The role of laboratory work-up in the diagnosis of occupational lung diseases

mahmetbud al-kineka ayinahom mahlohot tashokhitot bi-dard shait

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ISRAEL
Translational Research = Bench to Bedside

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The role of laboratory work-up in the diagnosis of occupational lung diseases

1. Airways Disease
   - Occupational Asthma

2. Interstitial Lung Diseases
   - Occupational Granulomatous Diseases
airways

Smooth muscle
Respiratory epithelium
Tracheal cartilage

Right lung
Right primary bronchus
Secondary (lobar) bronchi
Tertiary (segmental) bronchi
Bronchioles

Cardiac notch
Bronchiole
Pulmonary vein
Alveolar duct
Alveoli
Pulmonary artery
Today, asthma affects as much as 15% of the population in developed countries too) and has increased four fold in the last 20 years.

Family doctors and patients alike do not have sufficient knowledge about Occupational Asthma - only 15% of the asthmatic patients are asked by their doctor if their symptoms are related to work.
Asthma is common in the general population, including those in the workforce. Work exposures can cause or exacerbate asthma and can also be associated with asthma variants (e.g., eosinophilic bronchitis and aluminum potroom asthma) as well as symptoms that mimic asthma (e.g., the irritable larynx syndrome). In addition, even non-work-related asthma can affect the ability to work. This review focuses on current data about occupational asthma, defined as asthma due to conditions attributable to work exposures and not to causes outside the workplace.

One important and common subtype of work-related asthma that is not addressed further in this review is work-exacerbated asthma. As recently reviewed, work-related exacerbation of asthma — ranging from single transient exacerbations after an unusual exposure to daily work-related worsening that can mimic occupational asthma — may occur in up to 25% of working persons with asthma.
Algorithm for Evaluating an Adult with Asthmalike Symptoms for Sensitizer-Induced Occupational Asthma

Patient with asthmalike symptoms and work and clinical history compatible with occupational asthma

Assessment for asthma
(on the basis of reversible airflow limitation, airway hyperresponsiveness, or both and immunologic testing if possible)

No evidence of asthma

Asthma

Patient is working

Patient is not working

Consider return to work

Patient is working

No asthma
Investigate alternative conditions (e.g., rhinitis, hyperventilation, and vocal-cord dysfunction)

No asthma

Possible

Serial monitoring of PEF, with or without methacholine challenge, with or without sputum eosinophil counts at work and away from work, or specific inhalation challenge in the laboratory or at work if available

Specific inhalation challenge in the laboratory not available

Specific inhalation challenge in the laboratory available

If occupational asthma is strongly suspected from history, a combination of objective evidence of asthma plus a positive skin test for specific IgE antibodies to the suspected agent has high predictive value for occupational asthma

Negative test results do not rule out the diagnosis, but the history alone is poorly predictive, underscoring the need for early suspicion and early investigations when the patient is still working

Negative

Sensitizer-induced occupational asthma unlikely

Positive

Occupational Asthma

Negative

Non-Work-Related Asthma
Comprehensive clinical and occupational/environmental history

Associated disorders? Rhinitis, urticaria, dermatitis, food allergy

Asthma diagnosis:
• Reversible airflow limitation
• Bronchial responsiveness to pharmacologic agents

Immunologic assessment
• Skin prick testing and/or specific IgE tests

Identification of the culprit agents:
Specific inhalation challenges
Serial PEF or spirometry recording
Serial measurements of BHR

Inflammatory components
• Induced sputum
• Nitric Oxide
• Exhaled Breath condensate

Assess relationship of asthma to work
Comprehensive clinical and occupational/environmental history

Associated disorders? Rhinitis, urticaria, dermatitis, food allergy

Asthma diagnosis:
• Reversible airflow limitation
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• Exhaled Breath condensate

Specialized centers

Assess relationship of asthma to work
**Age:** 26 years  
**Height:** 5 ft, 8 in  
**Weight:** 197 lb  
**Sex:** Male  
**Race:** Hispanic

<table>
<thead>
<tr>
<th>Spirometry</th>
<th>Prebronchodilators</th>
<th>Postbronchodilators</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Predicted</td>
<td>LLN</td>
<td>Actual</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>5.20</td>
<td>4.34</td>
<td>5.18^a</td>
</tr>
<tr>
<td>FEV(_1), (L)</td>
<td>4.37</td>
<td>3.64</td>
<td>3.55^b</td>
</tr>
<tr>
<td>FEV(_1)/FVC (%)</td>
<td>84</td>
<td>75</td>
<td>68^c</td>
</tr>
<tr>
<td>FEF(_25%-75%)</td>
<td>4.74</td>
<td>3.11</td>
<td>2.41</td>
</tr>
</tbody>
</table>

---

A = FVC (before bronchodilators), this is > LLN and thus does not show a restrictive pattern  
B = FEV\(_1\) (before bronchodilators)  
C = FEV\(_1\)/FVC ratio (before bronchodilators), this is < LLN and thus shows an obstructive defect  
D = FVC percentage of predicted (before bronchodilators)  
E = FEV\(_1\), percentage of predicted (before bronchodilators)  
F = FVC (after bronchodilators)  
G = FEV\(_1\) (after bronchodilators)  
H = FEV\(_1\)/FVC ratio (after bronchodilators)  
I = A 0.88-L increase in FVC is a 16% increase  
J = A 1.09-L increase in FEV\(_1\) is a 30% increase

The above indicates reversibility because at least one of the two (FVC or FEV\(_1\)) increased by at least 0.2 L and by at least 12%
Broncho-provocation tests

Airways hyperreactivity can be tested with bronchoprovocation tests:

Methacholine
Adenosine Challenge
Methacholine/Adenosine challenge

- **Methacoline** challenge involves administering a cholinergic agonist which will cause bronchospasm in patients with airways hyper reactivity.

