ISRAEL SOCIETY OF PULMONARY MEDICINE

ANNUAL SCIENTIFIC MEETING

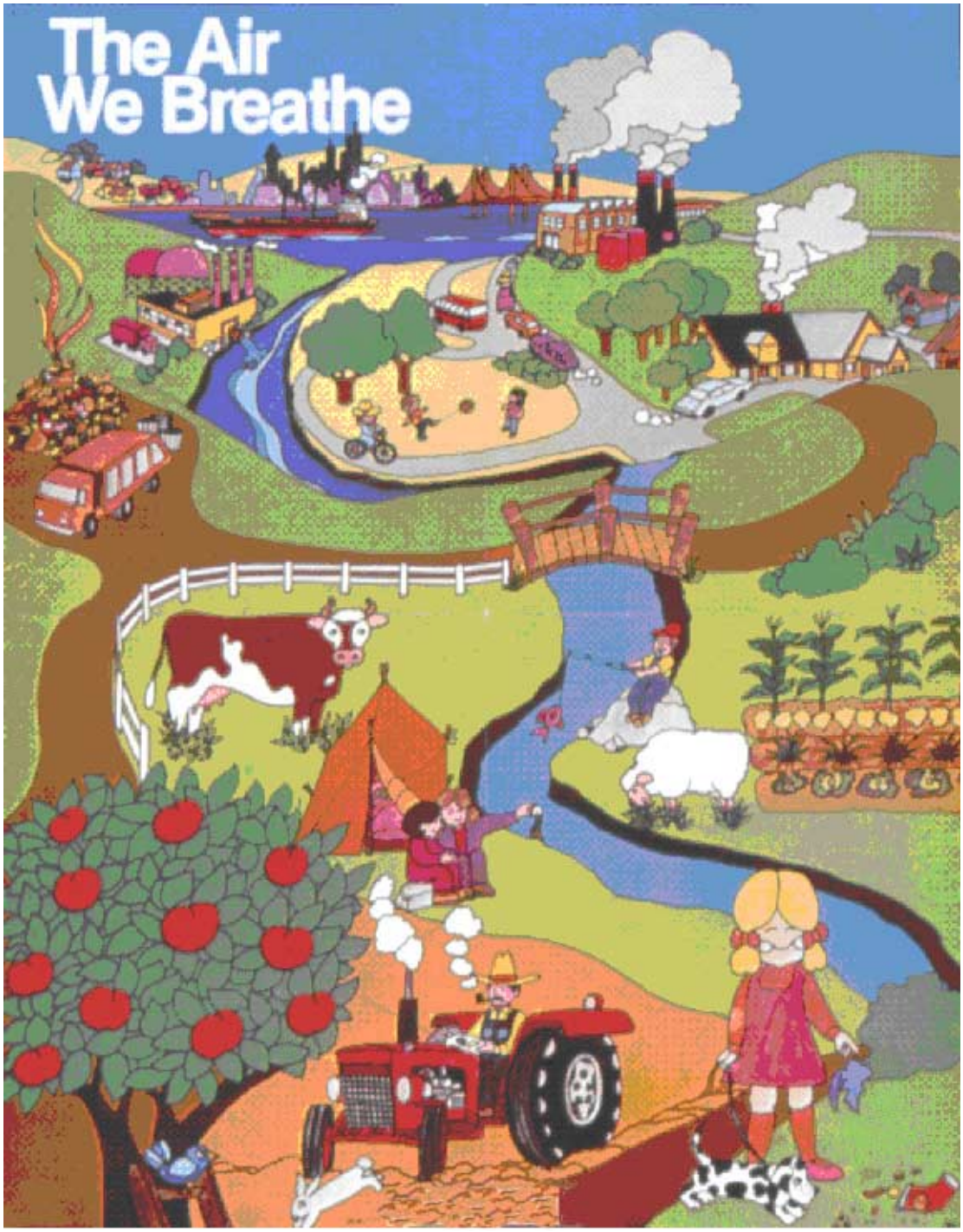
May 3- 5 2007

VENUE :

DAN CESAREA HOTEL

Cesarea

ABSTRACT BOOK



Scientific Program Coordinators :
Israel E. Priel, MD
Marcel Topilsky, MD
Amnon Ariel, MD, MPH

Welcome Note

Dear Attendant,

On behalf of the Organizing Committee, we welcome you to the Annual Scientific Meeting of the Israel Society of Pulmonology Dan Cesarea Hotel , May 3-5, 2007

It is with great pleasure we introduce this event, in hope that the success of last year's meeting at the Dead Sea will be reproduced.

The last year imposed a tremendous burden on the Israeli Health System
The financial strain grew , and the impact of the war is well known to all of us

We are therefore thrilled with the overwhelming response to share the results of scientific work done in Israel , under next to impossible conditions .
Indeed , this indicates the victory of spirit over matter .
We are proud to present studies at the cutting edge of science , important epidemiologic issues and a few state of the art presentations

The marked variability and the richness of the studies underline the important scientific work performed in this country

We are highly indebted to all contributors for their efforts and the willingness to share .

We truly hope that you shall enjoy the scientific meeting , the opportunity to exchange of ideas as well as the friendly atmosphere and the beautiful views at this historical site .

The Organizing Committee:

Israel E, Priel, MD, Marcel Topilsky, MD, Amnon Ariel, MD , MPH

THURSDAY					
1400-1600	**Welcome Reception, Meeting/Hotel Registration**				
1600-1700	**Opening Exhibition ; Coffee & Refreshments**				
Hall A - Rose : PLENARY SESSION;					
Israeli Asthma Guidelines Chairs : Amnon Ariel MD, Menachem Rottem MD, Tommy Schonfeld.MD					
1700-1725	Amnon Ariel, MD	In Favor of GINA 2006 based asthma guidelines – a local endeavor of knowledge translation is more relevant than re-writing the Israeli asthma guidelines.			
1725-1740	Menachem Rottem, MD	GINA guidelines 2006: The role of allergy and immunology in the pathophysiology and treatment of asthma			
1740-1755		Panel Discussion; Towards Asthma guideline implementation in Israel			
Hall A – Rose:			**Hall B – Caesar:**		
Asthma, COPD & Smoking Chair: Marcel Topilsky, MD			**Inflammation & Cystic Fibrosis** Chairs :Elizabeth Fireman, PhD, Neville Berkman, MD		
1800-1815	Shmuel Prints, MD, MPH	May pulmonologist's supervising improve current LABA misuse in outpatient practice?	1800-1815	Elizabeth Fireman, PhD, Shtark Moshe MD , Israel E. Priel MD, Robert Shiner MD , Ram Mor, MD, Joel Greif, MD and Shmuel Kivity MD,	Oxidative stress biomarker in Exhaled Breath Condensate vs Eosinophils count in Induced Sputum in the assessment of lung disease
1820-1835	David Segev MD,MBA, Shani Afek MD , Esther Burstein, BA, Horesh Ilan MD.	Intensive counseling was the most effective factor for smoking cessation in a multicausal prospective study in the primary care setting	1820-1835	Martin Kohan MSc, Raphael Breuer MD and Neville Berkman MD	Osteopontin: A novel glycoprotein involved in allergen-induced airway inflammation and remodeling
Thoracic Surgery Chair: Alon Yellin, MD					
1840-1855	Alon Yellin, MD, David Simansky, MD, Nona Zeitlin MSc, Maher Deeb, MD	Complete VATS Lobectomy – Initial experience	1840-1855	Zvi G Fridlender, MD MSc, Asaf Schwartz MD, Martin Kohan MSc, and Neville Berkman MD	The LPS receptor CD14 in Sarcoidosis
1900-1915	Ilan Bar , MD , FCCP , Michael Papiashvili , MD, David Stav ,MD, Gershon Fink , MD, Judith Sandbank , MD	Does cervical mediastinoscopic lymphadenectomy reduce unforeseen N2 disease in patients with non-small cell lung cancer ?	1900-1915	Malena Cohen-Cymberknoh,MD, Martine Klein,MD, Shoshi Armoni, RN, David Shoseyov, MD, PhD, Marina Orevi, MD, Roland Chisin,MD and Eitan Kerem, MD.	^{18}FDG- PET/CT contribution to the assessment of lesion severity in Cystic Fibrosis
2030	**WELCOME GREETINGS (Gershon Fink, MD) & POOLSIDE DINNER**				
2130-2300	**GARDEN SHOW Moshe Becker Music Show**				

FRIDAY					
Hall A – Rose:			**Hall B – Caesar:**		
Tuberculosis Chairs : Moshe Lidji, MD, Zeev Weiler, MD			**BioTerrorism** Chair: Israel E. Priel, MD		
0800-0815	Ahmed Atamna, MD , Abigail Fraser, MSc, Leonard Leibovici , MD	Close contacts of MDR Tuberculosis – Infection and treatment	0800-0815	Major Ariel Rokach MD MHA, Prof Robert Cohen PhD, Naomi Shapira RN Shmuel Einav RN Alex Mandibura RN Col. Yaron Bar-Dayan MD MHA	Preparedness for Anthrax Attack- The effect of knowledge on willingness
				Interventional Pulmonology Chairs: Y. Schwarz, MD; Alex Guber, MD	
0820-0835	Zohar Mor, MD, MHA; Ziva Amitai, MD, MPH; Gerald Baum, MD; Orly Roich, MPH; Daniel Chemtob, MD, MPH.	Pulmonary Tuberculosis Outbreak in an Internal Medicine Ward in a University Hospital in Central Israel.	0820-0835	Y. Schwarz,MD, J. Greif, MD, B. Tiran, MD, I Pumin , MD, A. Man, MD	Trans bronchial needle aspiration using Real-Time Electromagnetic Navigation Bronchoscopy with Overlaid CT Images for diagnosis and staging of mediastinal lymph nodes.
0840-0855	Zohar Mor, MD, MHA; Alex Adler, MD, Alex Leventhal, MD, MPH, MPA; Irina Volovic, MD, MPH; Edna Rosenfeld, RN; Mark N Lobato, MD, MPH; Daniel Chemtob, MD, MPH	Tuberculosis Behind Bars in Israel: Policy Making Within a Dynamic Situation	0840-0855	Ben Fox MD , Krylov Y, MD, Leon P, MD, Peled N, MD PhD, Ben Zvi I, MD, Shitrit D, MD, Kramer MR, MD	A randomized controlled trial of adding Labetolol to standard sedation during fiberoptic bronchoscopy
Hall A – Rose : PLENARY SESSION					
Chair: Gershon Fink, MD					
0900-0920	Daniel Chemtob, MD, MPH	The national Tuberculosis Program in Israel – a decade of implementation			
0930-0950	Mordechai R. Kramer, MD	Living Donor Lobar Lung Transplantation			
0955-1015	**COFFEE BREAK**				

FRIDAY (cont'd)					
Hall A – Rose:			**Hall B – Caesar:**		
Lung Transplantation and Pulmonary Hypertension Chair: Mordechai R. Kramer			**Sleep Related Breathing Disorders** Chair : Clement Cahan, MD		
1015-1030	Ben Fox, MRCP (UK), Ilanit Bin Nachum, MD, H Berenstein, MD, A.Amital, MD, D Shitrit, MD, MR Kramer, MD	Effects of side – mismatrching for single lung transplantation - role of quantitative lung perfusion scintigraphy	1015-1030	Nir Peled, MD, PhD M. Kasirer, MD O. Rogowski, MD D. Shlomi , MD B. Fox, MD, AS. Berliner, MD, MR. Kramer , MD D. Shitrit, MD	Increased erythrocyte adhesiveness and aggregation in OSA
			Cancer Chairs: Joel Greif, MD, Amir Onn, MD		
1035-1050	Mordechai Ygla, MD et al	Development of Pulmonary hypertension after arterio- venous access formation among end – stage renal disease patients - another piece of the puzzle	1035-1050	Amir Onn, MD	Perspectives on novel therapies for advanced Non Small – Cell Lung Cancer
Respiratory Physiology Chair : I Ben Dov, MD; Gershon Fink, MD					
1055-1110	Issahar Ben-Dov, MD , R. Zlobinsky, MD T Shulimzon, MD, M Gaides, MD, PhD, Z. Yemini, RT, and G. Zeilig, MD	What can be learned from the effect of posture on the ventilatory response to hypercapnia in quadriplegia ?	1055-1110	Helena Grinberg-Rashi,Msc, Shai Izraeli. MD, et al.	**A** Gene Expression Signature In Primary Tumors Predicts A Metastatic Spread To The Central Nervous System In Patients With Non-Small Cell Lung Carcinoma.
1115-1130	David Shitrit, MD	The 15 step climbing exercise oximetry test in patients with Idiopathic Pulmonary fibrosis	1115-1130	Olga Polansky ,MD Alex Starr, MD , Akiva Vexler, MD, Abraham Eliraz MD, Yosef Yarden, MD Rami Ben-Yosef, MD and Joel Greif, MD.	Inhibition of growth and metastasis of orthotopic human non-small cell lung cancer in athymic mice by anti-ErbB-4 monoclonal antibody
1135-1150	B Fox , MD, J Cohen , MD, MR Kramer , MD, P Singer, MD	Tissue perfusion may be assessed at the bedside with ETCO2-derived dead-space estimation – a pilot study	1135-1150	Amir Onn, MD	An Animal Model for the Study of the Biology and Management of Malignant Pleural Effusion.
1155-1215	**COFFEE BREAK**				

FRIDAY (cont'd)					
Hall A – Rose:			**Hall B – Caesar:**		
1215-1230	Mark Gaides, MD, PhD	Physiological dissociation of ventilation and perfusion in a normal lung.	**FIBROSIS** Chairs : Raphael Breuer, MD, Elizabeth Fireman, PhD 1215-1230	Regina Golan-Gerstl, MSc, Shulamit B Wallach-Dayan, PhD, and Raphael Breuer MD	The role of FLIP in regulating lung myofibroblast's Fas signaling of apoptosis and proliferation
1235-1250	E.Klainman MD, A.Caspi, MD R.Vishnizer, MD, I. Moshe, MD, A.Yarmulovsky MD and G.Fink, MD	Evaluation of Beta-Blocking Treatment in hypertensive patients with and without left ventricular dysfunction by Cardio-Pulmonary Exercise testing	1235-1250	Pazit Y. Cohen MSc, Shulamit B. Wallach-Dayan, PhD, and Raphael Breuer, MD	The Mechanisms of Thy1-Mediated Regulation of Lung Myofibroblasts Apoptosis and Proliferation
1255-1310	Shupak A, MD, Wiener P, MD Ertracht O, MD Abramovich A, MD, Keynan Y,MD , Adir Y,MD	Respiratory Muscle Training in Oxygen divers: reduced dyspnea and increased endurance	1255-1310	Shulamit B Wallach-Dayan PhD, Regina Golan-Gerstl MSc, and Raphael Breuer MD	Myofibroblast's Escape From Immune Surveillance: A Mechanism for Tissue Fibrosis
1315-1330	Eyal Leshem MD, Prativa Pandey MD, David R. Shlim, MD Yehezkel Sidi,MD, Eli Schwartz , MD	Clinical Features of Patients with Severe Altitude Illness- in Nepal. Diagnosis and Prophylaxis Guidelines.	1315-1330	Zvi G Fridlender MD MSc, Nissim Arish MD, Shulamit Wallach-Dayan PhD, Regina Golan-Gerstl, MSc and Raphael Breuer MD	Telomerase Activity of Epithelial Cells in Bleomycin-Induced Lung Fibrosis
Special Session for AFFILIATES Chair; Yochai Adir, MD					
1335-1400	Ariela Velner , RT	The challenge of Metacholine Challenge : Theory and Practice	1335-1350	Nissim Arish MD, Zvi G Fridlender MD Msc, Shulamit Wallach-Dayan PhD, and Raphael Breuer MD	Over-expression of Telomerase Protects Lung Epithelial Cell From Bleomycin- and Fas-Induced Apoptosis
1400	**LUNCH**				
1730-1900	**QUO VADIS - Israeli Pulmonology ? session (Poolside or Terrace, non-formal attire)** Opening remarks : Dr Fink **OPEN AIR & OPEN MINDED DISCUSSION - ACTIVE MEMBER PARTICIPATION!!**				
2000	**DINNER**				
2200	**ISRAELI JAZZ – BLUES EVENINIG (Hotel Lobby)**				

SATURDAY – SOCIAL PROGRAM		
0700-1100	**BREAKFAST**	
1030-1300	**Rali Museum Guided Tour (Gratis)**	**Cesarea Park Guided Tour (40 IS per person – Registration required)**
1300-1430	**LUNCH**	
	LATE CHECKOUT	

ASTHMA, COPD & SMOKING

L’Asthme

Pigal Edme Jean
1798- 1872

In Favor of GINA 2006 based asthma guidelines – a local endeavor of knowledge translation is more relevant than re-writing the Israeli asthma guidelines.

