Environmental Influence in Autoimmune Diseases

Mark Gourley, MD
Traffic Pollution May Damage Sperm Quality

(Reuters) - Traffic pollution may affect male fertility by damaging sperm, Italian scientists said on Wednesday. After studying 85 attendants at tollgates on Italian motorways, researchers at the University of Naples in southern Italy discovered the men had poorer-quality sperm than other young and middle-aged Italian workers in the same area. “The sperm count did not differ significantly between our study group and the controls, but in general the sperm of the study group was more feeble and less active, so it has a lower fertility potential,” said Dr. Michele de Rosa, a researcher at the university. More ...

- Traffic pollutants affect fertility in men - abstract (Human Reproduction)
- Shanghai pollution hits male fertility - Nov 2000 (BBC)
- Environmental causes of infertility (USF) | Message board

Pollution can affect male fertility: study

(Apr 30, 2003)

Traffic pollution damages men’s sperm

-New Scientist (Apr 30, 2003)

Traffic ‘damages male fertility’

-BBC (Apr 30, 2003)

Car Exhaust Chokes Sperm

-HealthScout (Apr 30, 2003)

Traffic Pollutant May Damage Sperm Quality

-Reuters (Apr 30, 2003)
Study: Small Amounts of Lead Can Cause Neurological Damage in Children

Low Levels of Lead Damage Children
(HealthScout) -- Two studies offer more worrisome news about the harm done to children by lead exposure. One study says IQs are lowered significantly by levels of lead in the blood below those now regarded as acceptable by U.S. health officials. The other finds delayed puberty in girls with elevated levels of the metal in their blood. The first study, of 172 children in the Rochester, N.Y., area, found lower IQs in those with blood lead levels of 10 micrograms per deciliter, which the U.S. Centers for Disease Control and Prevention (CDC) lists as acceptable.

- Study abstract (NEJM) | Lead's Toxic Toll (Detroit Free Press)
- Yahoo Health: Lead Poisoning | Message board

News Stories
- Even lower levels of lead can hurt kids
- Rochester Democrat & Chronicle (Apr 17, 2003)
- Lead levels believed safe found harmful
- Baltimore Sun. (Apr 17, 2003)
- Child lead-poisoning warning for Sydney
- Sydney Morning Herald (Apr 17, 2003)
- Ontario power plant tied to pollution jump
- Toronto Star (Apr 17, 2003)
- Canadian polluters worse than in U.S., report says
- Globe and Mail. (Apr 17, 2003)
- Forecast clouded by ozone alert
- The Canadian (Apr 17, 2003)
**Toxic Shock: What We’ve Got in Our Bodies**

You may never have heard of phthalates or organophosphates, but according to a CDC report last week, you probably carry both types of chemicals in your body. The agency measured 27 chemicals in Americans. The findings:

**Lead:** Levels of this heavy metal continue to drop in kids—encouraging, since it causes learning and behavioral problems. But children in some cities are still at high risk.

**Dimethylphosphate:** One of six pesticide byproducts measured, it was detected in most Americans. Some of DMP’s parent pesticides cause cancer in animals, but researchers aren’t sure how DMP itself affects humans.

**Mono-benzyl Phthalate:** MBzP causes birth defects in animals. A byproduct of a chemical used in cosmetics, MBzP was found in most people—but it’s not proven to harm humans.

**Cotinine:** Cotinine levels—which indicate exposure to tobacco smoke—have dipped since the late ‘80s, offering proof that no-smoking regulations have public-health benefits.
Current Knowledge of Environment and Myositis

Environment

Genes → Autoimmunity
What Is an Environmental Exposure?

- Defined - susceptibility factors for an illness that are not inherited
- Two types:
  - Macroenvironment (uncontrolled)
    - Atmospheric pollution
    - Water contamination
  - Microenvironment (controlled)
    - Workplace
    - Diet
    - Leisure time
Immune-mediated Disease (IMD) Autoimmunity

- Hundreds of acquired disorders in which the immune system likely play a pathogenic role
- Third most common group of diseases in the U.S. - After cardiac disease and cancer - and are becoming more common
- High rate of chronic illness and death resulting in great costs to society
- Pathogenesis are poorly understood but likely involve chronic immune activation after environmental exposures in genetically susceptible individuals
Types of Immune-mediated Disease

- Hypersensitivity and allergic disorders (allergic rhinitis, sinusitis, asthma)
- Adverse reactions to drugs, biologics, medical devices, foods (drug-induced lupus, vasculitis)
- Immune suppression and decreased ability to resist disease (polychlorinated biphenyls & respiratory infections)
- Organ-specific autoimmune diseases (Hashimoto’s thyroiditis, type 1 diabetes)
- Systemic autoimmune diseases (myositis, rheumatoid arthritis, lupus, systemic sclerosis)
Possible Environmental Triggers of Immune-mediated Diseases