- **Adenosine** challenge involves administering a mast cells agonist which will cause degranulation in patients with airways hyper reactivity.
Methacholine challenge

Direct agonists
- Methacholine

Indirect agonists
- Exercise
- Adenosine
- Hypotonic or hypertonic aerosols

Nerve
Mediators
Airway with limited airflow
Mast cell
SO₂
Bradykinin
Methacholine challenge

Concentration provoquant une baisse de 20 du YEMS post diluant ou CP_{20} YEMS : 0,6
Asthma diagnosis:
- Reversible airflow limitation
- Bronchial responsiveness to pharmacologic agents

Comprehensive clinical and occupational/environmental history
Associated disorders? Rhinitis, urticaria, dermatitis, food allergy

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Specialized centers

Inflammatory components
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Assess relationship of asthma to work
Specific Immunologic Testing

OA and rhinitis caused only by HMW proteins in the work environment are associated with specific IgE antibody production and tested by skin prick test.

RAST responses to HMW may be negative if they are tested after not being exposed for a prolonged period and for LMW chemicals in vitro testing for specific IgE antibodies are less indicated.

American College of Chest Physicians Consensus Statement Chest. 2008; 134:1S-41 Susan Tarlo et al
Comprehensive clinical and occupational/environmental history

Associated disorders? Rhinitis, urticaria, dermatitis, food allergy

Asthma diagnosis:
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Specialized centers

Assess relationship of asthma to work
Serial PEFRs in the Diagnosis of WRA


For individuals who are currently working at the job in question, the optimal record is a minimum of four times daily for at least 2 weeks at work and 2 weeks off work.
Serial Measures of **Airway Responsiveness** in the Diagnosis of WRA


- Methacholine or histamine challenge should be performed toward the end of a work week and repeated at the end of a period (usually 10 to 14 days) away from the exposure
- A 20% fall in FEV1 (PC20) at work vs off work beyond the normal variability of the test would provide additional evidence to support the diagnosis of sensitizer-induced OA.
Asthma diagnosis:
- Reversible airflow limitation
- Bronchial responsiveness to pharmacologic agents

Immunologic assessment
- Skin prick testing and/or specific IgE tests

Identification of the culprit agents:
- Specific inhalation challenges

Serial measurements of BHR
- Serial PEF or spirometry recording

Inflammatory components
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Comprehensive clinical and occupational/environmental history

Associated disorders? Rhinitis, urticaria, dermatitis, food allergy

Assess relationship of asthma to work
Specific Inhalation Challenge

• SIC is intended to demonstrate a direct relationship between exposure to a test agent and an asthmatic response.
• The SIC has often been referred to as the "gold standard" for the diagnosis of sensitizer-induced OA.
• It is a useful research and diagnostic test, SICs are performed in only a few centers in the world, require specialized facilities and expertise, and generally are not available in the United States and many other countries.
Comprehensive clinical and occupational/environmental history

Associated disorders? Rhinitis, urticaria, dermatitis, food allergy

Asthma diagnosis:
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• Bronchial responsiveness to pharmacologic agents

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Assess relationship of asthma to work

Specialized centers
Emerging Diagnostic Tests: Noninvasive Measures of Airway Inflammation

American College of Chest Physicians Consensus Statement Chest. 2008; 134:1S-41 Susan Tarlo et al

Noninvasive Measures of Airway Inflammation

Induced Sputum

This method consists of inducing sputum production by the inhalation nebulized hypertonic saline solution, processing the sample, and differential cell counts.

FeNO

The fraction of nitric oxide in the exhaled air. The magnitude of FENO is increased in proportion to bronchial wall inflammation or induced-sputum eosinophilia.

EBC

Exhaled breath condensate (EBC) likely contains aerosolized droplets of airway lining fluid and volatile compounds.
There is evidence that monitoring sputum eosinophils can help in the management of occupational asthma.

**Occupational eosinophilic asthma**

Fig. 9 - Eosinophil

Lemiere C.  
Fig. 8 - Neutrophil

Occupational neutrophilic asthma
What kind of cells and materials we can recover from the pellet fraction?

**NEUTROPHILS**
- Neutrophilic inflammation

**EOSINOPHILS**
- Eosinophilic inflammation

*Figure 1- Neutrophilic induced sputum in chronic obstructive pulmonary disease*
Figure 1 Proportion of various inflammatory phenotypes according to cellularity of induced sputum in a large cohort of asthmatics.
Figure 2 Sputum cytopspins showing the four inflammatory subtypes of asthma: (a) neutrophilic asthma; (b) eosinophilic asthma; (c) mixed granulocytic asthma; (d) paucigranulocytic asthma.
The asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS) opportunities and challenges.

Abstract

PURPOSE OF REVIEW: Some individuals share characteristics of asthma and chronic obstructive pulmonary disease (COPD). The asthma-COPD overlap syndrome (ACOS) has been defined as symptoms of increased variability of airflow in association with an incompletely reversible airflow obstruction. In this review, we present the latest findings in the diagnosis, characterization and management of ACOS.