Amnon Ariel, MD. Lung Unit, Emek Medical Center, Afula 18101[1].

The Process of Guideline Development: Clinical practice guidelines are systematically developed statements to help clinicians and patients with decisions about appropriate health care for specific clinical circumstances. The process of guideline evidence summary is a formidable task best filled by international collaboration of sufficient scope and size to carry out the systematic review and update it annually. **Knowledge translation**, the complex and multidimensional process of applying the evidence for improving local patient care, is the core of guideline implementation.

NHLBI and GINA Guidelines: The first asthma guidelines were published in the mid 1980s when asthma became a recognized public health problem in many countries. The Global Initiative on Asthma (GINA) was launched in 1995 as a collaborative effort between the NHLBI and the World Health Organization (WHO). The first edition was opinion-based but updates were evidence-based. Unfortunately, despite tremendous progress in asthma guideline development and the wide availability of inhaled corticosteroids, guideline recommendations are not being widely implemented. In fact, **contemporary surveys suggest that asthma is adequately controlled only in a minority of patients**.

GINA 2006 and the Israeli perspective: In an effort of narrowing the gap between asthma knowledge (the evidence) and asthma control (the effect), the 2006 GINA guidelines are **based on the development of a partnership** between the patient and the healthcare team in a continuous effort of **improving asthma control**. **The huge resources required for guideline development are locally unavailable. A local effort to develop updated asthma guidelines is entirely unnecessary. GINA guidelines can be easily translated and adapted for local use**, simplifying the important task of regular guideline update. Local endeavors should thus focus on the knowledge translation and guideline implementation which rely heavily on overcoming the multiple barriers on the journey from evidence to effect. **A joint effort of Israeli professional organizations and healthcare providers is necessary to achieve the desired improvement in asthma care.**

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GINA guidelines 2006: The role of allergy and immunology in the pathophysiology and treatment of asthma

Menachem Rottem, MD. Allergy and Immunology, Emek Medical Center, Afula .

Asthma is a chronic inflammatory disease. The process of inflammation is initiated at the level of the mast cells. Mast cells are major effector cells in the allergic process due to their widespread in many tissues and their ability to bind IgE molecules by the high affinitiy receptor for IgE located on their surface. Cross-linkage of the IgE receptors by antigens or the direct non-IgE stimulation of mast cells initiates the inflammatory cascade in the upper and lower airways, as well as in other tissues. In this context, the recommendation for use and the recognized efficacy of Anti IgE therapy in severe allergic support the recognition of asthma as an IgE-mediated disease. GINA 2006 guidelines continue to emphasize the need for allergy evaluation in asthma and states as one of its key points in diagnosis that measurements of allergic status can help to identify risk factors that cause asthma symptoms in individual patients. GINA guidelines chapter on management and prevention highlights the role of allergic rhinitis in asthma (ARIA). Allergy as a systemic disease is manifested by both rhinitis and asthma. Asthma and rhinitis are common co-morbidities, suggesting the concept of "one airway-one disease". The nasal and bronchial mucosa have many similarities. Although there are differences between rhinitis and asthma, upper and lower airways are affected by common triggers and share common effector pathways. Epidemiological studies have consistently shown that most patients with allergic and non-allergic asthma have rhinitis, and that up to 30% of patients with rhinitis have asthma. Allergic rhinitis is associated with and also constitutes a risk factor for asthma. Rhinitis frequently precedes asthma, and is both a risk factor for the development of asthma, and is associated with increased severity and health resource use in asthma. For these reasons, ARIA and GINA guidelines recommend that the presence of asthma must be considered in all patients with rhinitis, when considering a diagnosis of rhinitis or asthma the evaluation of both should be made, and that in planning treatment, both should be considered together. Asthma treatment includes the consideration of allergic and immunologic mechanisms. The role for anti-IgE therapy in severe asthma as been well documented. While allergen-specific immunotherapy has a limited role, it has merit in reducing the allergic sensitization towards a clinically relevant allergen in an allergic patient with asthma and rhinitis. In this regard, the GINA guidelines 2006 in its chapter on asthma treatments quotes Cochrane review that examined 75 randomized controlled trials of specific immunotherapy compared to placebo that confirmed the efficacy of this therapy in asthma in reducing symptom scores and medication requirements, and improving allergen-specific and non-specific airway hyperresponsiveness.

In conclusion, GINA guidelines 2006 as in previous editions recognize and emphasize the importance of allergic and immunologic mechanisms in asthma diagnosis and management.

May pulmonologist's supervising improve current LABA misuse in outpatient practice ?

Shmuel Prints , MD, MPH South Distict of Leumi Sick Fund, Israel

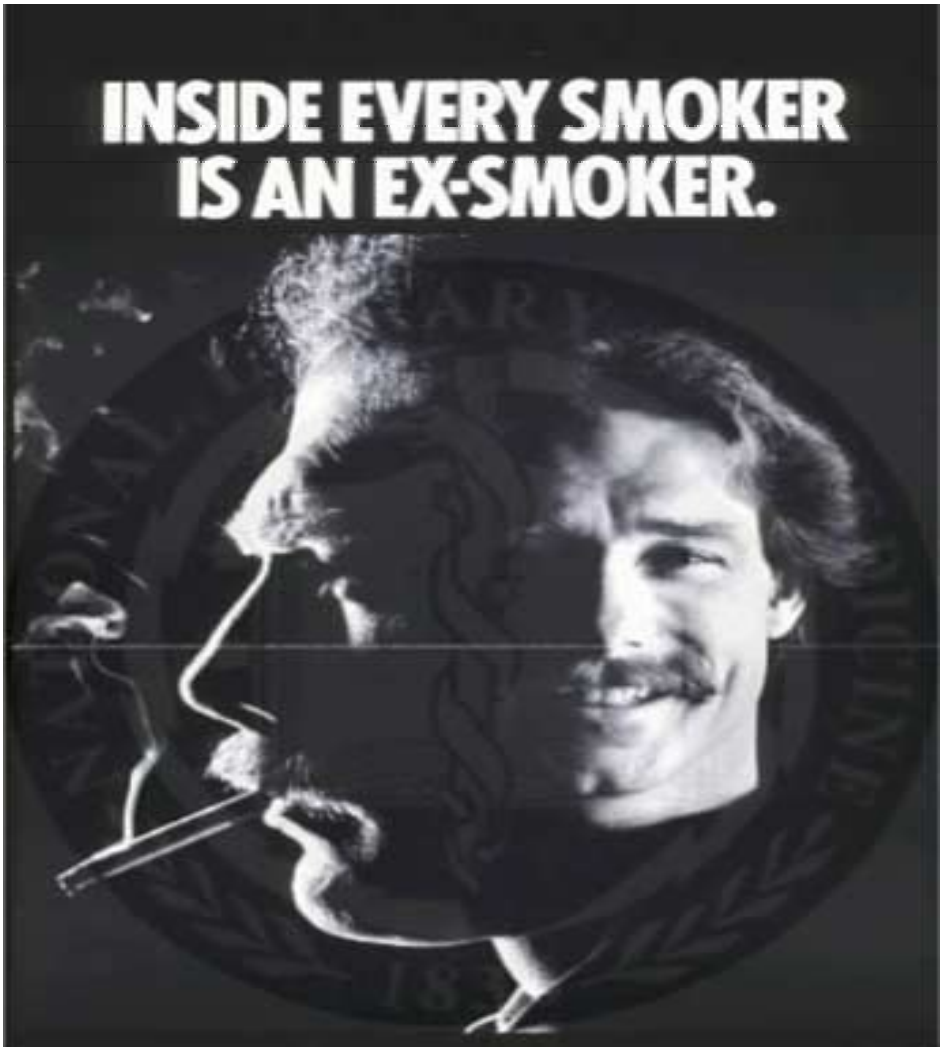
Background: The last bronchial asthma's studies emphasize danger from permanent treatment by long-acting agonists without accompanying anti-inflammatory therapy. The current study evaluates the factors that lead to this inappropriate approach in the South district of the Leumit Sick Fund (Israel).

Methods: The demographic details, select medicine's consumption and the medical service facilities in the same year were studied for each one of patients who purchased long-acting agonists devices three times or more in 2005.
Those who used the medicines for the prevention of the bronchial inflammation in the sufficient amount (right therapy) during the period of the study were compared to all the other (malpractice therapy) by logistic regression multivariate examination.

Results: Two of the studied factors influence the treatment's efficiency: the pulmonologist's examination for the estimated year (OR=2.8 CI 1.47; 5.41) and outpatient service in the Bedouin living area of Negev (OR= 3.35 CI 1.05; 10.66). In the same time the medical facilities consumption in this sector situated high when compared with the customers who received the right treatment in the other expanses of the district.

Conclusions: Primary physicians of all specializations continue to use the insufficient anti-inflammation therapy for permanent bronchial asthma patients in spite of current recommendations. Pulmonologist's supervision may improve the quality of treatment in this field.

SMOKING CESSATION



Intensive counseling was the most effective factor for smoking cessation In a multicausal prospective study in the primary care setting.

[1]Segev David (MD,MBA), [2]Afek Shani (MD) , [2]Burstein Ester (BA), [2]Horesh Ilan(MD).
[1] Head of Sharon District, Sharon Shomron County , Clalit Health Services, Israel.
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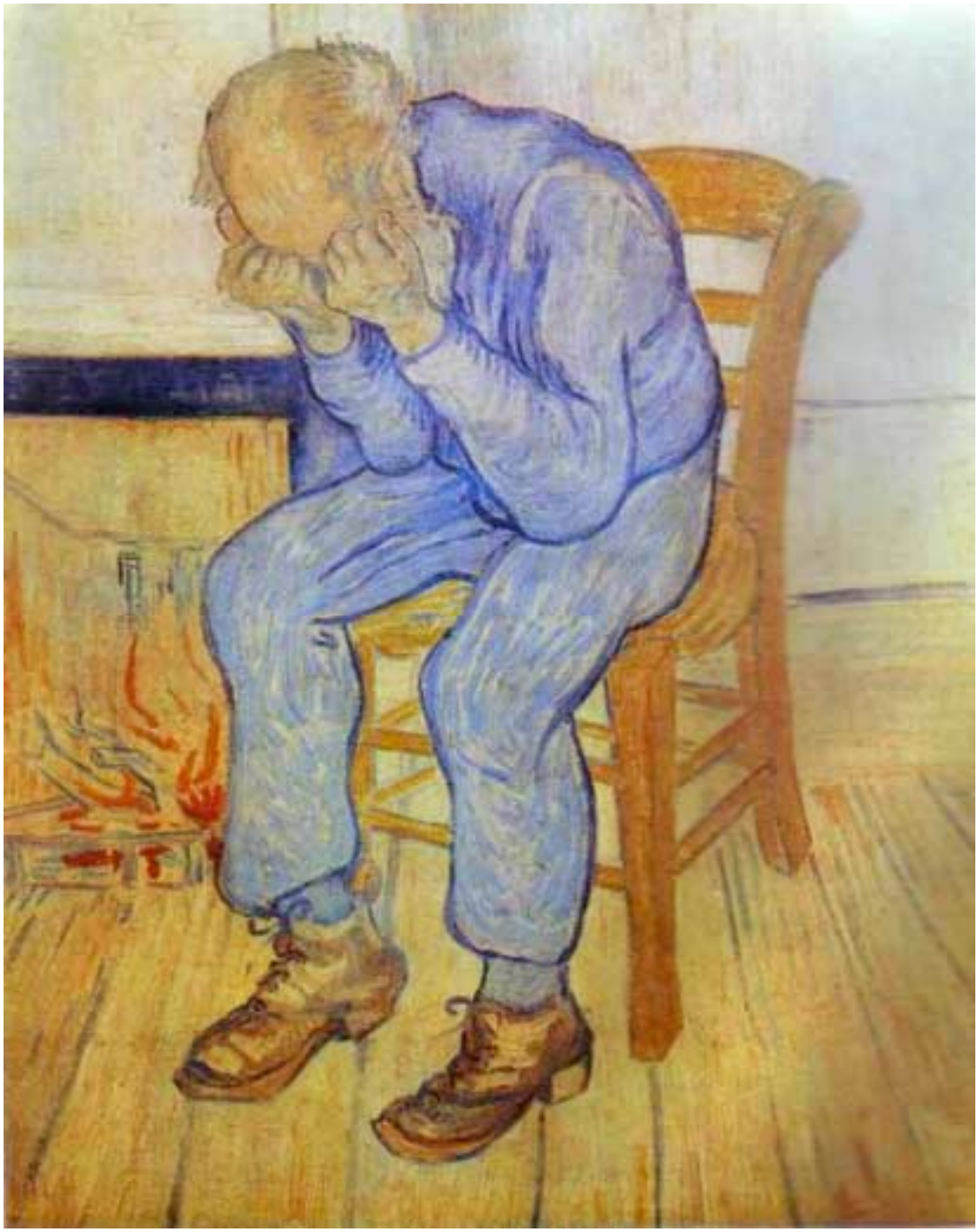
Context: smoking cessation is probably the most important step that smokers can do to improve their health status, still many patients continue to smoke and fail to stop. Smoking cessation group counseling is one of the main options of providing a successful treatment for tobacco dependence combining both behavior counseling and pharmacotherapy.
Objective: The main purpose of our study was to evaluate the abstinence rate and the different factors which may influence smoking cessation success of supporting groups in the primary care setup.
Design: we conducted a prospective study in which we followed for a year 289 patients who participated in the smoking cessation groups between the years 2004-2005. The evaluation of smoking status was conducted at the end of the smoking cessation group sessions, and after a year.
Setting: The patients were enrolled by the primary care teams by suggesting the intervention to every smoking patient attending the primary care clinic.
Intervention: the group therapy continued for 8 weeks and the participants themselves together with the instructor decided on which pharmacotherapy to choose: Nicotine replacement therapy and/or Bupropion SR.
Results: More than 85% percent of the study population had smoked more than 20 cigarettes a day with a moderate to high Fagerstrom nicotine dependence scale. The participants had high compliance to the group behavior therapy with about 75% of attendance at the eight sessions and a moderate to high self -confidence about success. At the end of the eight weeks treatment phase of group behavior therapy 71.6% of the participants had stopped smoking ,after 6 month 52.8% had continued successfully and after a year 43% of the participants had declare of being a non smoker. Participating in more group sessions was a positive predictor of success where as high level of Fagerstrom nicotine dependence scale was a negative predictor for smoking cessation success. Neither using NRT nor using Zyban had an additive effect on the quitting rate with group counseling.
Conclusions: smoking cessation in group counseling at the primary care setup is an effective way for smoking cessation. Compliance for the counseling is a positive predictor for smoking cessation where as high level of nicotine dependence is a negative one. Treating patients in this setup with nicotine replacement therapy, Bupropion SR or both do not significantly improve the smoking cessation rate. Future research should be done to identify those who will benefit the most from using pharmacotherapy at such intensive behavioral therapy.

