is not dyspneic, no treatment is recommended



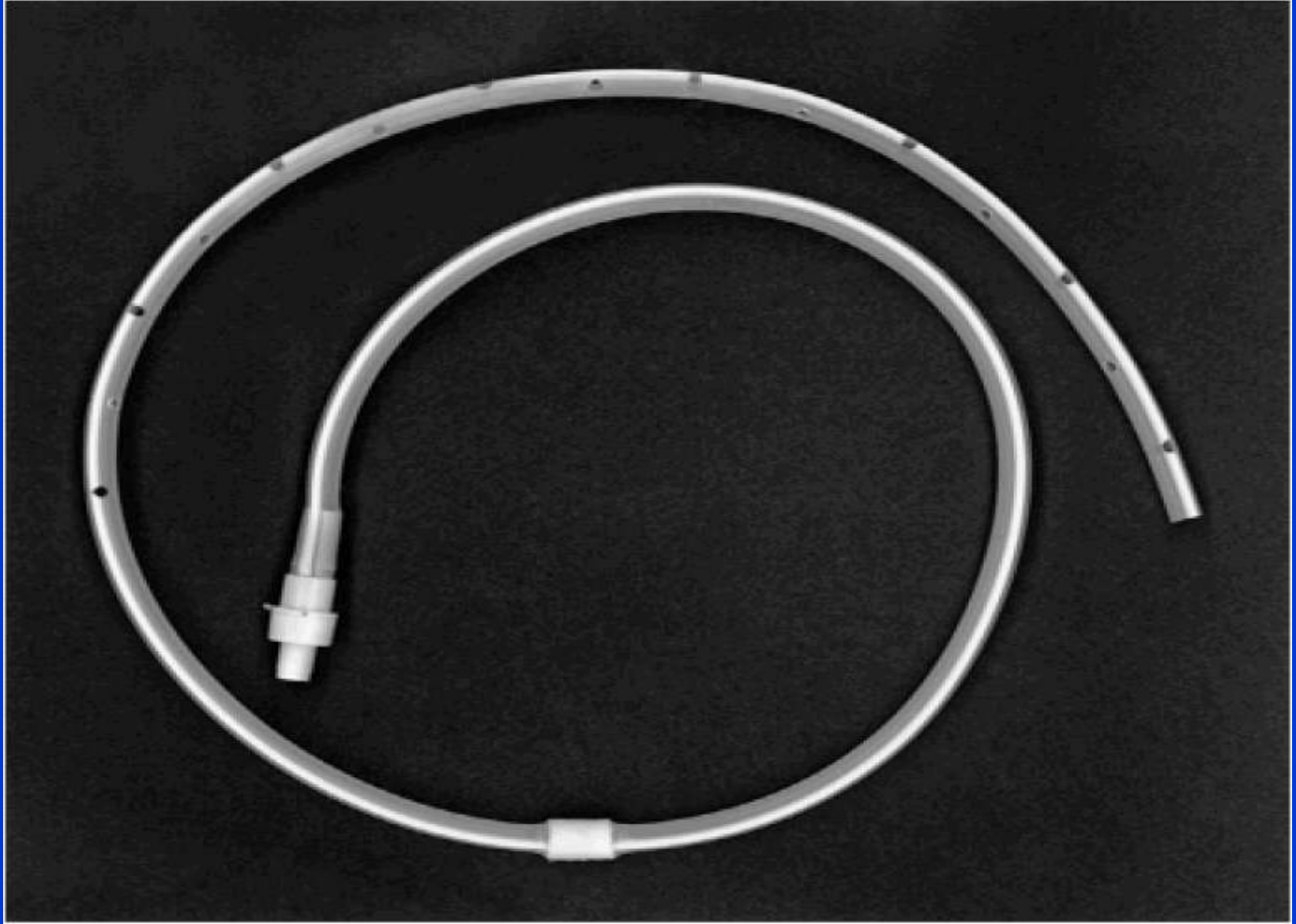
Philosophy of Treatment

- The life expectancy of the patient is limited (90 – 120 days)
- Surgery cannot cure the patient because the pleural effusion indicates that the malignancy is disseminated
- Main symptom from pleural effusion is dyspnea
- Goal is to alleviate the dyspnea via methods that require the shortest (or no) hospitalization and cause the patient the least distress
- Two primary treatment options are the implantation of an **indwelling catheter** or **pleurodesis**