RECENT FINDINGS: Around 15-26% of COPD patients may have an ACOS. Patients with ACOS are characterized by increased reversibility of airflow obstruction, eosinophilic bronchial and systemic inflammation, and increased response to inhaled corticosteroids, compared with the remaining patients with COPD. Patients with ACOS have more frequent exacerbations, more wheezing and dyspnoea, but similar cough and sputum production compared with COPD.

SUMMARY: The relevance of the ACOS is to identify patients with COPD who may have underlying eosinophilic inflammation that responds to inhaled corticosteroids. So far, the previous diagnosis of asthma in a patient with COPD is the more reliable criterion for ACOS. Ongoing studies will clarify if concentrations of blood eosinophils may be useful to identify this subgroup of patients with COPD. If this is the case, the interest of ACOS may shift to that of eosinophilic COPD, which is easier to diagnose and has clear therapeutic implications.

PMID: 25405071 [PubMed - indexed for MEDLINE]
Parenchyma
• **Sarcoidosis**, is a disease involving abnormal collections of inflammatory cells (granulomas) that can form as nodules in multiple organs.

• In the lung, sarcoidosis can be divided into four stages:
  
  Stage 0 — No intrathoracic involvement
  
  Stage I — Bilateral hilar adenopathy
  
  Stage II — Pulmonary parenchyma involved
  
  Stage III — Pulmonary infiltrates with fibrosis
  
  Stage 4 — end-stage lung disease with pulmonary fibrosis
Sarcoidosis

Sarcoidosis is a disease of unknown cause that leads to persistent nodular inflammation of the tissues.

Unknown???????
**Granulomatous Diseases and Possible Etiologies of Sarcoidosis**

<table>
<thead>
<tr>
<th>Type of disease</th>
<th>Possible Etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious disease</td>
<td><em>Histoplasma</em> species, <em>Aspergillus</em> species, <em>Coccidioides</em> species</td>
</tr>
<tr>
<td>Protozoa</td>
<td><em>Toxoplasma</em> species, <em>Leishmania</em> species</td>
</tr>
<tr>
<td>Metazoan</td>
<td><em>Schistosoma</em> species</td>
</tr>
<tr>
<td>Spirochetes</td>
<td><em>Treponema pallidum</em></td>
</tr>
<tr>
<td>Mycobacteria</td>
<td><em>Mycobacterium tuberculosis</em> complex, <em>Mycobacterium leprae</em>, nontuberculous mycobacteria</td>
</tr>
<tr>
<td>Bacteria</td>
<td><em>Yersinia</em> species, <em>Brucella</em> species, <em>Borrelia</em> species, <em>Propionibacterium</em> species</td>
</tr>
<tr>
<td>Virus</td>
<td>Epstein-Barr virus, herpesvirus, cytomegalovirus, <em>Coxsackie</em> virus</td>
</tr>
<tr>
<td>Neoplastic disease</td>
<td>Carcinomas, sarcomas</td>
</tr>
<tr>
<td>Metals</td>
<td>Beryllium, aluminum, titanium, zirconium</td>
</tr>
<tr>
<td>Inorganic dusts</td>
<td>Silica, talc, silicone, glass fiber</td>
</tr>
<tr>
<td>Organic dusts</td>
<td>Hypersensitivity pneumonitis</td>
</tr>
<tr>
<td>Autoimmune diseases</td>
<td>Crohn disease, primary biliary cirrhosis, giant cell arteritis, common variable immunodeficiency, hypogammaglobulinemia</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Wegener disease, Churg–Strauss disease, lymphomatoid granulomatosis, polyarteritis nodosa, bronchoceleic granulomatosis</td>
</tr>
<tr>
<td>Others</td>
<td>Leukocyte oxidase deficiency, Blau syndrome</td>
</tr>
</tbody>
</table>
Beryllium Induced Diseases in Israel

Case Communication

Beryllium disease: first reported case in Israel

Fireman E, Kramer MR, Kaufman N, Muller-Quernheim J, Lerman Y.

What is Chronic Beryllium Disease???
Chronic beryllium disease (CBD) is a systemic granulomatous disorder that affects the lungs predominantly. T lymphocytes recognize beryllium as an antigen triggering cell proliferation, release of inflammatory mediators, and accumulation of inflammatory cells in the target organ. This results in formation of the typical pathologic lesion, the noncaseating granuloma, as well as the accumulation of mononuclear cell infiltrates and fibrosis.
Proposed sequence of pathologic events resulting in chronic beryllium disease
Work-up by Laboratory of Pulmonary Diseases Tel-Aviv Medical Center.

- PFT
- BeLPT = Beryllium Lymphocyte Proliferation Test
- Induced sputum
- SEM = Scanning Electron Microscope
BeLPT = Beryllium Lymphocyte Proliferation Test

1) Obtain peripheral blood from beryllium-exposed worker

2) Culture lymphocytes, the immune system cells in blood, with beryllium salts in the lab for 4-6 days

3) Assess proliferative response to beryllium
BELPT = Beryllium Lymphocyte Proliferation Test

Stimulation Index

10(-4M) 10(-5M) 10(-6M) 10(-7M) 10(-8M)