LUNG CANCER



Old man in Sorrow
Vincent van Gogh
1890

Novel Therapies for Advanced Non-Small-Cell Lung Cancer.

Amir Onn, M.D., The Chaim Sheba Medical Center.

Recent research in lung cancer biology has translated into improvements in patient survival and quality of life, with the introduction of the molecular targeted therapies erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), and bevacizumab, a monoclonal antibody to vascular endothelial growth factor (VEGF). In this review I present recent advances in the development of these agents. **Erlotinib (Tarceva).** In a randomized, placebo-controlled trial (NCIC BR.21), single-agent erlotinib was shown to prolong survival in NSCLC patients after first- or second-line chemotherapy. Overall response to erlotinib was 9%, and the overall survival durations were 6.7 months for erlotinib and 4.7 months for placebo (P = .001). On the basis of this study-- the first randomized trial to confirm that an EGFR TKI prolongs survival after first- or second-line chemotherapy -- erlotinib received approval by the US Food and Drug Administration and in other countries including Israel. However, a study of chemotherapy with or without erlotinib failed to show a survival benefit or improvement in response rate to patients treated with chemotherapy plus erlotinib over chemotherapy alone. **Predicting Response:** Better understanding of the biology of the EGFR system in lung cancer has been the subject of intense research in recent years, and many groups are focusing on identifying markers of response or resistance to biological therapy. Studies examined gain-of-function somatic mutations of EGFR in exons 18-21 and correlated them with response to EGFR inhibitors. Compiling these data reveals that EGFR mutations are identified in 80% of responders, whereas mutations in *K-ras* (exon 2) are associated with lack of sensitivity to erlotinib. Others studied extensively the role of EGFR gene copy number as a predictor of response to EGFR TKIs. Their findings suggest that high EGFR gene copy number identified by fluorescent in situ hybridization may be an effective molecular predictor for drug efficacy. **Clinical Perspectives**: Despite the turmoil surrounding the development of EGFR inhibitors in recent years, erlotinib is considered a good therapeutic option for patients with advanced lung cancer. Safety issues, and especially the development of interstitial lung disease (ILD), which may be fatal, slowed the study of these agents in the Far East. In contrast, in western patients, ILD is rare; the common adverse events are relatively easy to tolerate; and the recommendations for managing drug-associated rash or diarrhea are straightforward and easy to follow. Of note, although rash is considered by some to be a clinical marker of response to erlotinib, it is still a controversial issue. Encouraged by dramatic responses of erlotinib-treated patients who were considered hopeless, oncologists are now searching for guidelines for patient selection. Based on recent data, most experts recommend therapy with erlotinib according to the clinical profile of the individual patient: women; patients with adenocarcinoma, especially with bronchioloalveolar features; never-smokers; and patients of Asian origin seem to be the best candidates for this therapy. To date, patient selection outside of a clinical trial should not be made on the basis of any biological marker or profile.
Bevacizumab (avastin). Bevacizumab acts synergistically with chemotherapy and has been shown to improve survival in patients with colorectal, breast, and lung cancers. In a phase 2 lung cancer trial, an unusual and unexpected toxic effect was the development of life-threatening hemoptysis in 6 patients, which resulted in 4 fatalities. Hemoptysis did not appear to be dose dependent, since all but one of these cases occurred in the low-dose bevacizumab arm. Bleeding arose from centrally

located tumors close to major blood vessels, and cavitation or necrosis had occurred in most cases. Because multivariate analysis identified squamous cell histology as a risk factor, a phase 2/3 NSCLC study comparing bevacizumab (15 mg/kg) plus carboplatin and paclitaxel with chemotherapy alone included only patients whose tumors were of nonsquamous histology. Median survival was longer (12.3 vs 10.3 months) in the group assigned to chemotherapy plus bevacizumab, as compared with the chemotherapy-alone group ($P = .003$). The median progression-free survival in the 2 groups was 6.2 and 4.5 months, respectively ($P < .001$), with corresponding response rates of 35% and 15% ($P < .001$). Rates of clinically significant bleeding were 4.4% and 0.7%, respectively ($P < .001$). There were 15 treatment-related deaths in the chemotherapy-bevacizumab arm, including 5 from pulmonary hemorrhage. The researchers concluded that in selected NSCLC patients, the addition of bevacizumab to chemotherapy has a significant survival benefit, with increased risk of treatment-related deaths.

Combination of Molecular Targeted Therapies: Dual targeting of the VEGF and the EGFR pathways has been tested in preclinical and clinical studies. Encouraging results from those studies prompted the development of multiple nonselective TKIs. In addition, the combination of erlotinib and bevacizumab has been studied in patients with several malignancies based on a promising NSCLC phase 1/2 study. **Clinical Perspectives:** The addition of bevacizumab to paclitaxel with carboplatin was shown to improve patient outcome in nonsquamous NSCLC patients, making it a very popular first-line therapeutic regimen. Supporting these data are the positive results of bevacizumab when combined with chemotherapy in patients with other malignancies, such as colorectal cancer, breast cancer, or renal cell carcinoma. Bevacizumab has been studied in combination with cisplatin-based regimens, and the results will be reported shortly. Furthermore, bevacizumab is being tested in patients with squamous cell carcinoma and in patients with small-cell lung cancer. Safety and patient selection are the major issues related to therapy with this agent. To date, a cautious approach that takes into consideration patients' cardiovascular and renal condition, history of airway bleeding, and tumor location is recommended. More specific guidelines are emerging as additional clinical data are reported.

Discussion: Management of patients with lung cancer has changed considerably in recent years, based on the understanding that a combination of clinical parameters plus biological profile can predict patient outcome. Targeted agents, such as erlotinib and bevacizumab, are becoming a standard of care in advanced disease. Clinical research related to these agents is primarily focused on patient selection for therapy, definition of predictors of response, and safety issues. This is also the appropriate time for physicians from other disciplines to join medical oncologists in the evaluation and management of these patients with NSCLC. For example, dermatologists are needed to evaluate skin reactions in erlotinib-treated patients, pulmonologists to screen patients with hemoptysis, and imaging specialists to address radiographic changes that are characteristic with molecularly targeted therapy.

A Gene Expression Signature In Primary Tumors Predicts A Metastatic Spread To The Central Nervous System (CNS) In Patients With Non-Small Cell Lung Carcinoma.

Helena Grinberg-Rashi Msc (PhD student)[1],Efrat Ofek-Marovsky,MD[6], Marina Perelman, MD[6], Pnina Yaron, MSc[2] ,Jasmin Jacob-Hirsch, MSc[1], Naftaly Kaminski, MD[1], Ninette Amariglio, PhD[1], Meir Krupsky, MD[2], David A. Simansky, MD [3], Zvi Ram, MD [4], Raphael Pfeffer, MD[5] , David Steinberg, PhD[7], Issahar Ben-Dov, MD[2], Gideon Rechavi, MD [1], Shai Izraeli, MD[1].

[1] Cancer Research Center, [2]Pulmonary Medicine, [3]Thoracic Surgery, [4]Neurosurgery, [5]Radiation Oncology and [6]Pathology Departments, Sheba Medical Center.[7]Dpt. of statistics Tel Aviv University

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Metastasis is the major cause of morbidity and mortality in human cancer. Metastases to the central nervous system (CNS) are especially debilitating and are associated with extremely short life expectancy. In adults, lung cancer is the most common primary tumor to spread to the CNS. Prophylactic cranial irradiation and/or intrathecal chemotherapy for high risk patients in certain diseases (e.g. leukemias) prevents CNS relapse. Presently, however, there are no biological or clinical parameters that identify patients with localized non-small cell lung cancer (NSCLC) at high risk for CNS metastasis. Here we tested the hypothesis that specific gene expression patterns in primary NSCLC could predict metastatic spread to the CNS.

Using DNA microarray studies on both primary lung tumors and on brain metastases we compiled a short list of twelve candidate genes whose expression in primary tumors might be associated with development of CNS metastasis. We then quantified their expression by Real-Time PCR in 142 *independent* frozen tissue samples of NSCLC tumors with known pathology, staging and clinical outcome (31 with known CNS metastases, 37 with known metastases to other sites and 74 without known metatases). Multivariate Cox regression analysis showed that the expression of three genes in the primary tumors were significantly correlated with metastatic spread to the CNS. Using these genes we built a risk score for the prediction of metastatic spread to the CNS in NCSLC patients. The two year CNS metastasis free survival in patients with early stage disease (I-II) and a low risk score was 90.0 ± 9.5 % in contrast to only 62.7 ± 12% in patients with a high risk score ratio. The same predictive power was evident for patients with advanced lung cancer (stages III-IV): 88.9 ± 10.5% for low risk score compared with 36.6 ± 18.1% for high risk score.

Thus, we propose a gene expression score that enables the identification of patients with lung cancer that are at very high risk for developing of CNS metastasis. Such patients may be good candidates for specific prophylactic therapy such as cranial irradiation that may prevent or delay this devastating complication.

An Animal Model for the Study of the Biology and Management of Malignant Pleural Effusion.

Amir Onn, MD

The Chaim Sheba Medical Center, Tel Hashomer

Rationale: Recurrent malignant pleural effusion is a debilitating clinical problem with no effective therapy. It is associated with high levels of vascular endothelial growth factor (VEGF), also known as vascular permeability factor (VPF).
Methods: We used our recently developed orthotopic model of human lung cancer in nude mice (Onn, Clin Cancer Res 2003) to study malignant pleural effusion, and examined the effect ZD6474 (ZACTIMA™), a novel tyrosine kinase inhibitor, on H441 human pleural effusion producing adenocarcinoma tumor cells, injected orthotopically into the lungs of nude mice.
Results: Microscopic nodules were identified 5 days (median), and bloody malignant pleural effusion was detected 15 days (median) after tumor implantation (0.5×10^6 cells in matrigel). Pleural metastasis was necessary for effusion production. Immonohistochemical staining revealed that the developed tumors expressed VEGF, VEGF receptor (VEGFR) and activated VEGFR, and ELISA revealed high VEGF level in the effusion. Groups of mice (n=10) injected with H441 cells were randomized on day 15 to receive daily vehicle (control) or oral ZD6474 (50 mg/kg). The mice were sacrificed 3-4 weeks later. Therapy with ZD6474 diminished pleural seeding from 80% to 10% and amount of pleural effusion from 220 micro litter to 50 (control vs. treatment, median), caused no change in VEGFR level and decreased expression of phosphorylated VEGFR on primary tumor cells. Using the same therapeutic regimen we determined in another study that ZD6474 improved mouse survival from 30 to 80 days (control vs. treatment, median).
Conclusions: These data suggests that VEGF/VPF has an important role in malignant pleural effusion production, and its inhibition with molecular targeted therapy may be used for the management of this condition. A human clinical trial is planned.

Inhibition of growth and metastasis of orthotopic human non-small cell lung cancer in athymic mice by anti-ErbB-4 monoclonal antibody

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Introduction. Non-small cell lung cancer (NSCLC) is a major source of mortality from cancer in western world. Patients with metastatic NSCLC have a dismal prognosis because there is no effective treatment for this disease. Since ErbB-4 signaling cascade is important in the growth and metastasis of NSCLC (Starr et aI., Int. J. Cancer 119: 269-74, 2006), its blockade has been hypothesized to inhibit tumor growth. Using human poorly differentiated NSCLC cells - H1299 (clone 22 with high ErbB-4 expression) we found that blockade of ErbB-4 by the anti-ErbB-4 monoclonal antibody (Mab) inhibited the proliferation of these cells *in vitro*.

Goal of the study was to determine an efficacy of Mab therapy for human NSCLC growing subcutaneous or in the lungs of nude mice.

Materials/methods. Tumor cells in Matrigel were injected subcutaneous (s.c.) or percutaneously into the left lung (intra-lung) of CD-1 nude mice. The mice were randomized 7 days after tumor implantation to receive twice/week following i.p. treatments: Mab (600 μg/mouse) or saline (control). The mice were killed and necropsied when control animals became moribund. Treatment efficacy was estimated by weekly measuring the size of s.c. tumors or by weighting of the lung with tumors at the end of the experiment.

Results. In both cases the tumors generated by H1299 clone 22 cells were formed from a single focus and developed very fast. In the case of intra-lung cell implantation, tumor progressed to a widespread and fatal thoracic process characterized by diffuse dissemination of lung cancer in both lungs and metastasis to intra- and extra-thoracic lymph nodes. Mab treatment significantly decreased the growth of s.c. tumors, reduced the weight of lung tumors and significantly inhibited lymph node metastasis.

Conclusion. Our data suggest that in lung cancer, ErbB-4 signaling may have an important role to control tumor growth and metastasis. The combination of targeted molecular therapy with conventional chemo- and/or radiotherapy may be the basis of future lung cancer therapy.

THORACIC SURGERY

Surgery for chest wound
Tagault Jean, 1545

Complete VATS Lobectomy – Initial experience

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Introduction: Pulmonary and thoracic operations by thoracoscopy have become a standard approach in recent years. Yet, so far VATS lobectomy has not been performed in Israel. This study reports an initial experience in three hospitals.
Patients and methods: Eleven pts were planned for VATS lobectomy (5F, 6M), 9 with NSCLC, 1 carcinoid and 1 metastasis. Surgery was performed at SMC, SZMC and a private hospital. All operations were done with a collapsed ipsilateral lung. Access was via a 5 cm lateral and two 1.5 cm incisions using ordinary surgical tools according to McKenna's method and avoiding rib retraction. Pain was managed mainly by oral analgesics without an epidural catheter. Consumption of pain medication, pain level (analog scale), incision length and duration of hospitalization were measured prospectively and compared to those of pts undergoing open lobectomy.
Results: In 3 cases surgery was converted to open lobectomy due to bleeding (1), anesthetic problem (1) and anatomic considerations (1). In 8, VATS lobectomy was successful, requiring no transfusion and lasting an average of 140 minutes. There was no in hospital mortality and one pt had air leak. The demand for pain medication, pain level and duration of hospitalization were significantly lower in pts undergoing VATS compared to open lobectomy. The esthetic result was improved, whereas the duration of surgery was longer and the need for disposable equipment was higher in VATS lobectomy.
Conclusions: VATS lobectomy is possible in Israel too. This method has important advantages over the open method but requires a learning period. In our opinion VATS lobectomy is the preferred method in a large fraction of pts undergoing lobectomy.

Does cervical mediastinoscopic lymphadenectomy reduce unforeseen N2 disease in patients with non-small cell lung cancer ?