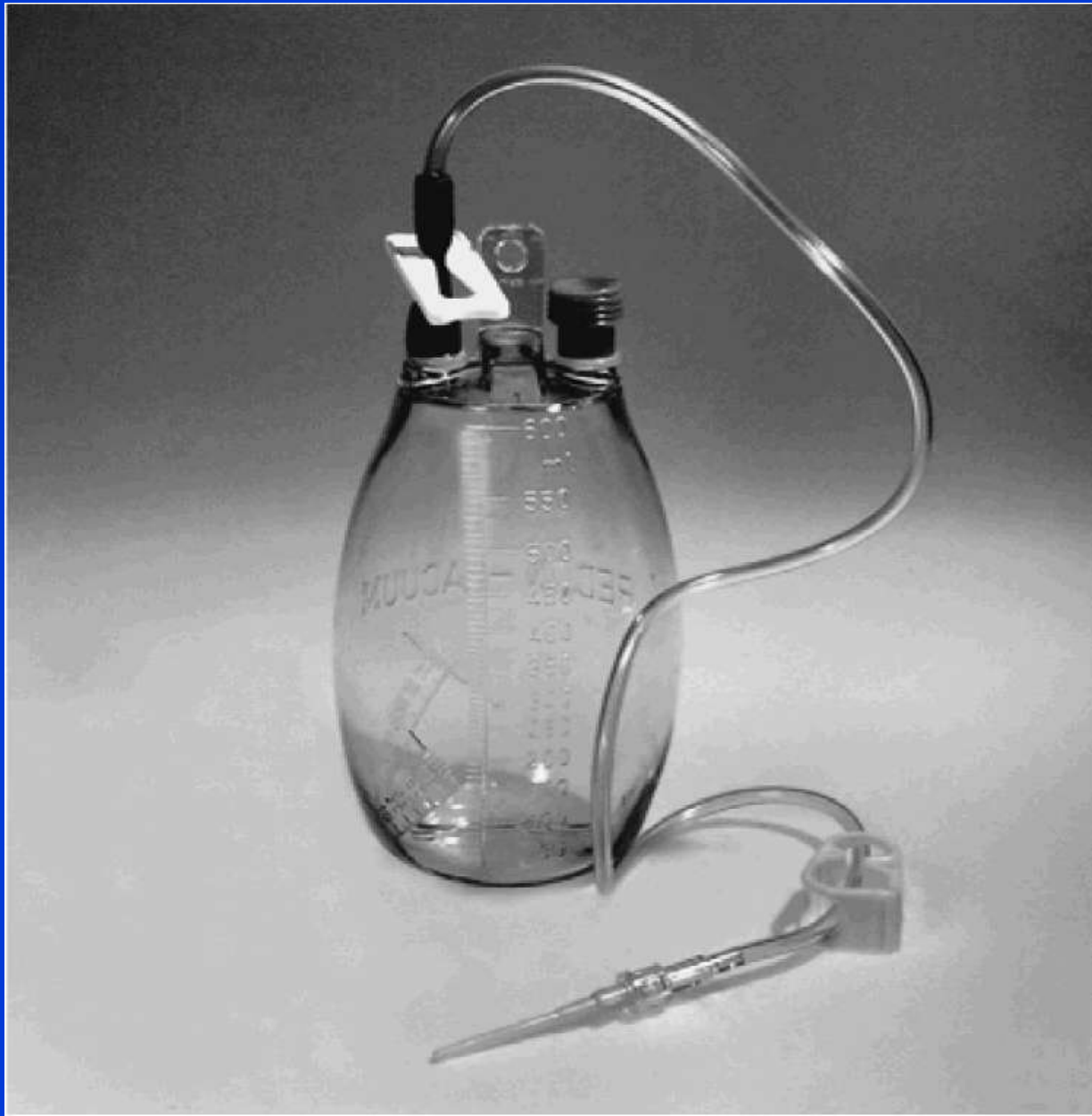
Indwelling Pleural Catheter

- **Pleurx is a 16.5 Fr silicone rubber catheter 66 cm long**
- **One way valve on end of Pleurx which allows drainage**
- **Intermittent drainage via vacuum bottles qod**