Be₂SO₄
מדינת ישראל
מ不錯ה העבודה והורחות

år פיקוד על העבודה
טל: 02-5670932
פקס: 02-6752307

25 יולי, 2001

חותה של מינה

איסור’esמאות בריגולים ובכלים שביניהם

משרדיבי, בשירות עופי מסדר הריגול, והל valido לاصرור את השימוע לשימור
בריגולים המופע שהוריכו והחפצים המסריגים, שלולית בבריגול למחזורים אחרים
(בריגוליות). בבריגולים בבוד barangים נעל הלוכדיםitone שימור
משרדי העבודה והורחות
מקהל חומרים. מעבר החלק הפרוסים והרודס על הלוכדים הספנות הדירות,
אני ממליץ לפי הפסוק מ‘ספינות ואת השימוע בבריגול חצי הלוכדיםincinn
לוכדים, כ改變בורה של קיימ. החלק שבירח

ככל שימועים אטרים על בריגול,_CONN: מ‘ספינות ומפרטים, אריא
וחלפים סבירים. תגוביהם בעינה זו ומאמזים בצומת רמיאי محمود תקנות

משרדי העבודה והורחות.
The next step was to test the hypothesis that other cases of CBD in Israel were not previously reported because these patients were misdiagnosed as having SA.

METHODS: Forty-seven patients with confirmed-SA from our outpatient clinic were recalled in order to reevaluate their occupational exposure history.

We performed the beryllium lymphocyte proliferation test (BeLPT) on each patient with a potentially positive environmental exposure anamnesis to beryllium.

Supported by Israel Chief Scientist Office-Ministry of Health
Table I: Demographic and clinical parameters of the study population

<table>
<thead>
<tr>
<th></th>
<th>Women (n)</th>
<th>Men (n)</th>
<th>Age range (y)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study population</strong></td>
<td>26</td>
<td>21</td>
<td>29-79</td>
<td>47</td>
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<tr>
<td><strong>Patients with</strong></td>
<td>4</td>
<td>10</td>
<td>40-69</td>
<td></td>
</tr>
<tr>
<td><strong>occupational history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>of beryllium exposure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sarcoidosis staging</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>by chest X-ray</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Stage 0: n=3
- Stage I: n=10
- Stage II: n=24
- Stage III: n=8
- Stage IV: n=2
Results: 3/14 positive BeLPT

✓ 3/14 who all had a positive occupational exposure to beryllium.

✓ 2/14 patients with evidence of granulomas in lung tissue (pulmonary involvement).

✓ 1/14 with extra pulmonary involvement.
and histopathologically indistinguishable from sarcoidosis. Chronic beryllium disease is distinguished from sarcoidosis by a history of beryllium exposure and by laboratory evidence of immunologic sensitization to beryllium using blood or lavage cells in a beryllium lymphocyte proliferation test. A recent study from Israel illustrates the need to exclude chronic beryllium disease prior to accepting a diagnosis of sarcoidosis. In this study, Fireman and colleagues performed the blood beryllium lymphocyte proliferation test in 14 patients in their sarcoidosis clinic who, on repeat questioning, reported employment in industries with the potential for beryllium exposure (e.g., metal extraction, ceramics, electronics, space and atomic engineering, dental laboratories). Three of the 14 patients were found to be beryllium sensitized and were therefore diagnosed as having chronic beryllium disease. The study highlights the importance of a thorough occupational history in patients with granulomatous lung disease. In addition to the infectious
Table 1 Exposure assessment of the exposed workers referred to our outpatient clinic between 2001-2008 (n=98) *

<table>
<thead>
<tr>
<th>Source of exposure</th>
<th>Exposed individuals (n=98)</th>
<th>% (~)</th>
<th>CBD diagnosed (n=21) ‡</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental technicians</td>
<td>36</td>
<td>36</td>
<td>12</td>
<td>33.3</td>
</tr>
<tr>
<td>Metal workers</td>
<td>21</td>
<td>21</td>
<td>1</td>
<td>4.7</td>
</tr>
<tr>
<td>Jewelry industry</td>
<td>6</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Machinery</td>
<td>6</td>
<td>6</td>
<td>2</td>
<td>66.6</td>
</tr>
<tr>
<td>Aircraft industry</td>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electricians &amp; computers</td>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dental physicians &amp; assistants</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Military</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>33.3</td>
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<tr>
<td>Constructions</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>33.3</td>
</tr>
<tr>
<td>Welders</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>50.0</td>
</tr>
<tr>
<td>Aluminum industry</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copper industry</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>Telecommunications</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluorescent industry</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>100</td>
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<tr>
<td>Laboratory technician</td>
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<tr>
<td>Chemical industry</td>
<td>1</td>
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<td></td>
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<tr>
<td>Nuclear industry †</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>66.6</td>
</tr>
</tbody>
</table>

Exposure in the United Kingdom, Russia (n=2) and Chernobil (n=1)

‡ Patients were identified in 8 different types of professional workplaces and diagnosis was based on a (+) BeLPT result and a positive transbronchial biopsy showing noncaseating granuloma.
Work-up by Laboratory of Pulmonary Diseases Tel-Aviv Medical Center.

- PFT
- BeLPT=Beryllium Lymphocyte Proliferation Test
- Induced sputum
- SEM=Scanning Electron Microscope
CD4/CD8 ratio in lung diseases
CD4/CD8 ratio in Sarcoidosis

CD4 lymphocytes

CD4/CD8 ratio
N=1-2.5
Sarcoidosis-Berylliosis >2.5
Work-up by Laboratory of Pulmonary Diseases Tel-Aviv Medical Center.