• Infectious agents
  – Bacteria / parasites: Streptococci, Borrelia, others
  – Viruses: +RNA, DNA, retroviruses, others

• Non-infectious agents
  – Foods: L-tryptophan, adulterated rapeseed oil
  – Drugs: D-penicillamine, hydralazine, many others
  – Biologics: Vaccines, cytokines
  – Medical devices: Collagen and silicone implants
  – Occupational exposures: Silica, beryllium, vinyl chloride
  – Other exposures: UV light, mercury, petrochemicals
Examples - Caprine Arthritis Encephalitis

Caused by a virus
Erythema Infectiosum (Fifth Disease)

Caused by a virus
Some infections are decreasing while autoimmune disease is increasing.
Certain strains of mice develop diabetes when raised in specific germ free environments.

Bacteria and viruses can be helpful for the immune system.
Xenobiotics

- Chemicals found in the environment, drugs or in food that are not produced by the human body.
- Xenobiotics are capable of influencing the immune system.
- The number of xenobiotics that are capable of causing autoantibody formation is growing.
Animal Models of Autoimmunity Triggered by Xenobiotics

<table>
<thead>
<tr>
<th>Xenobiotic</th>
<th>Animal Strain</th>
<th>Autoimmunity</th>
<th>Human counterpart</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercury</td>
<td>Rats</td>
<td>Ab disease</td>
<td>Lupus</td>
</tr>
<tr>
<td>Gold</td>
<td>Rats</td>
<td>IC-kidney disease</td>
<td>Kidney inflammation</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>Mice</td>
<td>Ab to a receptor</td>
<td>Myasthenia Gravis</td>
</tr>
<tr>
<td>Procainamide</td>
<td>Mice</td>
<td>ANA, lung disease</td>
<td>Lupus</td>
</tr>
</tbody>
</table>
Chemicals Associated With Autoimmunity

- **SLE**
  - Allopurinol, Carbamazepine, Cocaine, Dapsone, Gold, Hydralazine, INH, Penicillamine, Procainamide, Sulfonamides

- **Scleroderma**
  - Bleomycin, Silicon, Trilene, Vinyl chloride

- **Cytopenias**
  - Methyldopa, Gold, Penicillamine, Penicillin

- **Renal disease**
  - Cadmium, Gold, Mercury

- **No good associations for myositis**
Mechanisms Leading to Impaired Immunologic Tolerance

- Abnormal cytokine secretion
- Modified self antigen
- Abnormal MHC molecule expression
- Failure to delete autoreactive lymphocytes
- Lack of tolerance to autoreactive lymphs
- Abnormal adhesion molecule expression
- Antigen mimicry

Many different ways disease may occur
Genes are very important
Evidence for the Environment’s Influence

- Less than 50% of identical twins get the disease
- Strong timing connection with some environmental exposures and disease onset
- Dechallenge = disease improvement after agent removal
- Rechallenge = disease recurrence after re-exposure
- Evidence from animal models
- Epidemiology studies between exposures and diseases
Myositis

- Group of syndromes whose hallmarks are chronic muscle weakness from muscle inflammation of unknown cause
- About 0.01% of US population affected; more common in women, frequent onset age 30s and 40s
- Dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM) are the most common clinical forms
- Common problems include: muscle weakness, swelling of the hands and feet, pain and stiffness of the joints; rashes; GI (reflux, dysphagia and constipation); lung (ILD, fibrosis) involvement; Non-specific symptoms such as extreme fatigue, generalized weakness, weight loss, and vague aching of muscles, joints and bones
Global UV Light Levels Predict the Proportion of DM Around the World

UV Exposure (Joules/ m$^2$)