THE PLEURX CATHETER



THE COLLECTING SYSTEM



First Large Series

- Retrospective analysis of 250 tunneled pleural catheter insertions in 223 patients at a single center
- 4.4% failed insertion
- Symptom control complete in 39%, partial in another 50%
- No further procedure necessary in 90.1% with successful insertions
- Concluded that tunneled pleural catheters should be first line treatment in malignant pleural effusion
- Tremblay, A et al. Chest 2006; 129:368

Second Large Series

- Inserted 295 catheters in 263 patients at Rush Medical Center in Chicago over 8 year period
- Unsuccessful in 10 (No fluid pocket found)
- 58.6% of catheters removed after a mean of 29.4 day
 - Only 5/173 (2.9%) had reaccumulation of fluid that produced dyspnea
- Catheters more likely to be removed in patients with breast or GYN primary tumors, absence of chest wall irradiation, and complete re-expansion of the lung
 - Warren WH et al: *Europ J Cardio-thoracic Surg* 2008; 33:89-94

Pleurodesis With Indwelling Pleural Catheter

- **Spontaneous pleurodesis occurs in approximately 50% of patients at a median of 25 days post catheter insertion**
- **Presently studies are underway in which the sclerosant is injected through the Pleurx**
- **Biggest advantage is that entire pleurodesis procedure can be done as outpatient**

The Future of Indwelling Catheters

- The indwelling catheter will be increasingly used throughout the world for symptomatic pleural effusion
 - It can be inserted as an outpatient
 - Its insertion is associated with minimal complications
 - It controls the symptoms of the effusion for the patient's life in ~90% of patients
- Patients who receive the Pleurx catheter have less total days in the hospital and less days in the hospital related to the pleural effusion than patient who receive pleurodesis
- It is important to take time to teach the family how to manage the Pleurx
 - An alternative is to provide home health care but this is expensive

Questions About the Indwelling Catheter

- How often should the effusion be drained?
Daily, every other day, when the patient becomes dyspneic
- Is there a less expensive alternative to the drainage bottles?
- What is the optimal treatment if the effusion become infected?
- Will there be more spontaneous pleurodeses if the catheter is impregnated with a sclerosant such as silver nitrate?
- Can the combination of the indwelling catheter and the injection of a pleurodesing agent decrease the time of the catheter

Pleurodesis

- A pleurodesis occurs when the covering of the lung (the visceral pleura) and the covering of the inside of the chest wall (the parietal pleura) fuse
- If the two pleural surfaces are fused, then fluid cannot accumulate
- Pleurodesis is usually produced by injecting an inflammation producing agent is injected into the pleural space
- Resulting inflammatory reaction leads to pleural fibrosis such that the visceral and parietal pleurae fuse

Agents For Pleurodesis

- Talc
- Tetracycline derivatives
 - Tetracycline, doxycycline, minocycline
- Antineoplastic agents
 - Bleomycin, mitoxantrone, nitrogen mustard
- Silver nitrate
- Iodopovidone (Betadine)

PLEURODESIS TALC

- Most popular agent for producing pleurodesis at present time
 - Perceived to be effective and cost is minimal
- Talc preparations are quite inhomogeneous
- Big problem - intrapleural talc can lead to the acute respiratory distress syndrome
 - Fatal in 1 - 2 %
 - Talc disseminated throughout body
- No such problems with bleomycin or tetracycline