- PFT
- BeLPT=Beryllium Lymphocyte Proliferation Test
- Induced sputum
- SEM=Scanning Electron Microscope
The Best Just Got Better
TestAll technology software upgrade

(X-ray tube) XRF Alloy Analyser

Rapid, accurate results for confident decision making

Instant quantitative positive alloy grade identification.

Highest sensitivity and measurement accuracy
What happen with sarcoid exposed individuals but with BeLpT negative?
Metals Lymphocyte Immunostimulation Assay (MELISA®)
Vera Stejskal (Stockholm, Sweden)

### Explaining the details on your test report

#### Negative control
This is a value showing the growth of your cells without addition of an allergen. It is expressed in “cpm” which means “counts per minute”.

#### Positive control
Pokeweed is a substance that all white blood cells react to, used here to make sure the cells are reacting as they should.

#### Test report
1541-3
Test report number
Every test is given a unique number.

#### Test report for
Smith, Mary
7 July 1963

<table>
<thead>
<tr>
<th>Code</th>
<th>Substance</th>
<th>Stimulation Index</th>
<th>Morphology</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PWM</td>
<td>Pokeweed</td>
<td>211</td>
<td>&gt;100</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>1. Cu</td>
<td>Copper I</td>
<td>0.7</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Copper II</td>
<td>2.1</td>
<td>blasts present</td>
<td>Weakly Positive</td>
</tr>
<tr>
<td>2. Hg</td>
<td>Inorganic Mercury I</td>
<td>4.4</td>
<td>many blasts</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Inorganic Mercury II</td>
<td>10</td>
<td>many blasts</td>
<td>Positive</td>
</tr>
</tbody>
</table>

#### Referring clinic
Medical clinic; United Kingdom

#### Test date
13 February 2012

#### Substance name & concentration
Stimulation Index
As explained above
Morphology
This is an evaluation of
MeLPT = Metals Lymphocyte Proliferation Test

Diagram:
- Whole blood and saline
- Centrifugation
- Separated blood
- Ficoll Isopaque
- Antigen suspension
- Culture medium
- Glass fibre filter
- Measure radioactivity
We performed a study with the aim

To identify sensitization to other metals than beryllium that cause granulomatous lung disease
## Study Population

<table>
<thead>
<tr>
<th>Number</th>
<th>Gender</th>
<th>Age (yrs)</th>
<th>Occupational exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>68</td>
<td>Copper industry</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>70</td>
<td>Military Industry</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>61</td>
<td>Metal Worker</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>63</td>
<td>Jewelry industry</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>58</td>
<td>Aircraft Industry</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>70</td>
<td>Welder</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>63</td>
<td>Welder</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>63</td>
<td>Military Industry</td>
</tr>
<tr>
<td>9</td>
<td>Male</td>
<td>45</td>
<td>Dental technician</td>
</tr>
<tr>
<td>10</td>
<td>Male</td>
<td>50</td>
<td>Dental technician</td>
</tr>
<tr>
<td>11</td>
<td>Female</td>
<td>40</td>
<td>Dental technician</td>
</tr>
<tr>
<td>12</td>
<td>Female</td>
<td>45</td>
<td>Teacher</td>
</tr>
<tr>
<td>13</td>
<td>Female</td>
<td>35</td>
<td>Silicone Implants</td>
</tr>
<tr>
<td>14</td>
<td>Female</td>
<td>40</td>
<td>Silicone Implants</td>
</tr>
</tbody>
</table>
Fig 1a and b: Magnification X 1500 of biopsy specimen.
Fig c: X-ray spectra of representative particles identified
# Chemical Compounds Used for MELPT