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Objective: Accurate preoperative staging of the mediastinum is important for the treatment of non-small cell lung cancer patients. Enlarged mediastinal lymph nodes on chest computed tomography scan are found positive for malignancy by mediastinoscopy in half of the patients . After negative mediastinoscopy, there are cases of positive nodes found at thoracotomy . The aim of this study was to attempt to possible remove all lymph nodes accessible by cervical medastinoscopy (lymphadenectomy) and re-evaluate the same mediastinal stations at thoracotomy for the matter of residual lymph nodes .
Methods: Between 1999 and 2003 , 30 patients with operable non-small cell lung carcinoma and enlarged mediastinal lymph nodes (more then 1 cm in diameter on computed tomography scan) that found to be negative at cervical mediastinoscopy , subsequently underwent pulmonary resections with complete lymph nodes dissection.
Results : The total number of lymph nodes dissected was 329 (143 at mediastinoscopy and 186 at thoracotomy) ; the mean number of nodes dissected at mediastinoscopy was 4.8 and 6.2 at thoracotomy . After thoracotomy, 2 patients were restaged from N0 to N2 disease (6.6%). Ten residual lymph nodes (6.5%) were detected at thoracotomy in mediastinal stations R4, L4 nd 7. 33.3% patients (9 patients) upstaged after thoracotomy by there T and N status.
Conclusion: Cervical mediastinoscopy is an accurate diagnostic method for the staging of the mediastinum in non-small cell lung cancer patients; complete lymphadenectomy may substantially reduce the number of cases of unforeseen N2 disease.

INTERVENTIONAL PULMONOLOGY

Chevalier Jackson (portrait), ca. 1886-1916

1886 graduate of Jefferson Medical College ; Professor of Laryngology, Jefferson Medical College, 1916-1924 ; and Professor of Bronchoesophagology, 1924-1930
Invented the modern science of endoscopy of upper airway and esophagus

Trans bronchial needle aspiration (TBNA) using Real-Time Electromagnetic Navigation Bronchoscopy (SDBS) with Overlaid CT Images for diagnosis and staging of mediastinal lymph nodes (MLy)

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Background: Mediastinal lymph nodes (MLy) can be evaluated by TBNA for diagnosing and staging lung cancer, avoiding more invasive techniques for cytopathology examination of MLy, but it still remains underutilized. A new, real-time, electromagnetic navigation (EN) system for bronchoscopic procedures, utilizing a micro-sensor and overlaid with previously acquired CT images to facilitate approaching MLy with a greater diagnostic accuracy was used.
Objectives: Demonstrate the ability to reach a diagnosis by TBNA of MLy guided by the SDBS.
Methods: 30 patients (pts) underwent EN guided TBNA. Anatomical landmarks and the lesion were identified and marked on the digitized CT images. The same landmarks were marked during bronchoscopy with an electromagnetic sensor in the tip of the bronchoscope, thus correlating between the CT images and the patient's body. The localization sensor incorporated to the bronchoscope enabled navigation towards the MLy. The position of the sensor is overlaid upon previously acquired CT images and displayed on the monitor, allowing a real-time EN to target. Biopsies or cytology aspirations were obtained. Final diagnosis was confirmed by mediastinoscopy, surgery or resolution on follow-up.
Results: a true positive diagnostic (TP=70.2%) was obtained in 18 pts (47 lymph nodes were aspirated). Malignancy was seen in 12 and 6 had Sarcoidosis.
A true negative (TN=23.4%) was seen in 9 pts (11 Mly) , 5 pts with lung cancer negative Mly after surgery and 4 pts had an inflammatory disease which resolved
False negative aspirations were obtained in 3 patients (FN=6.4%). Overall sensitivity 96% and specificity 100 %, The success of diagnosing Mly using SDBS was 93.6% per MLy, and 90% per patient.
Conclusions: TBNA with SDBS is an effective method that significantly improves the yield for the diagnosis of MLy.

Funding by superDimension, Ltd., Israel

A randomized controlled trial of adding labetalol to standard sedation during fiberoptic bronchoscopy

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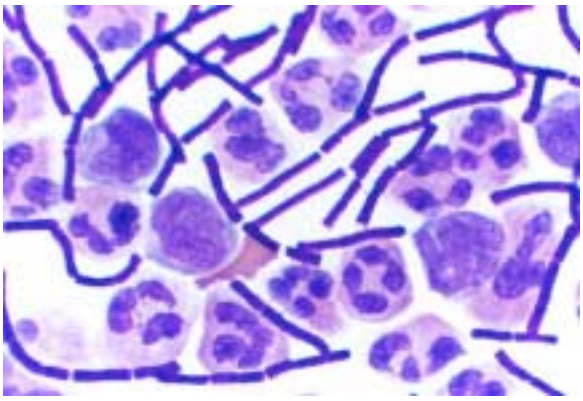
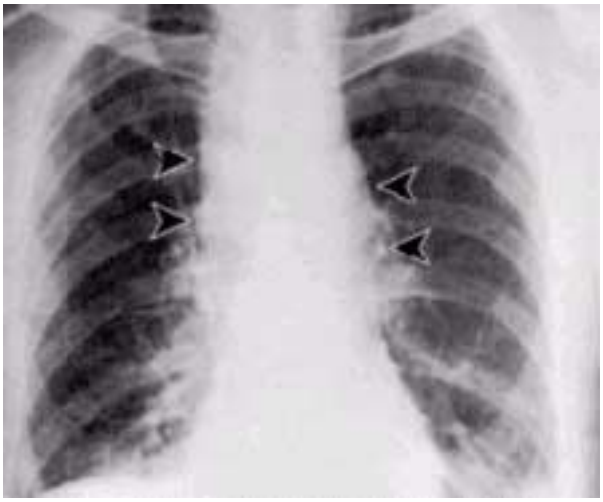
OBJECTIVE
Although usually performed under sedation, fiberoptic bronchoscopy (FOB) is frequently associated with tachycardia and hypertension. In certain patients, this may cause deleterious cardiovascular effects. We hypothesized that adding a bolus of the short-acting beta-adrenergic antagonist labetalol to standard sedation would lead to a smoother cardiovascular course during FOB.
DESIGN
We performed a randomized controlled trial of 120 patients undergoing FOB in our institution.
SETTING
A teaching hospital bronchoscopy suite.
PARTICIPANTS
All patients attending for FOB age 18+ were eligible for inclusion in the study. Exclusion criteria were refusal or inability to give informed consent, known intolerance of beta-adrenergic antagonists, pregnancy, concomitant use of non-dihydropyridine calcium channel blockers, intention to use propofol for sedation, bradycardia (pulse <60) or hypotension (systolic pressure <100) at screening.
INTERVENTIONS
All patients received standard sedation with midazolam (Dormicum) and alfentanyl intravenously as required and topical lidocaine given with the spray-as-you-go technique. In addition, patients were randomized to receive either labetalol 10mg iv or saline placebo.
MAIN OUTCOME MEASURES
Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and the rate-pressure product (RPP=HR*SBP÷100) were measured at baseline, every 5 minutes during FOB and during recovery. In addition, we recorded adverse events of hyper- and hypo-tension, tachy- and brady-cardia, and hypoxia.
RESULTS
The two groups were analysed with intention-to-treat. Baseline parameters were similar in both groups. Physiological data was analysed with repeated-measures ANOVA - there were no differences between the groups at baseline, during and following bronchoscopy. Adverse events were the same in both groups. Bronchoscopy was similar in duration, sedation requirements and patients satisfaction.
CONCLUSIONS
We did not find evidence that adding labetalol to standard midazolam-opiate sedation was beneficial or harmful to patients undergoing fiberoptic bronchoscopy.

BIOTERRORISM

Is there an Anthrax Doctor in the audience ?

Colin Powel holding a model vial of anthrax while speaking at the US Security Council





Preparedness for Anthrax Attack- The effect of knowledge on willingness

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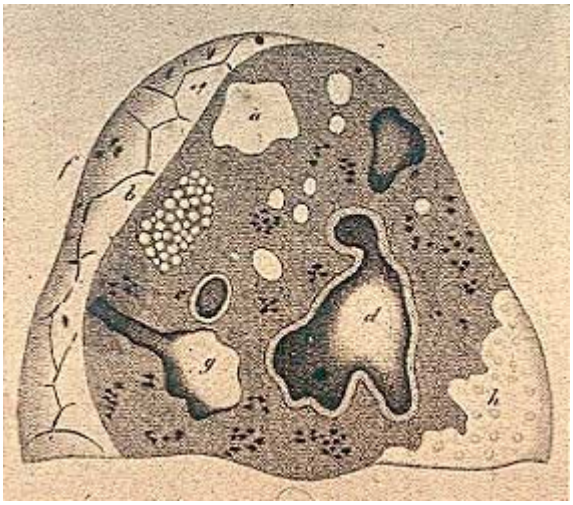
Objective - Bioterrorism is a real threat. The willingness of physicians and nurses to care for patients during bioterrorism attack is crucial. Little is known about this willingness. We hypothesized that several factors might have an effect on the willingness to care for patients.
Design- On May 2006 we conducted a survey among nurses and physicians randomly selected.
Setting- Emergency rooms of three public hospitals.
Participants- One hundred nurses and physicians were asked to answer the survey. Seventy-six nurses and physicians agreed to participate.
Intervention- The survey included general information (Age, gender, family status, number of children, profession and experience in the profession), 11 multiple-choice questions about Anthrax and five questions about willingness to care for patients with Anthrax.
Main outcome measures- Statistical analysis was done in order to find correlation between willingness to treat patients and medical knowledge. Statistical analysis was also done in order to find correlation between willingness to treat and one of the basic parameters- Age, gender, family status, profession (physician or nurse) and experience in profession.
Results- we classified the scores in the knowledge test to three groups- Group 1: 80-100, group 2: 50-79, and group 3: less then 50. Ninety percent of the physicians and nurses in-group 1 were willing to treat anthrax patients, seventy two percent in group 2 were willing to treat and only 60% of physicians and nurses in group 3 were willing to treat anthrax patients. This difference was statistically significant (P=0.01). Physicians and nurses with a better score in the test were more likely to fulfill their duty to treat anthrax patients. Age, gender, profession, family status and experience had no correlation to willingness.
Conclusions- Medical knowledge about anthrax increases the willingness of physicians and nurses to treat patients infected by anthrax.

TUBERCULOSIS



Laennec’s drawing of tuberculous lung, with cavity

The National Tuberculosis Control Programme in Israel - a decade of implementation

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Background: Israel, a low tuberculosis (TB) endemic country, experienced mass immigration from high and intermediate TB endemic countries in the 80' and 90', after that its previous TB infrastructure was dismantled. As a result, several levels of TB endemicity are present in Israel, according to sub-populations. In the lecture, we are presenting the epidemiological situation in Israel, the National TB control programme and its results.

The National Tuberculosis Control Programme [1]:

The programme complies with the five core elements of the World Health Organization strategy and also includes specific additional measures addressing the needs of immigrants. The five core elements are: 1) Political commitment of MoH (legislating new TB regulations and establishing a dedicated National TB department, with an independent budget); 2) Adequate laboratory diagnostic facilities (in two regional TB labs); 3) Standardized short-course chemotherapy, free of charge, and administrated under Directly Observed Treatment (DOT); 4) Consistent drug supply and 5) a permanent reporting system.

These recommendations were enhanced by using existing health care networks (horizontal structures) and by strengthening the mission and the personnel of the 15 District Health Offices (DHO), involved in epidemiological enquiries for each active case, and in supervising the work done by the nine dedicated TB centres. DOT is done for each active case and for the full period of treatment. Contact investigation of each TB case is performed, and treatment of latent TB infection is available. DHO supervision allows for a full collaboration of the four primary health providers that were also deeply involved in the establishment of the program. Cultural sensitivity to new immigrants (both documented and undocumented) and legal sanctions for absconders are also part of the programme. Hospitalization takes place in two dedicated regional TB wards.

Results: Better and clearer organization of TB treatment in all its aspects has been obtained. Some fifteen law/regulations/guidelines were mostly created (and for some, updated only). Compliance improved from less than 27% for successful outcome before the new programme to about 80% after. However, mortality increased from 5% before the implementation of the program to 10% after. Finally, incidence started to decrease (from 11 cases/100,000 in 1998 to 5.8 cases/100,000 in 2005). Multi-Drug resistant (MDR)-TB cases mostly originated from countries with a limited TB control program, and are often complex cases facing psycho-social-cultural difficulties.

Conclusions: Due to different TB epidemiological situations among sub-populations, both TB control and TB elimination strategies were successfully implemented in Israel. Yet, persistent efforts need to be sustained (especially for complex TB cases), in an era of the emergence of extensively drug resistant (XDR)-TB cases.

Reference: [1] Chemtob D, Leventhal A, Berlowitz Y, Weiler-Ravell D. The new National Tuberculosis Control Programme in Israel, a country of high immigration. *Int J Tuberc Lung Dis* 2003;7(8):828-836.

Pulmonary Tuberculosis Outbreak in an Internal Medicine Ward in a University Hospital in Central Israel.

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Orly Roich[1], MPH; Daniel Chemtob[1], MD, MPH.

Introduction:

Mycobacterium tuberculosis is transmitted by droplets nuclei from infected patient to terminal air passage of another person. Hospitalized pulmonary tuberculosis (PTB) patients may spread the infection to other patients or to health care workers.
Internal medicine wards in general hospitals, which admit PTB patients, are expected to implement infection control measures to protect other patients and staff, until the PTB patient is transferred to a designated tuberculosis hospital.

Aim:

Ascertaining the risk of admitting PTB patient in general hospitals and the importance of addressing infection control measures to protect hospitalized patients and staff.

Methods:

Describing epidemiologic investigation of tuberculosis outbreak among health care workers in an internal medicine ward in a generalized hospital.

Results:

In October 2001, an HIV positive work immigrant from Nigeria was hospitalized in an internal medicine ward and was further diagnosed as PTB patient. During the following next 3 years, 5 health care workers were diagnosed with PTB.
Following a detection of each of these PTB cases, an epidemiologic investigation was conducted. Using molecular biology, it was found that all of the PTB patients shared an identical strain, demonstrating direct transmission. Additionally, 25 staff members and 10 people previously hospitalized in that ward were diagnosed as having latent tuberculosis infection.
Investigating team reported limited compliance of ward staff to performing tuberculin skin tests, partial adherence with preventive tuberculosis therapy and paucity of measures available for the employer to encourage health care workers to take precautions in tuberculosis control.
The ward's physical conditions did not allow appropriate isolation of airborne communicable disease.

Conclusions:

The outbreak emphasizes the difficulties of treating PTB patient in internal wards and highlights the challenges of tuberculosis control in hospital setting.
In order to control PTB in health care setting, it is important to comply with the current guidelines: respiratory isolation of PTB patients until transfer to tuberculosis designated hospital, prompt screening of health care workers upon employment and periodically thereafter and adherence to preventive therapy regime in latent infections.

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TUBERCULOSIS BEHIND BARS IN ISRAEL: POLICY MAKING WITHIN A DYNAMIC SITUATION

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Introduction:

Pulmonary tuberculosis (PTB), a droplet transmissible disease, poses a threat for both inmates and staff in correctional facilities. The crowded environment, the frequent turnover of inmates, in addition to the social and medical background of the inmates, may facilitate transmission. Furthermore, the regular contact between inmates and the outside community can spread the disease to non-incarcerated individuals. Although PTB is considered as a major health problem in correctional facilities worldwide, the exact incidence of TB in Israeli prison is yet unknown.