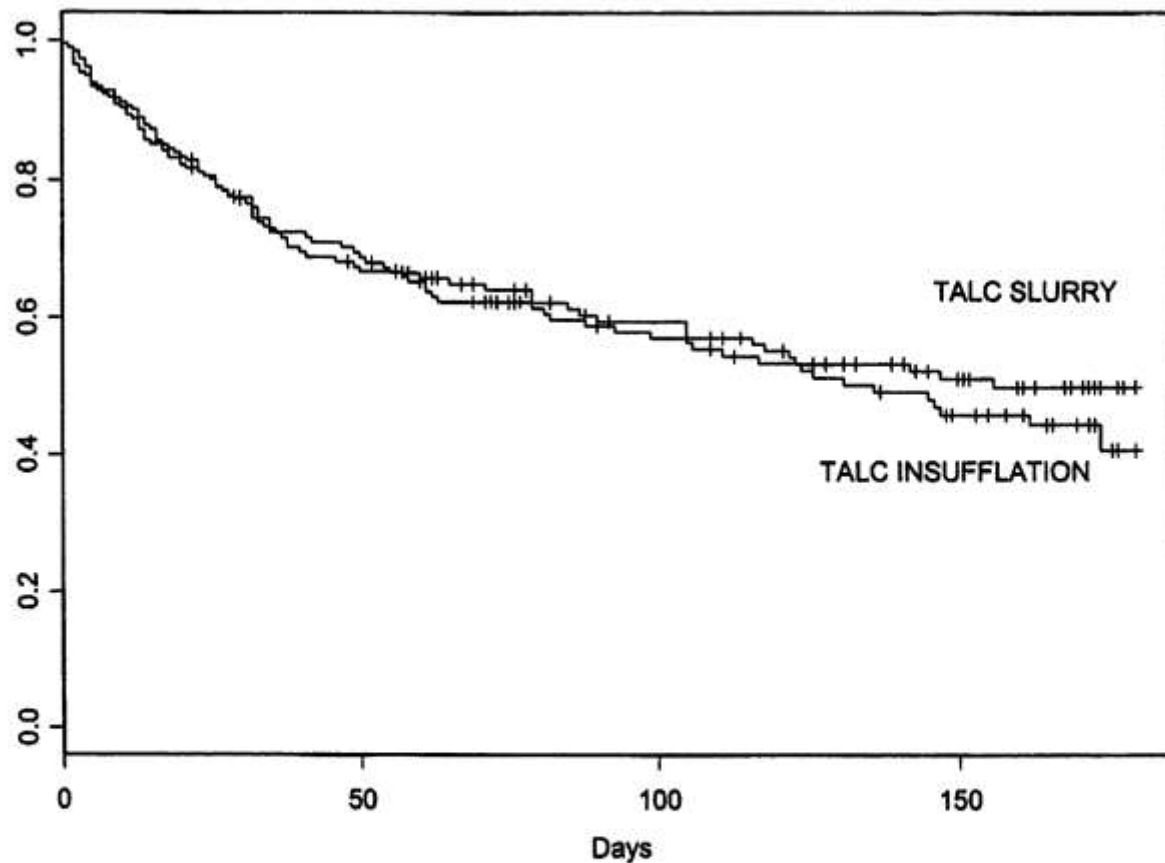
The Future of Pleurodesis

- Talc will be used less frequently in the future
- Still worry about the induction of ARDS
- Remember talc is just dirt

LARGE CALGB STUDY

- 242 patients received talc slurry and 244 patients received talc insufflation
 - 60% alive at 30 days without recurrence
 - 18% alive at 30 days with recurrence
 - 11 (2.5%) deaths from ARDS or respiratory failure
-
- Dresler CM et al. Chest 2005; 127:909

TIME TO RECURRENCE OF MALIGNANT PLEURAL EFFUSION



Number of patients at risk for given time points

Treatment	0 days	30 days	60 days	90 days	120 days	150 days	180 days
Slurry	221	135	89	66	59	44	26
Insufflation	228	144	84	61	51	38	19
Total	449	279	173	127	110	82	45

The Future of Pleurodesis

- Talc will be used less frequently in the future
- Still worry about the induction of ARDS
- Remember talc is just dirt
- An agent that is better than talc at producing a pleurodesis will become available. We have shown that the intrapleural injection of TGF- β produces better pleurodesis than does talc or doxycycline