<table>
<thead>
<tr>
<th>Compound Name</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Aluminium chloride.</td>
<td>Al Cl₃</td>
</tr>
<tr>
<td>2 Titanium dioxide</td>
<td>TiO₂</td>
</tr>
<tr>
<td>3 Titanium sulphate</td>
<td>Ti(SO₄)₃</td>
</tr>
<tr>
<td>4 Chromium chloride</td>
<td>CrCl₂</td>
</tr>
<tr>
<td>5 Sodium silicate solution</td>
<td>Na₂SiO₂</td>
</tr>
<tr>
<td>6 Gold sodium thiosulfate</td>
<td>AuNa₃O₆S₄</td>
</tr>
<tr>
<td>7 Mercury (II) chloride</td>
<td>HgCl₂</td>
</tr>
<tr>
<td>8 Iron oxide</td>
<td>Fe₃O₄</td>
</tr>
<tr>
<td>9 Molybdenum chloride</td>
<td>(MoCl₅)₂</td>
</tr>
<tr>
<td>10 Nickel chloride</td>
<td>NiCl₂</td>
</tr>
<tr>
<td>11 Palladium chloride</td>
<td>PdCl₂</td>
</tr>
<tr>
<td>12 Copper sulphate</td>
<td>Cu₂SO₄</td>
</tr>
<tr>
<td>13 Silver acetate</td>
<td>AgCOOCH₃</td>
</tr>
<tr>
<td>14 Beryllium sulfate</td>
<td>Be₂SO₄</td>
</tr>
<tr>
<td>15 Tin chloride</td>
<td>SnCl₂</td>
</tr>
<tr>
<td>16 Platinum sulfate</td>
<td>PtSO₄</td>
</tr>
<tr>
<td>17 Cobalt chloride</td>
<td>CoCl₂</td>
</tr>
<tr>
<td>18 Manganese chloride</td>
<td>MnCl₂</td>
</tr>
<tr>
<td>19 Tungsten chloride</td>
<td>WCl₂</td>
</tr>
</tbody>
</table>
Results
## Results of SEM, BeLPT and MeLPT performed in all patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Metals tested by SEM</th>
<th>Metals tested by Melisa</th>
<th>McLPT</th>
<th>BeLPT</th>
<th>Industry</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 SA; NCG(+)</td>
<td>Al, Cu, Si</td>
<td>Al, Cr, Si, Ti, Hg</td>
<td>Ti(+)</td>
<td>Be(-)</td>
<td>Copper industry</td>
</tr>
<tr>
<td>2 SA; NCG (+)</td>
<td>Fe, Ti, Al, Si</td>
<td>Al, Si, Ti</td>
<td>(-)</td>
<td>Be(-)</td>
<td>Military Industry</td>
</tr>
<tr>
<td>3 SA; NCG (+)</td>
<td>Si, Cr, Ni, Fe</td>
<td>Cr, Fe, Ni, Si, Ti, Be</td>
<td>Ti(+)</td>
<td>Be(-)</td>
<td>Metal Worker</td>
</tr>
<tr>
<td>4 SA; NCG (+)</td>
<td>Si, Cr, Ni, Fe, Mo</td>
<td>Cr, Au, Hg, Pa, Ti, Ni, Mo</td>
<td>Ti(+) Pa(+)</td>
<td>Be(-)</td>
<td>Jewelry industry</td>
</tr>
<tr>
<td>5 SA; NCG (+)</td>
<td>Au, Zn, Si, Al, Be</td>
<td>Al, Au, Hg, Pa, Si, Ti, Zn</td>
<td>Hg(+)</td>
<td>Be(-)</td>
<td>Aircraft Industry</td>
</tr>
<tr>
<td>6 SA; NCG (-)</td>
<td>Al, Ag, Cu</td>
<td>Ag, Cu, Al</td>
<td>(-)</td>
<td>Be(-)</td>
<td>Welder</td>
</tr>
<tr>
<td>7 SA; NCG (+)</td>
<td>Al, Si, Fe, Zn</td>
<td>Hg, Ni, Si, Ti, Zn, Pb, Ti</td>
<td>Ti(+) Pb(+)</td>
<td>Be(-)</td>
<td>Welder</td>
</tr>
<tr>
<td>8 SA; NCG (+)</td>
<td>Al, Si Fe</td>
<td>Al, Au, Fe, Si, Ti, Be</td>
<td>Ti(+) Be(+)</td>
<td>Be(-)</td>
<td>Military Industry</td>
</tr>
<tr>
<td>9 CBD NCG (+)</td>
<td>(-)</td>
<td>Fe, Ni, Ti, Be</td>
<td>(-)</td>
<td>Be(+)</td>
<td>Dental technician</td>
</tr>
<tr>
<td>10 CBD NCG (+)</td>
<td>Al, Si Cr, Fe, Ni</td>
<td>Al, Cr, Fe, Ni, Si, Be</td>
<td>Si(+)Fe (+)Cr(+)</td>
<td>Be(+)</td>
<td>Dental technician</td>
</tr>
<tr>
<td>11 SA; NCG (+)</td>
<td>Si, Cr, Co, Fe, Ti, Ni, W, Mn</td>
<td>Cr, Co, Fe, Mn, Ni, Si, Ti, (-)</td>
<td>Be(-)</td>
<td>Dental technician</td>
<td></td>
</tr>
<tr>
<td>12 SA; NCG (+)</td>
<td>Fe, Cr, Ni, Si</td>
<td>Cr, Hg, Fe, Ni, Si, Ag, Sn</td>
<td>Si(+)Cr(+) Ni(+)</td>
<td>Be(-)</td>
<td>Teacher</td>
</tr>
<tr>
<td>13 SA; NCG (+)</td>
<td>Si, Au, Cr, Fe</td>
<td>Au, Hg, Ni, Pa, Pl, Si</td>
<td>Ni(+)</td>
<td>ND</td>
<td>Silicone Implants</td>
</tr>
<tr>
<td>14 SA; NCG (+)</td>
<td>Si</td>
<td>Au, Ni, Pa, Pl, Si</td>
<td>Ni(+)</td>
<td>ND</td>
<td>Silicone Implants</td>
</tr>
</tbody>
</table>

SA=Sarcoidosis; NCG= Non Caseating Granulomas; Al: Aluminum; Cu= Copper; Si=Silica; Fe=Iron; Ti= Titanium; Cr= Chrome; Ni=Nickel; Au; Gold; Mo=Molybdenum; Zn= Zinc; Hg=mercury; Mn=Manage; Co=Cobalt; Pb=Lead; W=Tungsten; Pa: Palladium
Granulomatous disease associated with pulmonary deposition of titanium

SUSAN REDLINE, BARBARA P BARNA, J F TOMASHEFSKI Jr, J L ABRAHAM

From the Department of Medicine, Cleveland Metropolitan General Hospital, Case Western Reserve University, and Channing Laboratory, Harvard Medical School and Brigham and Women's Hospital, Boston, Massachusetts, Department of Immunopathology; Cleveland Clinic Foundation, Cleveland, Ohio, Department of Pathology; Cleveland Metropolitan General Hospital, Case Western Reserve University, and the Department of Pathology, Upstate Medical Center