Aim:

Assesing TB incidence in the Israeli prison system, thus evaluating the need of commencing designated screening and program for prison inmates and staff.

Methods:

All prison clinic lung records from 1998 through 2004 in Israel were reviewed to identify pulmonary TB patients. Additionally, we reviewed tuberculosis epidemiologic investigation files from one prison (years 2002 through 2005) to evaluate possible tuberculosis transmission.

Results:

A total of 13,000 inmates are occupying the Israeli prison system annually, 23% are foreign born: 11% immigrated during last decade from the Former Soviet Union (FSU) and 10% of the total are drug users (2003). During the study period, 23 Israeli inmates had pulmonary tuberculosis (25 cases per 100,000 prisoners), which was 3.5 times higher than for the general population. In the evaluated prison, four pulmonary tuberculosis cases were reported, and 22% (149/670) of all inmates and staff were referred for treatment of latent TB infection.

Conclusions:

Considering incarceration conditions and a relatively higher TB rate among inmates (vs. the general population), screening policy should be commenced. The authors recommend the use of designated questionnaire, as part of inmates' clinical screening and a selective tuberculin skin testing for inmates who are infected with HIV/AIDS, those who inject drugs, and those who emigrated from the FSU after 1990. New staff should be screened by the two-step tuberculin skin test process. Inmates and staff should routinely complete a symptom review. Those who have tuberculosis symptoms should be isolated and evaluated for tuberculosis. Incarceration may be used as a point of detection for tuberculosis and a window of opportunity for treatment in this hard-to-reach population.

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EFFECTIVENESS OF PROPHYLACTIC TREATMENT IN CLOSE CONTACTS OF MDR-TB PATIENTS –A COHORT STUDY

Atamna Ahmed, MD , Abigail Fraser, MSc, Leonard Leibovici, MD

Background: Infections caused by multidrug-resistant (i.e. resistant to rifampin and isoniazid) *M. tuberculosis* (MDR-TB) pose a global threat. Management of MDR-TB is prolonged, expensive, more toxic than treatment of susceptible TB and often unsuccessful. The effectiveness of preventive treatment for close contacts of MDR-TB cases has been studied in only 2 observational studies, one prospective and one retrospective.
Objectives: To study the effectiveness of preventive treatment in close contacts of pulmonary MDR-TB cases.
Study design: Population based historical prospective cohort of all close contacts of pulmonary MDR-TB cases in Israel between 1998-2003. Data on close contacts of MDR-TB patients diagnosed between 1998-2003 were collected from patient files. The incidence of active disease among treated and untreated contacts was compared.

Significance: Mycobacterium Tuberculosis resistant to drugs that consist the mainstay of the antituberculous therapy (i.e. isoniazid and rifampin) 'poses a global threat . Management of MDR-TB is prolonged , expensive, more toxic than the treatment of susceptible TB and often unsuccessful, leading to further transmission of the disease. Thus, it is of great importance to ascertain that prophylactic treatment is effective in preventing the development of active disease and further disease spread.

Setting: Israel has a unique demography This country has a high incidence of TB and MDR-TB, 'mainly due to mass immigration from Ethiopia and countries of the former Soviet Union 'in which TB is endemic .Israel has formed a structural and efficent program for treatment and follow up of TB patiens and their close contacts . Between 1999-2002 Israel was among the countries in which the prevalence of MDR-TB IS greater than 10% .

Results: between 1999-2003 there were 78 cases of MDR-TB in Israel with '476 close contacts identified. The largest part of the contacts did not receive any treatment (81.3%) Of those who did receive treatment (18.7%) the vast majority (71 patients out of 89) received Isoniazid for prophylaxis .No contact developed active disease, whether he received prophylactic treatment or not .

Conclusion: most of the close contacts of MDR-TB patients didn't receive any prophylactic therapy. No contact developed active disease .
The effectiveness of prophylactic treatment for close contacts of MDR –TB is doubtful .

Key words: MDR-TB, treatment of latent TB, close contacts, population based cohort.

CYSTIC FIBROSIS

Frederic Chopin as portrayed by Eugene Delacroix in 1838

The differential diagnosis of Chopin's mysterious illness includes Cystic Fibrosis

"^{18}FDG- PET/CT contribution to the assessment of lesion severity in Cystic Fibrosis"

Malena Cohen-Cymberknoh[1], MD, Martine Klein, MD [2], Shoshi Armoni[1], RN, David Shoseyov[1], MD, , PhD, Marina Orevi[2], MD, Roland Chisin[2],MD and Eitan Kerem[1], MD.
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Rationale
Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations in the CF trans-membrane conductance regulator (CFTR) protein. The most characteristic feature of inflammation in the CF lung is the persistent infiltration of massive numbers of neutrophils into the airways. During an inflammatory process activated neutrophils use glucose as an energy source throughout their respiratory burst that can be measured by PET (Positron Emission Tomography) imaging by tracing the glucose analog ^{18}F-fluorodeoxyglucose (^{18}F- FDG).
Objective
The aim of this study was to assess the value of PET/CT using ^{18}F- FDG for the evaluation of the severity of lung inflammation/ infection in CF patients.
Design: Methods and Participants
Fifteen patients with CF (ages 14-54 yrs) were enrolled in the study. PET/CT results were interpreted by using the PET severity score (PSS) based on the number of foci and the maximum standardized uptake values (MSUV). In addition the outcome was correlated to clinical parameters.
Main outcome measures and results
In most patients hot foci varying in number and intensity were detected by FDG-PET. Correlation of the foci location with the corresponding CT image allowed accurate localization of the lesions. Total peripheral neutrophil counts could be correlated with PSS values, however, no association with FEV_1 was observed.
Conclusions
This study suggests the feasibility of using PET to assess lung inflammation or infection in CF. Larger studies are needed to validate these results and to determine if FDG-PET/CT can indeed predict the severity of disease progression in patients with CF.

This work was presented by Dr. M. Cohen-Cymberknoh at the 20th NACFC, Nov 2006 in Denver as a **Pediatric Clinical Fellows Session** lecture
e-mail of presenting author: malena@hadassah.org.il

LUNG TRANSPLANTATION

Living Donor Lobar Lung Transplantation

MR Kramer, MD
Rabin Medical Center

Although cadaveric lung transplantation (CLT) offers acceptable prospects for 5-year survival, donor shortage remain to be a major problem. In an effort to address the donor shortage issue, living-donor lobar lung transplantations (LDLLT) have been performed in some institutions.

As of 2007, LDLLT has been performed in approximately 350 patients worldwide. The survival appears to be similar to or even better than International Society for Heart and Lung Transplantation registry data on CLT.

The operation requires parallel 3 operative teams but technically is only slightly more complicated then a standard cadaveric transplant. This type of procedure has been performed recently in a case of pulmonary fibrosis post bone marrow transplantation in Israel however despite the technical success the patient died of multi-organ failure.

Although the possible risk for the donor with standard lobectomy is small it is not negligible and therefore LDLLT should be reserved only for very sick patients by a well-prepared program. This type of procedure should be applied mostly to young patients with cystic fibrosis but can be offered to restrictive, obstructive, infectious, and hypertensive lung diseases for both pediatric and adult patients who would die soon otherwise. A strong motivated and supportive family is needed to facilitate such a procedure.

Effects of side-mismatching for single lung transplantation – role of quantitative lung perfusion scintigraphy

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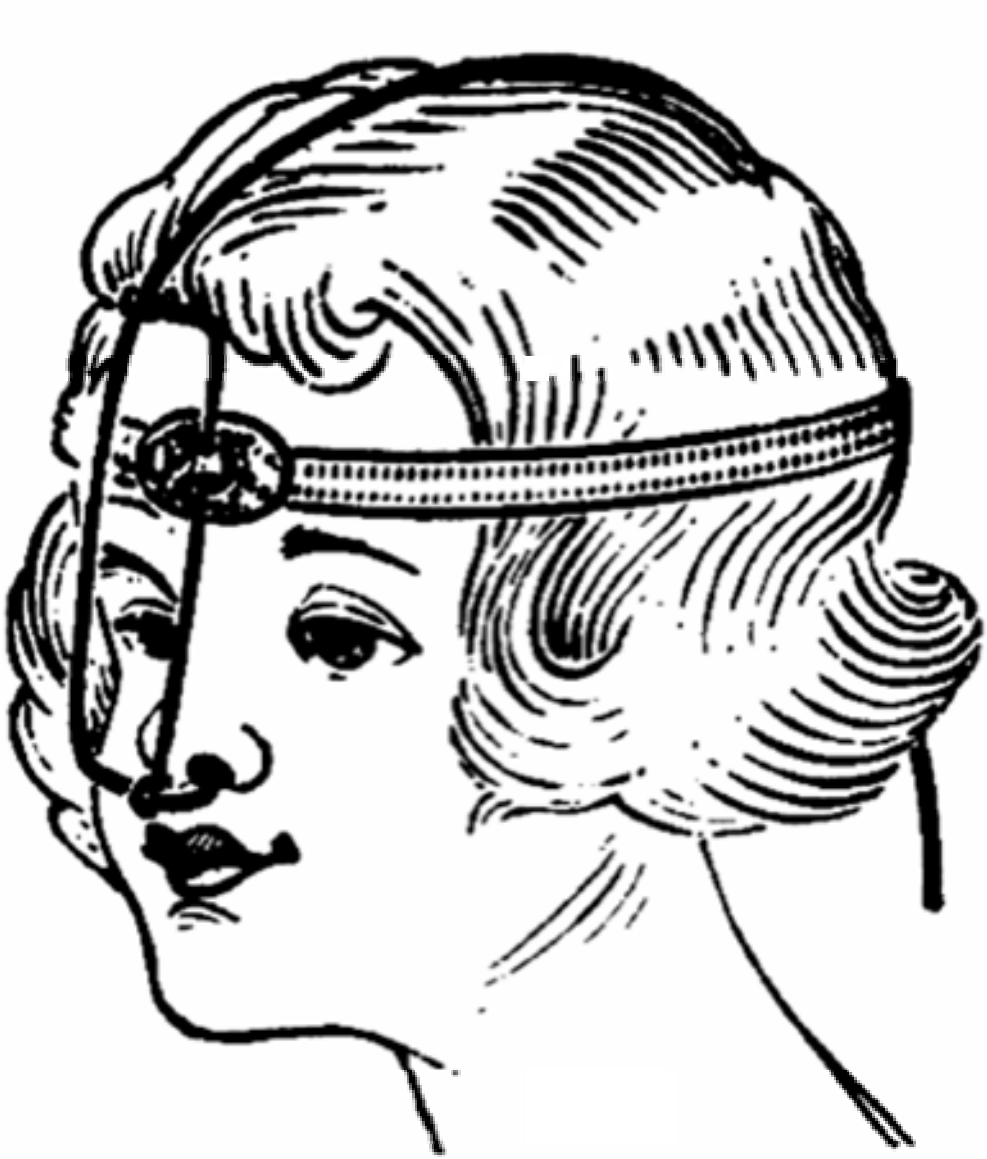
OBJECTIVE
When listing a patient for single lung transplantation, the preferred side to transplant is chosen according to the quantitative lung perfusion scintigraphy (QLPS). Ideally, the lung with preferential perfusion according to QLPS is retained. However, if grafts become available that are suitable for a particular donor in all aspects except the side, then transplantation is usually still performed – this is defined as *side-mismatching*. We performed a retrospective review of cases to determine whether side-mismatching leads to poorer outcomes than patients with side-matched grafts.
DESIGN
A retrospective review of 114 patients that underwent single lung transplantation in our institution.
SETTING
The pulmonary transplantation service based in Beilinson hospital.
PARTICIPANTS
One hundred and seventeen patients were reviewed, and three excluded since their pre-operative QLPS could not be established. Of these 114 patients, 17 patients received side-mismatched grafts, and 97 side-matched grafts.
INTERVENTIONS
Patients were defined as side-matched or mismatched a using a prospectively designed formula.
MAIN OUTCOME MEASURES
We examined FEV1, 6 minute walk, peak oxygen uptake at pre-transplant and after 6 months with ANOVA. Intra-operative parameters were requirement for cardiopulmonary bypass and ischemic time. Total graft perfusion at 6 months was recorded. All-cause mortality between the two groups was evaluated with the Kaplan-Meier technique.
RESULTS
There were no significant differences between the matched/mismatched groups in baseline and 6 month variables. All parameters improved significantly following transplantation. There was also no difference in intra-operative and mortality statistics between the two groups.
CONCLUSIONS
Side-mismatching of lung grafts according to QLPS does not seem to adversely affect outcome following single lung transplantation.

PULMONARY HYPERTENSION



This drawing of the use of nasal prongs to deliver oxygen dates to 1907

Development of Pulmonary Hypertension after arterio- venous access formation in end stage renal disease patients – another piece of the puzzle

Mordechai Ygla MD et al
Rambam Medical Center, Haifa

Abstract not submitted

SLEEP RELATED BREATHING DISORDERS

The Sleeping Beauty
Edward Burne –Jones
1890

Increased erythrocyte adhesiveness and aggregation in OSA

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[1]Pulmonary Institute, Rabin Medical Center & [2] Int. Medicine D, Tel Aviv Sourasky Medical Center.

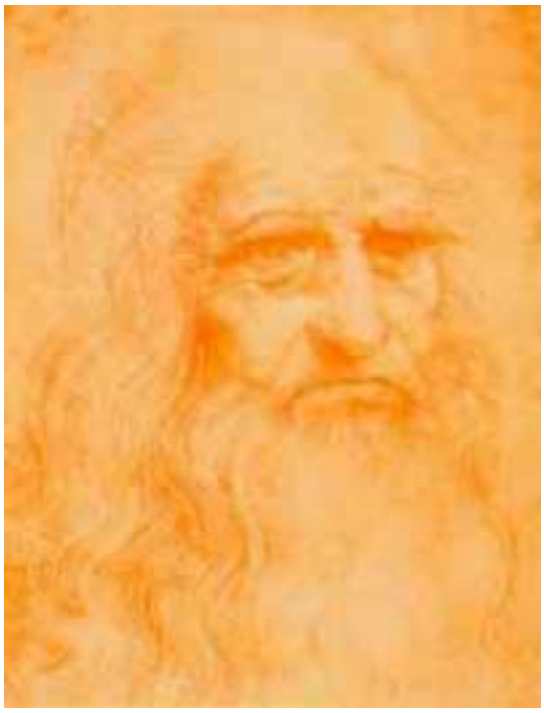
Background: Obstructive sleep apnea (OSA) is associated with an increased incidence of stroke and myocardial infarction as well as increased prothrombotic and inflammatory processes. Although erythrocyte adhesiveness/aggregation is known to be elevated in cardiovascular diseases, it has never been evaluated in OSA. The aim of this study was to examine the possible association of OSA and erythrocyte adhesiveness/aggregation.

Methods: The study was conducted in the Sleep Laboratory of a tertiary university-affiliated medical center in 79 patients (age 57.1±12.9 years) with a diagnosis of OSA (apnea hypopnea index 41.2±25.9). Findings were compared with data on 1079 controls without clinical symptoms of OSA, matched for sex, age, and body mass index. Overnight polysomnography and blood sampling for erythrocyte sedimentation rate, levels of fibrinogen, high-sensitivity C-reactive protein, and erythrocyte adhesion/aggregation test consisting of measures of erythrocyte percentage and vacuum range on image analysis.