Treatment of Malignant Pleural Effusions – The Future

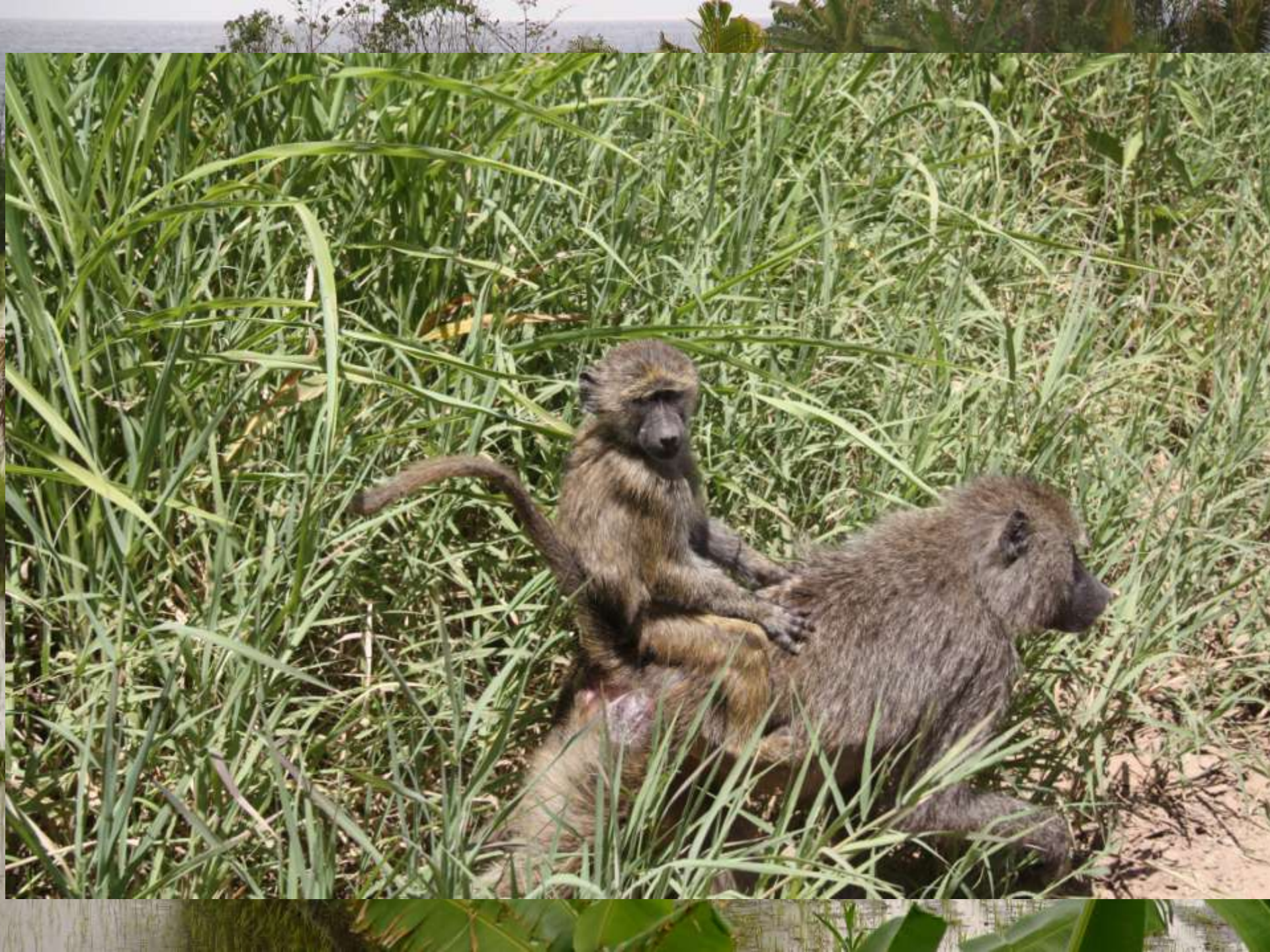
- Systemic anti-tumor therapy will improve such that treatment of the effusion is not necessary in some cases
- Intrapleural chemotherapy may prove to be useful
- Therapies may be developed which will decrease pleural fluid formation
- Cysmethynil significantly reduced MPE volume an adenocarcinoma model in mice.
 - [Magkouta S. et al. Oncotarget. 2016; 7:20249](#)
- Several other possibilities but none tried in humans yet

Malignant Pleural Effusion Treatment

Supportive Treatment

- **Either opiates or oxygen will alleviate dyspnea**
- **The advantage of the opiates is that they will also relieve the pain**
- **The disadvantage of the opiates is that they will produce constipation and sometimes mental clouding**
- **The disadvantage of oxygen is that it is expensive and non-portable**
- **Opiates are probably underused**
- **Recommend titrating opiates for dyspnea as is done for pain**







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SIXTH EDITION

PLEURAL DISEASES



Richard W. Light



Wolters Kluwer
Health

Lippincott
Williams & Wilkins