ABSTRACT A patient presented with granulomatous lung disease associated with the pulmonary deposition of various metallic particles. To evaluate the relation between the metallic dust and the granulomatous process, lymphocyte transformation tests to aluminium sulphate, titanium chloride, beryllium sulphate, and nickel sulphate were performed. A lymphocyte proliferative response to titanium chloride was observed on two separate occasions; no responses to the other metals were shown. These results are consistent with hypersensitivity to titanium, and suggest, in this individual, a possible aetiologcal role between the inhalation of titanium and a granulomatous disease process.
### Results of SEM, BeLPT and MeLPT performed in all patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Metals tested by SEM</th>
<th>Metals tested by Melisa</th>
<th>MeLPT</th>
<th>BeLPT</th>
<th>Industry</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 SA; NCG(-)</td>
<td>Al, Cu, Si</td>
<td>Al, Cr, Si, Ti, Hg</td>
<td>Ti(+)</td>
<td>Be(-)</td>
<td>Copper industry</td>
</tr>
<tr>
<td>2 SA; NCG (+)</td>
<td>Fe, Ti, Al, Si</td>
<td>Al, Si, Ti</td>
<td>(-)</td>
<td>Be(-)</td>
<td>Military Industry</td>
</tr>
<tr>
<td>3 SA; NCG (+)</td>
<td>Si, Cr, Ni, Fe</td>
<td>Cr, Fe, Ni, Si, Ti, Be</td>
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<td>Be(-)</td>
<td>Jewelry industry</td>
</tr>
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<td>5 SA; NCG (+)</td>
<td>Au, Zn, Si, Al, Be</td>
<td>Al, Au, Hg, Pa, Si, Ti, Zn, Be</td>
<td>Hg(+)</td>
<td>Be(-)</td>
<td>Aircraft Industry</td>
</tr>
<tr>
<td>6 SA; NCG(-)</td>
<td>Al, Ag, Cu</td>
<td>Ag, Cu, Al</td>
<td>(-)</td>
<td>Be(-)</td>
<td>Welder</td>
</tr>
<tr>
<td>7 SA; NCG (+)</td>
<td>Al, Si, Fe, Zn</td>
<td>Hg, Ni, Si, Ti, Zn, Pb, Ti</td>
<td>Ti(+) Pb(+)</td>
<td>Be(-)</td>
<td>Welder</td>
</tr>
<tr>
<td>8 SA; NCG (+)</td>
<td>Al, Si Fe</td>
<td>Al, Au, Fe, Si, Ti, Be</td>
<td>Ti(+) Be(+)</td>
<td>Be(-)</td>
<td>Military Industry</td>
</tr>
<tr>
<td>9 CBD NCG (+)</td>
<td>(-)</td>
<td>Fe, Ni, Ti, Be</td>
<td>(-)</td>
<td>Be(+)</td>
<td>Dental technician</td>
</tr>
<tr>
<td>10 CBD NCG (+)</td>
<td>Al, Si Cr, Fe, Ni</td>
<td>Al, Cr, Fe, Ni, Si, Be</td>
<td>Si(+)Fe (+)Cr(+) Ni(+) Be(+)</td>
<td>Be(+)</td>
<td>Dental technician</td>
</tr>
<tr>
<td>11 SA; NCG (+)</td>
<td>Si, Cr, Co, Fe, Ti, Ni, W, Mn</td>
<td>Cr, Co, Fe, Mn, Ni, Si, Ti, Be</td>
<td>(-)</td>
<td>Be(-)</td>
<td>Dental technician</td>
</tr>
<tr>
<td>12 SA; NCG (+)</td>
<td>Fe, Cr, Ni, Si</td>
<td>Cr, Hg, Fe, Ni, Si, Ag, Sn</td>
<td>Si(+)Cr(+) Ni(+) Be(-)</td>
<td>Teacher</td>
<td></td>
</tr>
<tr>
<td>13 SA; NCG (+)</td>
<td>Si, Au, Cr, Fe</td>
<td>Au, Hg, Ni, Pa, Pl, Si</td>
<td>Ni(+)</td>
<td>ND</td>
<td>Silicone Implants</td>
</tr>
<tr>
<td>14 SA; NCG (+)</td>
<td>Si</td>
<td>Au, Ni, Pa, Pl, Si</td>
<td>Ni(+)</td>
<td>ND</td>
<td>Silicone Implants</td>
</tr>
</tbody>
</table>
Allergic Contact Dermatitis Caused by Metals in Blackboard Chalk: A Case Report

Monica Corazza¹, Stefania Zauli¹, Antonella Pagnoni² and Anna Virgili³

Departments of ¹Clinical and Experimental Medicine, Section of Dermatology, and ³Chemistry, Atomic Spectroscopy Laboratory, University of Ferrara, Via Savonarola 9, IT-44121 Ferrara, Italy. E-mail: czm@unife.it
Accepted October 24, 2011.

Periorbital dermatitis has an incidence of 3.9–4.8% (1). It is most commonly caused by contact allergy (54%) (direct contact 44% or airborne contact 10.2%), irritant contact dermatitis (CD) (9.1%) and atopic dermatitis (25%) (1). Metals are reported among the main causes of airborne allergic CD, in particular in occupational settings (2). We report here an unusual case of periorbital airborne allergic CD together with direct allergic CD of the hands in a teacher. It was found to be due to metals in the powder of blackboard chalk.