Results: The study group had significantly higher values than controls of all three markers of inflammation ($p<0.001$ for erythrocyte sedimentation rate and fibrinogen; $p= 0.037$ for C-reactive protein). Erythrocyte percentage was significantly lower in the sleep apnea group (84.05±15.97 vs. 90.79±11.23%, $p<0.001$), and vacuum range was significantly higher (8.22±7.98 vs. 4.63±4.05 microns, $p<0.001$), indicating stronger erythrocyte adhesion/aggregation. Both these factors were significantly correlated with erythrocyte sedimentation rate and to h-CRP (percentage: r=-0.630; 0.258, p=0.005; 0.031; vacuum range: r=0.494; -0.328, p=0.001; 0.005 respectively).

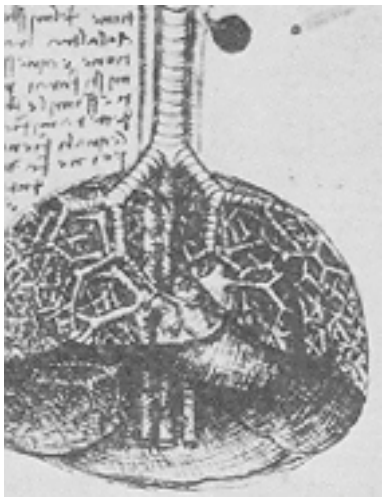
Conclusion: OSA is associated with increased erythrocyte aggregation/adhesion, which is correlated with an increase in inflammation markers. These findings might help explain the increased cardiovascular morbidity in OSA.

INFLAMMATION



Self Portrait

Leonaro da Vinci – 1515



Study of lungs

Oxidative stress biomarker in Exhaled Breath Condensate (EBC) vs Eosinophils count in Induced Sputum (IS) in the assessment of lung diseases

Elizabeth Fireman, PhD[1], Shtark Moshe, MD[1],Israel E. Priel, MD [2] Robert Shiner, MD [3], Ram Mor, MD [1], Joel Greif, MD [1] and Shmuel Kivity, MD[1],

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[3]Hertzelia Medical Center, Israel

Oxidative stress can be assessed and monitored through the determination of biomarker levels, such as hydrogen peroxide (H_20_2), which may be found in biological samples, among them serum, bronchoalveolar lavage, induced sputum (IS) and exhaled breath condensate (EBC). *Aim*: To compare the application of EBC and IS in the assessment of inflammation in pulmonary diseases. *Study Population:* We studied 55 patients who were referred to our laboratory for IS: 16 (mean age 59±10 years) had obstructive lung disease (OLD), 21 (42±15 years) had persistent cough (PC, cough duration >6months) and 18 (46±16 years) had interstitial lung disease (ILD). There were 10 (42±18 years) healthy controls (CO). *Methods:* EBC was collected by suspending a 1.5-m Teflon perfluoroalkoxy tube with a 0.5-cm internal diameter installed in a polystyrene foam container filled with ice and connected to a 10-mL polypropylene test tube. The subjects breathed tidally for 20'. At least 3 ml of EBC was collected for each case and tested immediately (within 30 min). IS was recovered after 20' inhalation of 3% saline with an ultrasonic nebulizer and 300 cells were differentially counted in cytospin Giemsa-stained slides. H_20_2 was measured by a method based on oxidation of phenolsulfonphthalein (phenol red) mediated by horseradish peroxidases (HRPO) and H_20_2. Pulmonary function tests were performed by conventional methods *Results:* H_20_2 levels in EBC were *significantly* different between groups: 0.24±0.16 μM in OLD, 0.11±0.12 μM in PC, 0.08±0.04 μM in ILD and 0.002±0.04 μM in CO ($p<0.05$ OLD vs ILD, PC and CO). % eosinophils in IS was also different: 8.2±8.3% in OLD, 1.3±1.6% in PC, 3.3±3.6% in ILD and 0% in CO ($p<0.05$ OLD and ILD and CO but not vs. PC). A positive and significant correlation was found for each group and for all patients combined between % eosinophils in IS and the levels of H_20_2 in EBC. *Conclusions*: Eosinophils in IS correlate to lung redox deviations in EBC in a wide spectrum of lung diseases

Osteopontin: A Novel Glycoprotein Involved in Allergen-Induced Airway Inflammation and Remodeling

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Hadassah – Hebrew University Medical Center, Jerusalem, Israel

Background: Airway remodeling is a central pathophysiological feature of chronic asthma. Extracellular matrix (ECM) components not only provide structural support to tissues, but also influence cellular migration, proliferation, differentiation, apoptosis, and mediator release. ECM composition is altered in chronic asthmatic lungs, suggesting that some ECM elements may be involved in the development of airway remodeling. Osteopontin (OPN) is an ECM glycoprotein with profibrotic properties; however its role in airway remodeling in asthma has not been explored.
Objective: Determine the expression and cellular sources of OPN and evaluate whether this glycoprotein affects structural changes in a murine model of allergen-induced airway inflammation and remodeling.
Methods: BALBc, C57BL/6 and OPN-knockout mice were sensitized and exposed to ovalbumin (OVA) or saline inhalations for 5 weeks and sacrificed 24 hours after the last inhalation. The following parameters of inflammation and remodeling were assessed: bronchoalveolar (BAL) fluids differential cell counts, collagen production (colorimetric biochemical assay), peribronchial smooth muscle content (immunohistochemistry followed by image analysis), and mucus expression (PAS staining). Matrix metalloproteinase-2 (MMP-2) activity was determined by zymography. OPN expression in BAL and lung tissue was determined by PCR and ELISA. Cellular sources and distribution of OPN were evaluated by immunohistochemistry and immunofluorescence.
Results: OPN expression is upregulated in lung tissue and BAL fluids of OVA-treated mice. Cells producing OPN include airway epithelium and cells of the submucosal inflammatory infiltrate (T cells, eosinophils, and macrophages). OPN deficiency is associated with reduction of lung collagen production, as well as reduction of MMP-2 activity, peribronchial smooth muscle area and mucus expression. Positive staining for OPN was also observed in bronchial tissue from human asthmatic subjects.
Conclusion: Our results demonstrate that OPN expression is associated with structural changes occurring in the lungs, suggesting a profibrotic role for this ECM glycoprotein in airway remodeling in asthma.

The LPS receptor CD 14 in Sarcoidosis

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Rationale: Sarcoidosis is a complex inflammatory disease of unknown etiology. It is generally accepted that genetic factors influence susceptibility for the development of sarcoidosis. Polymorphisms of the lipopolysaccharide (LPS) receptor "CD14" are associated with disease susceptibility in Crohn's disease. Taking into account the similarity in the immunopathophysiology of sarcoidosis and Crohn's disease (CD), we analyzed gene polymorphisms of CD14 (T/C at position -159) in patients with sarcoidosis and assessed the clinical significance of these differences. We also evaluated the levels of soluble CD14 (sCD14) in sarcoidosis patients compared to the general populations.

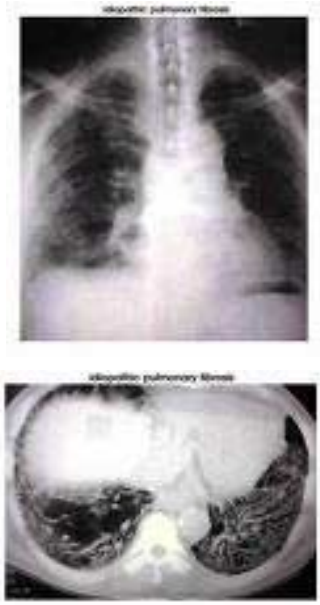
Methods: DNA was obtained from 74 sarcoidosis patients and 85 healthy individuals. Genotyping was performed by allele specific PCR. sCD14 levels were evaluated by ELISA. A detailed clinical interview was done with both the patients and their treating physicians.

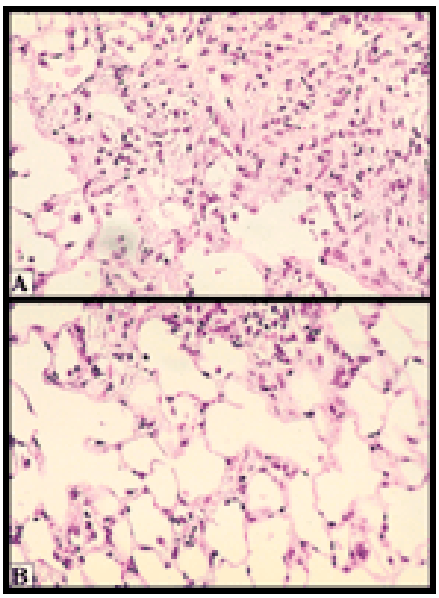
Results: Mean levels of sCD14 were 1.9 ± 0.96 □g/ml in the sarcoidosis patients, and 1.31 ± 0.77 □g/ml in the controls ($p = 0.001$). The frequency of TT genotype was 29.73% in the sarcoidosis group compared to 20% in controls ($p = 0.014$). We did not find a correlation between genotype and the level of sCD14. Patients with the TT phenotype were likely to be diagnosed at a younger age, have worse lung function tests, less extra-pulmonary features and shorter delay between onset of symptoms and initial diagnosis.

Conclusions: Our results suggest that the TT genotype of the CD14 promoter may increase susceptibility for developing sarcoidosis and may be associated with a specific disease phenotytpe. The level of sCD14 is a possible marker for sarcoidosis.

Pulmonary Fibrosis

Bleomycin induced pulmonary fibrosis





The role of FLIP in regulating lung myofibroblast's Fas signaling of apoptosis and proliferation

Regina Golan-Gerstl MSc, Shulamit B Wallach-Dayan PhD, and Raphael Breuer MD

Lung Cellular and Molecular Biology Laboratory, Institute of Pulmonary Medicine

Hadassah – Hebrew University Medical Center, Jerusalem, Israel

Background: Fibrosis is characterized by an excess growth of myofibroblasts. This fact may implicate that myofibroblasts possibly possess excessive proliferation or other mechanims to overcome inducers of their own apoptosis.
In spite Fas overexpression, a membranal receptor known to signal apoptosis via caspase-8 activation, their fibrotic lung myofibroblasts are resistant to Fas-induced apoptosis. Caspase-8/FLICE inhibitor protein (FLIP) was shown to deviate Fas-induced apoptosis towards proliferation by binding to Fas death domain (FADD).
Hypothesis: We hypothesize that fibrotic-lung myofibroblasts are resistant to Fas-induced apoptosis, but sensitive to Fas-induced proliferation, by a mechanism of FLIP upregulation.
Methods: Myofibroblast resistance to Fas-induced apoptosis and the sensitivity to Fas-induced proliferation or apoptosis is manipulated by down regulation of FLIP using small interference RNA (siRNA). Cell growth, was assessed by methylen blue, Annexin, PI, BrdU, trypan blue and microscope analysis. FLIP-FADD complex was detected by immunoprecipitation with anti-FADD-specific antibody.
Results: Fas activating mAb, in myofibroblats, signals proliferation rather than apoptosis. FLIP expression was upregulated in vivo and in lung myofibroblasts isolated from bleomycin treated mice. FLIP form complexes with FADD and this is dependent of Fas activation. Downregulation of FLIP regained the induction of myofibroblast Fas induced death.
Conclusions: Our results indicate that FLIP contribute to proliferation of myofibroblasts, isolated from murine fibrotic lungs, by inhibition of Fas induced death, this may contribute to progression of the fibrotic process.

The Mechanisms of Thy1-Mediated Regulation of Lung Myofibroblasts Apoptosis and Proliferation

Pazit Y. Cohen MSc, Shulamit B. Wallach-Dayan, PhD, and Raphael Breuer, MD

Lung Cellular and Molecular Biology Laboratory, Institute of Pulmonary Medicine
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Background: Abnormal accumulation of fibroblasts in the interstitium and alveolar space is characteristic of lung fibrosis. Two subpopulations of myofibroblasts, distinguished by expression of Thy1, have been detected in human and murine lungs. It has been shown that myofibroblasts proliferating in lungs of humans with IPF and of bleomycin-treated mice are $Thy1^-$. Fas-Fas ligand pathway has essential roles in the development of pulmonary fibrosis. Fas –FasL interaction does not always correlate cell death. Molecules such as FLIP appear to be able to block Fas-induced cell death. Fas has also been shown to transduce proliferation signals.
Hypothesis: We hypothesize Thy1 inhibits the proliferation and/or induces apoptosis of lung myofibroblasts, and regulates myofibroblast accumulation in lung fibrosis via modulation of the Fas/FasL pathway signaling.
The proliferation rate and Fas/FasL pathway molecules expression were studied in $Thy1^+$ or $Thy1^-$ myofibroblasts.
Methods: Cell proliferation was detected by two methods: cell mass measurement by methylene blue staining and DNA synthesis by BrdU. Fas and FasL expression was detected by flow cytometry analysis and FLIP expression was analyzed by Western blot.
Results: We show that, the proliferation rate of $Thy1^-$ myofibroblasts was higher than that of $Thy1^+$ myofibroblasts. Moreover, we show that the overexpression of Fas and FLIP in $Thy1^-$ rather than $Thy1^+$ myofibroblast subpopulation, while, FasL is overexpressed in $Thy1^+$ rather than $Thy1^-$ myofibroblasts.
Conclusion: These results demonstrate that Thy1 expression in lung myofibroblaststs is associated with lower proliferation rate which may be explained by their Fas, FLIP and FasL levels of expression.

Myofibroblast's Escape From Immune Surveillance:
A Mechanism for Tissue Fibrosis

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Lung Cellular and Molecular Biology Laboratory, Institute of Pulmonary Medicine
Hadassah – Hebrew University Medical Center, Jerusalem, Israel

Background: Lung fibrosis consists of impaired tissue remodeling after injury, with myofibroblast accumulation and collagen deposition. We showed that $FasL^+$ myofibroblasts from lungs of wild-type (*wt*) C57BL/6 mice with bleomycin (bleo)-induced fibrosis, but not from normal saline-treated lungs, kill Fas^+ lymphocytes *in vitro* and *in vivo*, resist Fas- and immune cells-induced apoptosis, and survive longer after being engrafted into air-pouches of allogeneic BALB/c mice.
Hypothesis: We hypothesize that fibrotic lung myofibroblasts possess an immune privilege phenotype which is dependent on FasL cytotoxic effects.
Methods: Assessment of myofibroblasts' "counterattack" of immune cells during fibrosis was performed by immunonofluorescence, in lung sections of bleo-induced fibrotic lesions of *wt* versus FasL-deficient- chimeric *gld*-mice. Assessment the FasL dependency of myofibroblasts prolonged survival in allogeneic mice was performed by quantitative fluorescence analysis in hosts lungs and air-pouches.
Results: $FasL^-$ myofibroblasts from lungs of bleo-treated chimeric *gld* mice, which had been reconstituted with *wt* ($FasL^+$) hematopoietc cells, show decreased accumulation in the lungs and air pouch of mice following alloengraftment.
Conclusion: This results define the role and mechanism of Fas and FasL molecules in myofibroblasts escape from immune surveillance during the evolution of lung fibrosis and hopefully identify possible therapeutic targets for interventions in this disease state.