% Dermatomyositis

$R = 0.939$, $P < 0.0000004$
<table>
<thead>
<tr>
<th>Exposure</th>
<th>Rheumatic disease</th>
<th>Comments (reference)</th>
<th>Odds ratio or relative risk (bars, 95% CI limits)</th>
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</thead>
<tbody>
<tr>
<td>Crystalline silica</td>
<td>RA</td>
<td>Swedish study—exposed men (6)</td>
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<tr>
<td></td>
<td>RA</td>
<td>US National Occupational Mortality Surveillance Study (7)</td>
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<tr>
<td></td>
<td>SLE</td>
<td>Southeastern United States study, 265 cases—medium exposure (9)</td>
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<tr>
<td></td>
<td>SLE</td>
<td>Southeastern United States study, 265 cases—high exposure (9)</td>
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<td></td>
<td>SLE</td>
<td>US National Occupational Mortality Surveillance Study—ever exposure (7)</td>
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<tr>
<td></td>
<td>Systemic sclerosis</td>
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<td></td>
<td>Systemic sclerosis</td>
<td>Italian study, 55 selected cases (11)</td>
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<td></td>
<td>Systemic sclerosis</td>
<td>French study, 80 consecutive cases (10)</td>
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<td></td>
<td>Wegener's vasculitis</td>
<td>Italian study, 16 cases (12)</td>
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<td></td>
<td>ANCA + glomerulonephritis</td>
<td>Belgian study, 16 cases (14)</td>
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<td></td>
<td>Primary systemic vasculitis</td>
<td>UK study, 75 cases, high silica exposure ever (15)</td>
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<td></td>
<td>ANCA + small-vessel vasculitis</td>
<td>US study, 51 cases (13)</td>
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<tr>
<td>Pesticides</td>
<td>RA</td>
<td>US study, 135 cases, mixing or applying (16)</td>
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<tr>
<td></td>
<td>SLE</td>
<td>Carolina Lupus Study, n=265, applying (44)</td>
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<td></td>
<td>ANCA + small-vessel vasculitis</td>
<td>US study, 51 cases (13)</td>
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<td></td>
<td>Wegener's granulomatosis</td>
<td>US study, 101 cases (58)</td>
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<tr>
<td>Solvents</td>
<td>RA</td>
<td>US Agricultural Health Study, 135 cases (16)</td>
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<td></td>
<td>SLE</td>
<td>Carolina Lupus Study, n=265, high or moderate exposure (44)</td>
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<td>Italian study, organic solvents (17)</td>
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<td>UK study, organic solvents (17)</td>
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<td></td>
<td>Systemic sclerosis</td>
<td>South Carolina study, men-only association (17)</td>
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<tr>
<td></td>
<td>Primary systemic vasculitis and Wegener's granulomatosis</td>
<td>US study, 75 cases, high ever exposure (15)</td>
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<tr>
<td>Mineral oil</td>
<td>RA</td>
<td>Swedish study, 1,419 cases, men-only association (18)</td>
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<tr>
<td>Furnaces</td>
<td>Systemic sclerosis</td>
<td>French study, 80 consecutive cases (10)</td>
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<tr>
<td>Mercury</td>
<td>SLE</td>
<td>Carolina Lupus Study, n=265, self-reported exposure (44)</td>
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Very Few Studies have looked at Myositis

<table>
<thead>
<tr>
<th>Pathogen or Condition</th>
<th>Disease</th>
<th>Key Findings</th>
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</thead>
<tbody>
<tr>
<td>Parvovirus B19</td>
<td>RA</td>
<td>B19 DNA in synovium (30)</td>
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<tr>
<td></td>
<td>RA</td>
<td>IgM to B19 &gt;6 months duration (32)</td>
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<td></td>
<td>JIA</td>
<td>76 monozygotic twins, IgG to B19 (31)</td>
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<tr>
<td>Juvenile dermatomyositis</td>
<td></td>
<td>No association with IgG to B19 (33)</td>
</tr>
<tr>
<td>URI (one year prior)</td>
<td>Polymyositis and/or dermatomyositis</td>
<td>Questionnaire, case–sibling control (34)</td>
</tr>
<tr>
<td>Streptococci</td>
<td>Childhood myositis</td>
<td>Case review (35)</td>
</tr>
</tbody>
</table>
Other Environmental Items

- Remember the sun – Ultraviolet rays
- Too much in excess
  - Stress, Drugs (recreational, anabolic steroids), Diet, Traumatic events
- Too little in excess
  - Sleep, take care of your body, diet
- Eat right, sleep right, exercise, moderation
What Can We Do To Limit Exposure?

- Eat right, sleep right, stress to a minimum, take care of our bodies
- Take you medications
- Photoprotection – it really works!
Possible Genotype-Ecotype-Phenotype Associations

Environmental history  Future norm of reaction  Health status

Susceptibility genotype (initial conditions)

A

B

Healthy

Sick

Present

Time
Twin Sibling Study

• Study of the environment’s influence on rheumatic disease
• RA, SLE, Scleroderma, Myositis
• Children and Adults
• Study
  • Genetics, microchimerism, microarray
  • Environmental exposures
• Follow 5 years
• Contact Adam Schiffenbauer or Fred Miller at the NIH in Bethesda, MD