Table I. Chemical analysis of the metal content of the patient’s blackboard chalks

<table>
<thead>
<tr>
<th>Colour of chalk</th>
<th>Metal content (μg/g ± 0.10)</th>
<th>Patch test results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chromium a</td>
<td>Nickel b</td>
</tr>
<tr>
<td>Yellow</td>
<td>2.98</td>
<td>&lt;0.53</td>
</tr>
<tr>
<td>Violet</td>
<td>2.47</td>
<td>&lt;0.53</td>
</tr>
<tr>
<td>White (brand 1)</td>
<td>2.03</td>
<td>2.30</td>
</tr>
<tr>
<td>Green</td>
<td>2.37</td>
<td>1.03</td>
</tr>
<tr>
<td>White (brand 2)</td>
<td>2.75</td>
<td>2.72</td>
</tr>
<tr>
<td>Red</td>
<td>2.23</td>
<td>0.82</td>
</tr>
<tr>
<td>Orange</td>
<td>2.18</td>
<td>&lt;0.53</td>
</tr>
</tbody>
</table>

Detection limit, μg/g = ppm: a0.63 μg/g, b0.53 μg/g, c0.32 μg/g, d0.79 μg/g.
The role of lymphocyte proliferation tests in assessing occupational sensitization and disease

Stella E. Hines, Karin Pacheco, and Lisa A. Maier

Purpose of review
Lymphocyte proliferation testing (LPT) is used in diagnosing occupationally acquired delayed-type hypersensitivity. It has been used in beryllium-health effects, and its role is expanding in metal allergy. It may find application in diagnosis of other sensitizers.

Recent findings
Use of the beryllium LPT (BeLPT) in medical surveillance identifies beryllium sensitization at low exposure with chronic beryllium disease (CBD) that leads to physiologic impairment and need for immunosuppressive medications. New studies indicate that both beryllium exposure and genetic variation are associated with increased risk of CBD. Borderline positive BeLPTs warrant inclusion into diagnostic algorithms. Furthermore, use of LPTs to diagnose metal allergy is being proposed in diagnosis of chromium allergy and hypersensitivity to surgical implants. New occupational sensitizers continue to be identified including metalworking fluids, the sterilizing agent orthophthalaldehyde and the solvent para-chlorobenzotrifluoride. Use of LPT in occupational surveillance to these agents and other known sensitizers may play expanding roles.

Summary
Lymphocyte proliferation testing serves a valuable role in diagnosing occupational sensitization, as demonstrated with beryllium-health effects, as cases continue to be found at low exposure levels. The use of LPTs in diagnosing contact allergy is expanding, and new applications may be identified in human and animal studies.

Keywords
beryllium, chronic beryllium disease, contact allergy, lymphocyte proliferation test, occupational surveillance, sensitization
• 93% quartz
• Polymer
• Pigments
ברל
עומר

עשות מעבדיו שיש לולע במעין הא啡ינו
במהלך רחואת קשמה, מיטסרוע וחותמת מרפה.
הסיבת לאטהויה היא עיוור משותי
אבו קים: הבדירה היא מהיועות
מעטרים על ביסם דינ רואים בפרשה
שאני עלייה אוזרות חלילות וטשולים
לייסי. האם כל זה ישים על הרכלה
הביאנויה של קייטрин המתמשית
המיבורית? רשמו עבצ + הורים מנג
CaesarStone Silicosis: Disease Resurgence among Artificial Stone Workers

Mordechai R. Kramer, Paul D. Blanc, Elizabeth Fireman, Anat Amital, Alexander Guber, Nader Abdul Bhatman and David Shifrin

DOI: 10.1378/chest.11-1321

The online version of this article, along with updated information and services, can be found online on the World Wide Web at: http://chestjournal.chestpubs.org/content/early/2012/06/29/chest.11-1321

Background: Silicosis is a progressive, fibrotic, occupational lung disease resulting from inhalation of respirable crystalline silica. This disease is preventable through appropriate workplace practices. We systematically assessed an outbreak of silicosis among patients referred to our center for lung transplant.

Methods: This retrospective cohort analysis included all patients with a diagnosis of silicosis who were referred for evaluation to the National Lung Transplantation Program in Israel from January 1987 through December 2010. We also compared the incidence of lung transplantation (LTX) due to silicosis in Israel with that of the International Society for Heart and Lung Transplantation (ISHLT) registry.

Results: During the 14-year study period, 35 patients with silicosis were referred for evaluation, including 10 patients who went on to undergo LTX. All patients were exposed to dry cutting a relatively new, artificial, decorative stone product with high crystalline silica content used primarily for kitchen countertops and bathroom fixtures. The patients had moderate-to-severe restrictive lung disease. Two patients developed progressive massive fibrosis; none manifested acute silicosis (silicoproteinosis). Three patients died during follow-up, without LTX. Based on the ISHLT registry incidence, 0.5% silicosis cases would have been expected instead of the 10 observed (incidence rate, 1.16; 95% CI, 0.92-2.01).

Conclusions: This silicosis outbreak is important because of the worldwide use of this and similar high-silica-content, artificial stone products. Further cases are likely to occur unless effective preventive measures are undertaken and existing safety practices are enforced.
.elementAt(0,0,0)
1. Where do you work???
   What is your job???

2. To refer your patient to our lab..
   For occupational work-up
kőszönöm  תודה! děkuji 谢谢!
mahalo 고맙습니다
thank you 你
merci 谢谢 danke 谢谢
Ευχαριστώ 你
شكرا 你
do ugari gatou 你 gracias 你