Telomerase Activity of Epithelial Cells in Bleomycin-Induced Lung Fibrosis

Zvi G Fridlender, MD, MSc, Nissim Arish MD, Shulamit Wallach-Dayan PhD, Regina Golan-Gerstl MSc and Raphael Breuer MD

Lung Cellular and Molecular Biology Laboratory, Institute of Pulmonary Medicine Hadassah – Hebrew University Medical Center, Jerusalem, Israel

Background: We have previously found that changes in telomerase activity play a role in lung epithelial cell apoptosis *in-vitro* by a mechanism that is independent of significant average telomere loss.
Aim: To evaluate *in-vivo* the role of telomerase and telomeric length in epithelial cells of bleomycin-treated lungs in mice.
Methods: C57Bl/6 mice were sacrificed at 1,3,7,14 and 21 days post Intratracheal instillation of bleomycin or saline. Lung inflammation was confirmed by broncho-alveolar lavage, and fibrosis by Sircoll-Red collagen assay. Lung epithelial cells (LEC) were isolated by negative selection using specific cell markers mAbs. Telomerase activity was assessed by the TRAPeze kit, and telomeric length by southern blot. mRNA encoding for the catalytic unit of telomerase (mTERT) was quantified by RT-PCR. Apoptosis (M30) and telomerase levels (mTERT) were evaluated by immunohistochemistry of lung sections.
Results: Immunohistochemical studies at day 7 showed increased apoptosis in bleomycin compared to saline-treated mice (24 and 5 cells per hpf respectively). Significant expression of telomerase was noted at days 7, 14 and 21 in bleomycin-treated mice. increased telomerase activity was detected in LEC which survived bleomycin compared to control mice at day 7 by 36%, and at day 14 by 68%, going down to only 7% at day 21. Average telomeric length showed no change between bleomycin and control mice at all time points.
Conclusions: The telomerase system may represent a defense mechanism of lung epithelial cells from bleomycin-induced injury, independent of change in the average telomeric length.

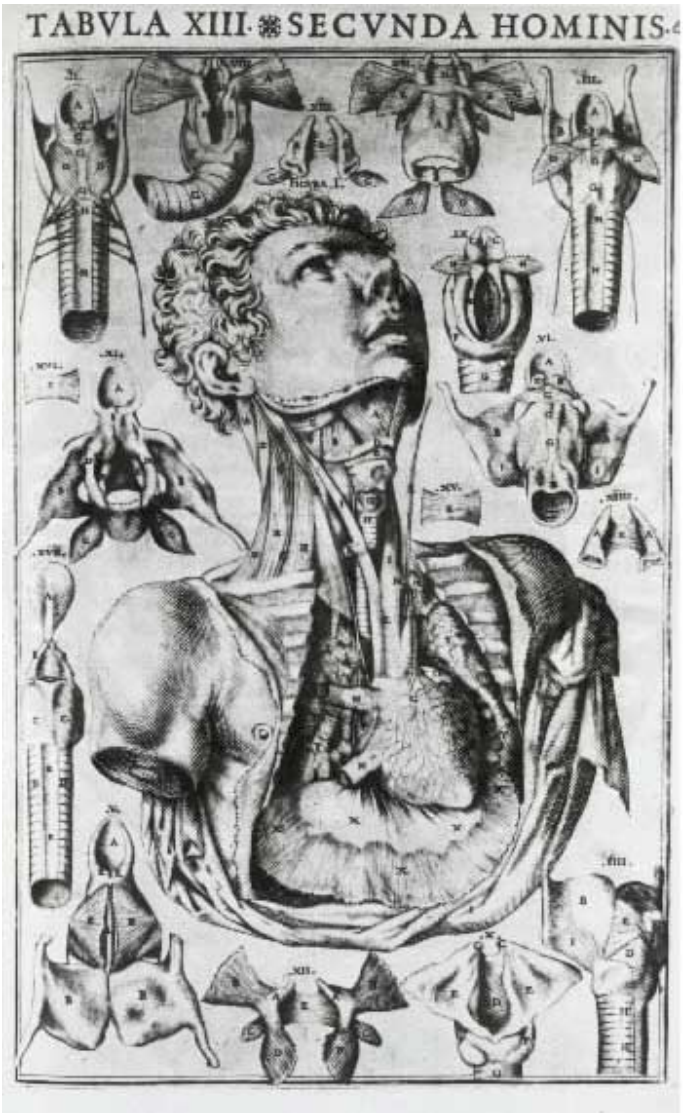
Over-expression of Telomerase Protects Lung Epithelial Cell From Bleomycin- and Fas-Induced Apoptosis

Nissim Arish , MD, Zvi G Fridlender MD, MSc, Shulamit Wallach-Dayan PhD, and Raphael Breuer MD

Lung Cellular and Molecular Biology Laboratory, Institute of Pulmonary Medicine Hadassah – Hebrew University Medical Center, Jerusalem, Israel

Background: we have previously confirmed that bleomycin and Fas molecule cause epithelial cell apoptosis *in vitro* and *in vivo*. Preliminary results in our laboratory show that inhibition of telomerase activity with TMPYP4 increased bleomycin induced cell death and apoptosis. No change in telometric length was noted.
Hypothesis: We hypothesized that up-regulation of telomerase activity in lung epithelial cells will attenuate bleomycin- and Fas-induced apoptosis.
Methods: Up regulation of telomerase was done by transfection of plasmid containing hTERT c DNA into MLE cells. MLE cells transfected with the same plasmid without the hTERT gene was used as control. Telomerse activity was evaluted by TRAPeze telomerase detection kit and apoptosis by Annexin V staining following FACS analysis.
Results: After transfection with hTERT gene, there was a 35% elevation in telomerase activity, compared to control. Bleomycin , and Jo2 anti-Fas mAb increased apoptotic cells in the control group. However decreased apoptosis was detected in the hTERT transfected cells.
Conclusion: Up- regulation of telomerase in lung epithelial cells may serve as a defense mechanism against bleomycin induced apoptosis and possibly the ensuing fibrosis.

Respiratory Physiology



Anatomy of the Respiratory System
Casserio Giulio 1616 ?

What can be learned from the effect of posture on the ventilatory response to hypercapnia in quadriplegia.

I Ben-Dov,MD, R Zlobinski, T Shulimzon,MD , M Gaides, MD, PhD, Z Yemini RT, and G Zeilig.
The Pulmonary Institute and the Neurological Rehabilitation Department, Tel Hasomer Medical Center and Sackler Merdical School, Tel-Aviv University

Background: Low cervical, C_{5-8} transection causes quadriplegia and paralysis of the intercostal muscles but leaves the diaphragm intact. Lung function in these patients is markedly reduced. However, it is not clear how the response to hypercapnia, which depends on the respiratory muscle and on its control system is modified in these subjects.
Subjects: 12 patients with chronic low cervical, C_{5-8} transection and 7 healthy controls.
Tests: Standard rebreathing (initial CO2 concentration of 7%) with plots of ventilation against PetCO2.
Findings: In the patients, the response to hypercapnia was largely posture dependent. The slope (SD) of the curve, $V_E/Petco_2$ (L/min/mmHg) is shown below.

	sitting	Supine
Patients	0.8 (0.4)	1.8 (0.7)
Controls	2.46 (0.6)	2.3 (0.6)

The only significantly lower slope was that of the patients at the sitting position.
Conclusion: Surprisingly, the response in low cervical, C_{5-8} transection to hypercapnea is normal at the supine position. This means that muscle weakness, by itself, can not account for the reduced hypercapnic response in these patients. Respiratory control factors, such as postural blood pressure fall at the supine position may modify the response.

The 15 Steps Climbing Exercise Oximetry Test in Patients with Idiopathic Pulmonary Fibrosis

David Shitrit, MD
Rabin Medical Center, Campus Beilinson

Background: Exercise-induced hypoxemia in patients with idiopathic pulmonary fibrosis (IPF) occurs commonly; it has major effect on quality of life and predicts survival. Although the measurement of maximal oxygen consumption (VO2max) is considered as a gold standard of functional capacity in IPF, no simple objective test has been obtained.
Objectives: To assess prospectively the value of 15 steps climbing exercise oximetry test, a simple walking test, in patients with IPF.
Patients and methods: The study samples consisted of 51 patients with idiopathic pulmonary fibrosis. All underwent pulmonary function tests (PFT's), cardiopulmonary exercise test (CPET) and 6-minute walk distance test (6MWD) according to the American Thoracic Society standards. In addition, 15 steps climbing exercise oximetry test was done as part of their regular follow-up visit. Using continuous oximeter recording we measured oxygen saturation during 15 steps of climbing, and quantified oxygen desaturation by measuring the "desaturation area", defined as area under the curve of oxygen saturation from the beginning of exercise through the lowest desaturation point and until recovery to the baseline level of oxygen saturation. Desaturation area was correlated to pulmonary function test, CPET and 6MWD.
Results: Statistically significant correlations were noted between VO2max and all 15 steps climbing test parameters including the lowest saturation (p=0.002, r=0.43), desaturation area (p=0.005, r=-0.39), lowest saturation (p=0.002, r=0.43), saturation difference (p=0.02, r=-0.33), recovery time (p=0.02, r=-0.32) and desaturation area (p=0.005, r=0.39).
A good correlations were also noted between DLCO and the climbing test parameters, including lowest saturation (p=0.0001, r=0.52), saturation difference (p=0.0002, r=-0.50), recovery time (p=0.0001, r=-0.53) and desaturation area (p=0.0001, r=-0.53).
15 steps climbing test parameters were also correlated with total lung capacity including recovery time and desaturation area
In stepwise linear regression analysis we found that predictor's variables for VO2 max were 15 steps test lowest saturation and 6MWD.
Conclusions: In patients with idiopathic pulmonary fibrosis the 15 steps oximetry test is a simple and accurate test for evaluation exercise-induced hypoxemia and functional capacity.

Tissue perfusion may be assessed at the bedside with ETCO2-derived dead-space estimation – a pilot study

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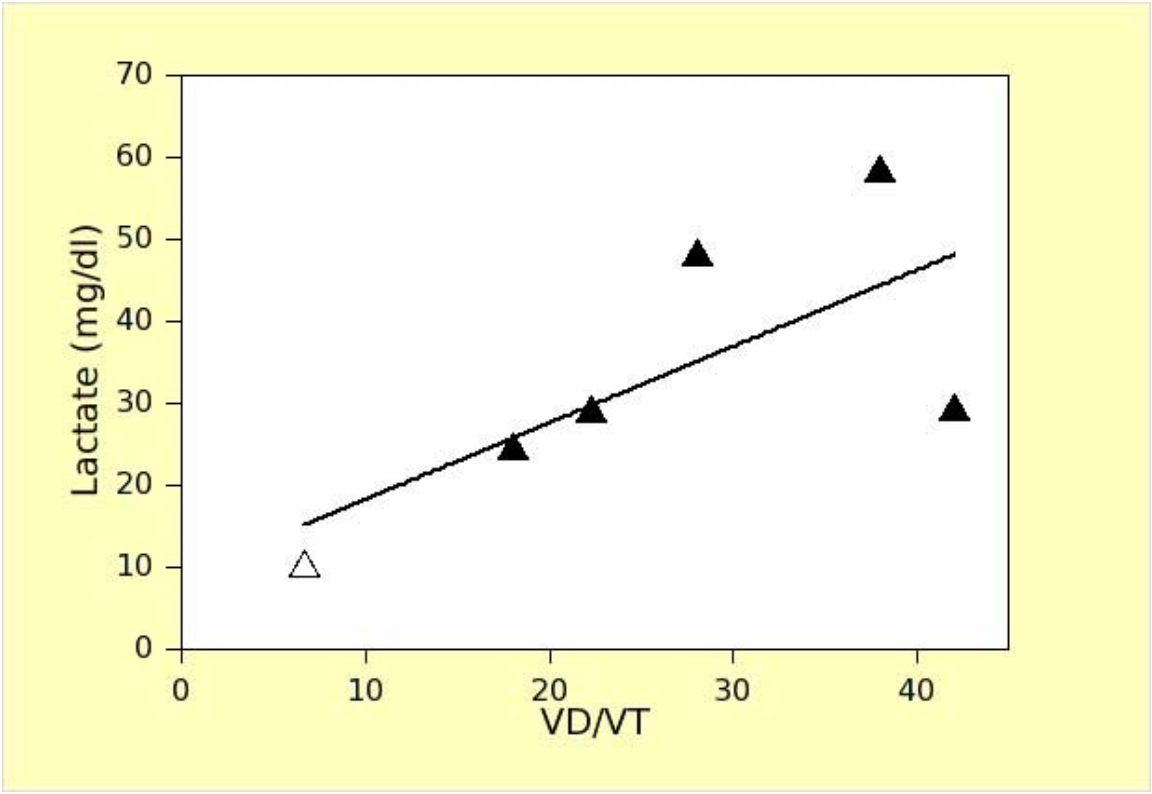
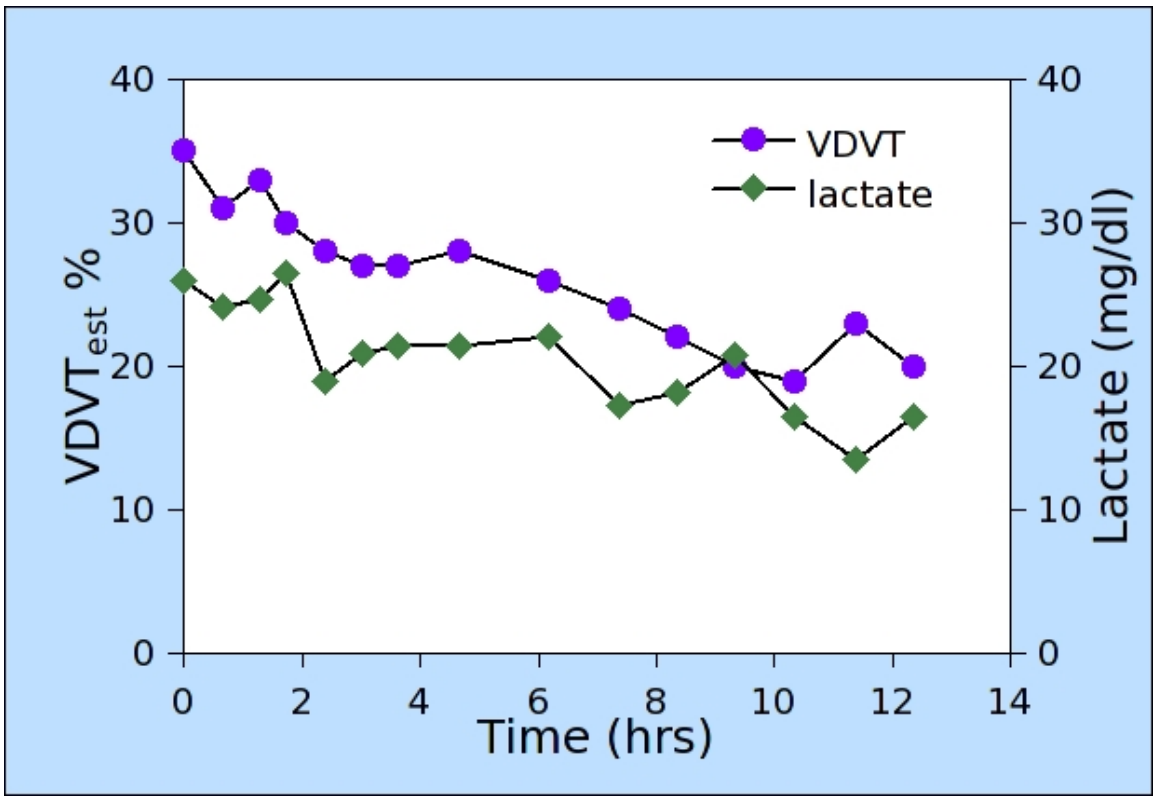
Rabin Medical Center, Petach Tikva, Israel

Objective
We evaluated bedside estimations of the alveolar dead-space as a marker of adequate resuscitation in the intensive care unit. Alveolar dead space is determined by the degree of ventilation/perfusion mismatch in the lung. Since the entire cardiac output must pass through the lungs, we hypothesized that global changes in tissue perfusion would correlate with changes in alveolar dead space. We used blood lactate as the endpoint of resuscitation.
Design
Prospective non-interventional observational study.
Setting
A teaching hospital intensive care unit.
Participants
Five mechanically ventilated patients with lactic acidosis (lactate >30 mg/dl). Four patients were Post-laparotomy, one had multiple trauma. Ages 36-87, APACHE-II scores 18-37, P:F Ratio203/470. One non-shocked patient was enrolled as a control.
Interventions
We recorded HR, MAP, CVP, $ETCO_2$ from the ICU monitor during the first 12 hours of resuscitation. We took arterial blood samples at 30 minute intervals for the first four hours of the study, then every hour for a total of 12 hours.
Main outcome measures
Dead space (VDVT) was calculated from a modification of the Bohr Equation: $VDVT = (PaCO_2 – ETCO_2) \div PaCO_2$. We calculated correlation between VDVT and blood lactate.
Results
On a within-patient analysis, there was a significant linear correlation ($p<0.05$) between VDVT and lactate in 4/5 shock patients. When analysed as a group, there was a linear correlation between VDVT and lactate ($r=0.67$; $p<0.05$), figure 1. Furthermore, when plotted against time, the trends in $VDVT_{est}$ and lactate are parallel (example data from study patient 1 are shown), figure 2.
Conclusions
In this pilot study we demonstrated linear correlation between estimated dead-space and lactic acid levels. We propose that this technique may be a useful end-point of resuscitation during shock. It is convenient to measure, requires no special equipment and is non-invasive. Further study is required to assess the technique's reliability across different patient populations and disease states.


Lactate (mg/dl)
VD/VT
0
10
20
30
40
50
60
70


VDVT
lactate
VDVT$_{est}$ %
Lactate (mg/dl)
Time (hrs)
0
2
4
6
8
10
12
14
10
20
30
40

Physiological dissociation of ventilation and perfusion in a normal lung.

Mark Gaides, Ph.D., MD [1, 2],
[1]The Cardio-pulmonary exercise laboratory, The Pulmonary Institute,
The Chaim Sheba Medical Center, Tel Hashomer.
[2]The clinical physiology laboratory, the Cardio-Surgical Medical Center, Yerevan, Armenia (1978).

Background: It is known, that gas-exchange functions in lungs are carried out by pulmonary functional units (LFU's) which consist approximately of 100 alveolar ducts and their vascular-capillary network. Out of every 6 LFU, only 1 ventilates and is perfused, while the other 5 LFU-s are resting (do not have ventilation and perfusion – functional reserve). It is believed that alveolar gas exchange happens in the active LFU's whereas in the rest there is no gas exchange at all. Therefore it is assumed that there is a high amount of reserve in the lungs.
Lung functional unit (LFU) consists of two subunits: ventilated (fanned) (VFU) and perfused (PFU) functional units.
Methods: In acute animal experiment (8 healthy dogs) separated latex injection into pulmonary vessels and into bronchi was performed.
Results: It was seen that VFU (alveoli) sustained a non perfused (empty) state, but non ventilated VFU (alveoli) sustained a perfused state.
Conclusions: Results of the experiment is shown that 1 out of every 6 LFU s there was ventilation without perfusion and in the rest LFU's there was perfusion without ventilation. Alveolar gas exchange did occur in the LFU's which had perfusion without ventilation.
This experiment shows that there are no reserves in the lungs, or there are very few.

This study was performed in 1978 at the Clinical Physiology Laboratory, the Cardio-Surgical Medical Center, Yerevan, Armenia

Evaluation of Beta Blocking Treatment in Hypertensive Patients with and without left ventricular dysfunction by cardiopulmonary exercise testing.

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[1]"Gefen"- Cardiac Health Center, Givatayim, [2])Cardiac and [3]Pulmonary Institutes, Kaplan MC, Rehovot, Israel

Objective: To evaluate the physiological effect of beta-blockers in hypertensive patients(pts) with and without LV dysfunction compared to lone hypertensive pts treated with vasodilators by cardiopulmonary exercise test(CPET).
Design and Methods: 63 pts, 42 males and 21 females, were studied. They were divided into three groups:
A)16 lone hypertensive pts treated only with vasodilator agents.
B)26 lone hypertensive pts treated only with beta-blocking agents.
C)21 hypertensive pts with LV dysfunction treated with beta-blockers along with other medications.
A CPET was performed in all the pts while taking their medications, including beta-blockers.
The following indices were monitored and measured breath by breath during exercise: HR, BP, O2-consumption(VO2), O2-pulse(O2P), Ventilatory anaerobic threshold(VAT), and Respiratory exchange ratio(RER).
Maximal exercise capacity was considered when RER reached value of 1.15 or more.
Peak values of the cardiopulmonary indices were compared among the three groups, for each index separately, and P values less than 0.05 were considered statistically significant.
Results: The following table summarized the results:

Group	N	age	peak-HR*	peak-VO2*	peak-O2P*	VAT(%VO2-max)	peak-RER
A	16	58+/-13	90+/-8#	96+/-9#	108+/-13#	55+/-8#	1.17+/-0.12
B	26	59+/-10	69+/-12&	69+/-11&	102+/-33#	43+/-9&	1.17+/-0.1
C	21	53+/-8	72+/-8&	57+/-10$	79+/-14&	34+/-5$	1.18+/-0.09

*Expressed by % related to normal predicted values.
Statistically significant (referred to each column separately): # vs & or $; & vs $.
The indices “age” and “peak-RER” show no differences among the three groups.
Conclusions: Beta-blocking treatment demonstrates a significant physiological disadvantage compared to vasodilators in pts with lone hypertension. The physiological function in hypertensive pts with LV dysfunction is worse, and it is still to determine the balance between the benefit and the disadvantage of beta-blockers in these patients.

RESPIRATORY MUSCLE TRAINING IN OXYGEN DIVERS: REDUCED DYSPNEA AND INCREASED ENDURANCE

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PURPOSE: Dyspnea is common among divers who use oxygen enriched breathing mixtures in semi-closed and closed-circuit diving apparatus and constitutes a major limiting factor in combat diving. When not related to mechanical dysfunction of the diving apparatus or reduced efficiency of the CO2 scrubber, the dyspnea may be secondary to exercise-related carbon dioxide accumulation, respiratory muscle fatigue or changes in the CNS control of respiration. CO2 pressures as low as 1-2 kPa can potentiate CNS oxygen toxicity underwater. Thus, although alleviate dyspnea may improve diver performance, it can lead to CO2 accumulation with increased risk of CNS oxygen toxicity. We investigated whether respiratory muscle training (RMT) in healthy, trained oxygen divers might improve respiratory muscle strength and endurance, change the perception of dyspnea, and affect their exercise-induced CO2 accumulation.
METHODS: Twelve oxygen divers were included in the study and 9 in the control group. We recorded spirometry, maximal inspiratory (PImax) and expiratory (PEmax) pressures as measures of inspiratory and expiratory muscle strength, perception of dyspnea according to Borg scale, respiratory muscle endurance by PMpeak, and the respiratory response to CO2 accumulation for both groups before and after 42 days of RMT. RMT was carried out using the Threshold Inspiratory Muscle Trainer up to 80% and 15% of PImax in the study and control groups respectively.
RESULTS: Respiratory muscle endurance was significantly improved in the study group (PMpeak 120 21, 150 34 cmH2O before and after RMT respectively; p_0.01, repeated measures ANOVA), and their perception of dyspnea was significantly reduced (p_0.0004). No significant changes were found in spirometry parameters and respiratory muscle strength. CO2 level was not increased in the trained group and their was no change in the respiratory response to CO2.
CONCLUSION: In oxygen divers RMT training improve respiratory muscle endurance and dyspnea perception without CO2 retention.
CLINICAL IMPLICATIONS: RMT may improve the performance of oxygen divers without accumulation of carbon dioxide and therefore not compromising their safety.

Clinical Features of Patients with Severe Altitude Illness- in Nepal. Diagnosis and Prophylaxis Guidelines.

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Increasing number of people travel to high altitude for hiking and mountaineering purposes. Acute mountain sickness (AMS) and its severe complications, high-altitude cerebral edema (HACE) and high-altitude pulmonary edema (HAPE) are prevalent in this population.

AMS is a syndrome that commonly affects travelers who rapidly ascend to high altitude. The symptoms of AMS include headache, insomnia, lassitude, anorexia, nausea, vomiting, dizziness and lightheadedness. Clinical signs consist of facial, and leg edema, retinal hemorrhages and an increased heart and respiratory rate.

HACE is a potentially fatal neurological syndrome which typically presents with AMS symptoms progressing to incoordination, disorientation, altered consciousness, clouding of consciousness, coma and death. Some cases manifest with hallucinations, irrationality and seizures.

Early HAPE manifests as increasing fatigue, breathlessness in mild effort, chest tightness and a persistent dry cough. Left untreated, symptoms often aggravate, and frank pulmonary edema occurs with dyspnea at rest, cough productive of frothy, blood tinged sputum and rarely orthopnea. Progression of HAPE may lead to syncope or severe hypoxemia and respiratory failure resulting in decrease in consciousness, coma and death.

In the study we recorded the demographic characteristics of severe AMS patients evacuated to Kathmandu, Nepal.

During the 7 years period of the study 406 consecutive patient were included in the study. Among them 327 were evaluated retrospectively and 79 prospectively.

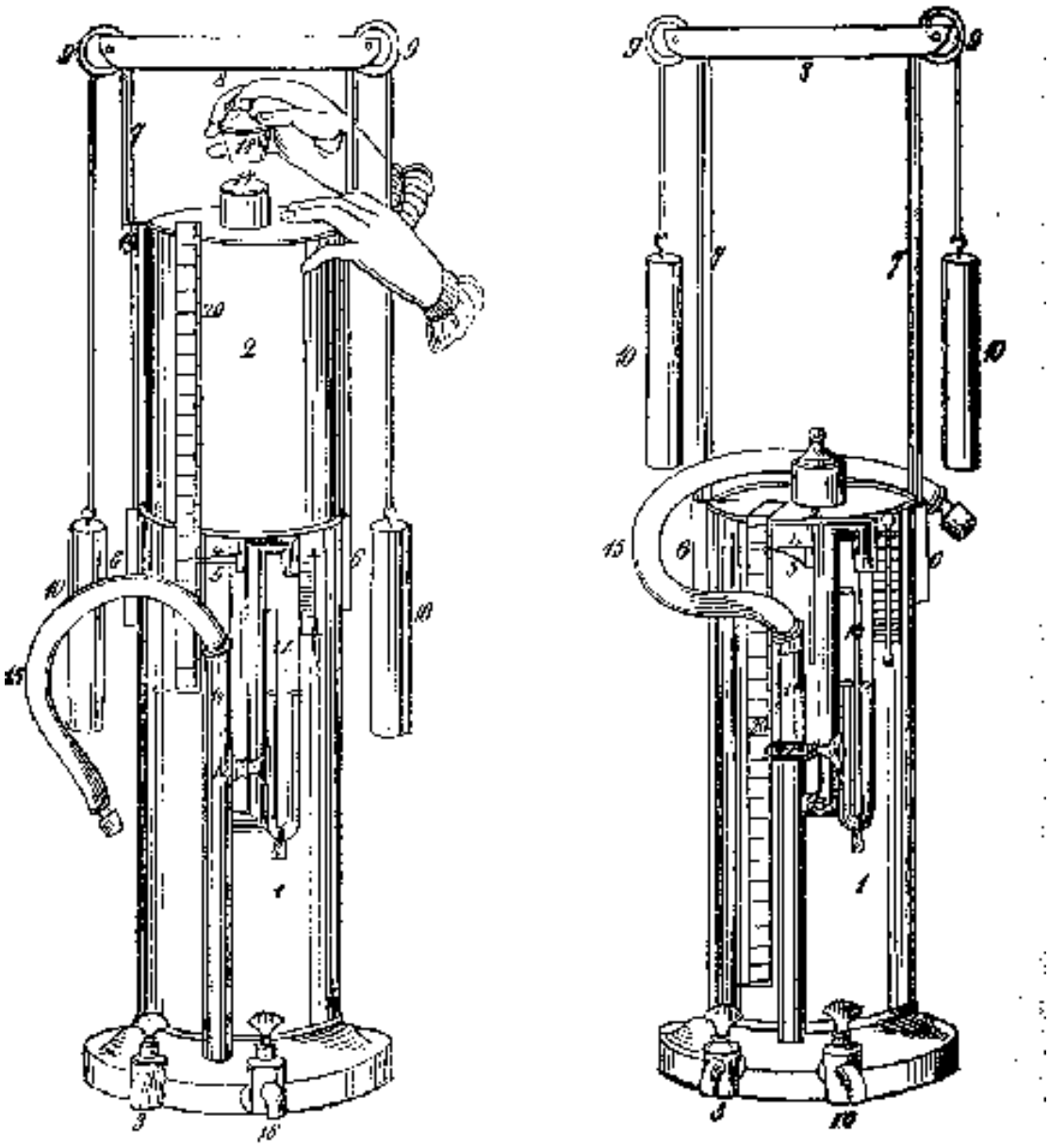
Patients in the study were significantly older than regular CIWEC patients (44 years old versus 31 years old respectively $p<0.0001$).

The most common trekking route in Nepal is the Annapurna region. The Relative Odds (OR) of severe mountain sickness of mountaineers compared to trekking in Annapurna region was 63, and the risk among trekkers in the Everest region was 21 times higher than in the Annapurna.

A large proportion of patients with severe AMS were those who trekked with groups and those who had concomitant infections. Most of the patients did not use AMS prophylaxis.

AMS prophylaxis consists of gradual ascent to altitude with an appropriate acclimatization schedule and pharmacological prophylaxis. Travelers planning to fly or rapidly ascent to 3000m altitude or above and those with previous history of AMS should consider Acetazoleamide prophylaxis (125-250mg bid) starting the day prior to the ascent. For travelers with past history of HAPE prophylaxis with Nifedipine (slow release 20-30mg bid) and inhaled Salmetrol (125mg bid) is recommended.

SPECIAL SESSION FOR AFFILATES



John Hutchinson's Spirometer

The Challenge of the Metacholine Challenge
Theory and Practice
Ariela Velner, RT
The Pulmonary Institute Chaim Sheba Medical Center

Methacholine challenge is commonly done and is highly sensitivity in asthma.
Due to its central role in the diagnosis of asthma, it is crucial that the challenge is done in a standard manner.
We will review the latest ATS recommendation that addresses background issues, indications and contraindications, safety issues of the subject and the technician, equipment, details on the various protocols and training demands.
We will also describe examples of individual tests including normal, abnormal and cases of special interest.
We will discuss new thoughts on patients with extreme response to methacholine and suggest a shortened version of the protocol, to improve the safety of these patients. At the conclusion of the presentation, we should be able to better standardize performance of methacholine challenge among the many centers in the country.

Francisco Jose Goya
Auto-portrait with Dr. Arietta
1820

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