Occupationally-associated Male Genitourinary Conditions

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NOTHING TO DISCLOSE

Why this topic; Why Now?

- Increase in Testicular Dysgenesis Syndrome –
  - Hypospadias, cryptorchidism, testicular cancer, poor semen quality
- In the past 15 years, multiple studies of declining sperm counts (sperm concentration, total sperm count, sperm progressive motility, and normal morphology) around the world.
- Unexplained increasing trend in testicular cancer
- Heavy Metals are STILL a concern with regards to effects on male GU
Occupationally-associated Male Genitourinary Conditions

Why this topic; Why Now?

- Male GU systems are particularly vulnerable to endocrine disrupters, e.g., phthalates & flame retardants, which are increasing in scope, manufacturing, and use in the U.S.
- Because Nanoparticles are burgeoning ... and are crossing the blood-testis barrier and we believe are affecting spermatogenesis...animal studies consistently show effects on spermatogenesis, sperm viability.
- Newly recognized effects of infectious agents – Ebola and Zika viruses are holding up in GU systems and causing questions about work, long term consequences, Workers Comp questions.

Occupationally-associated Male Genitourinary Conditions

Why this topic; Why Now?

- Old occupational cancers remain with unchanged rates (bladder cancers)
- Old, known carcinogens in the workplace remain
- Soldiers at work overseas, returning with more profound GU injuries than ever before – what to do?
- More seated work than ever – heating up scrotums, affecting fertility?
- Taxi cab syndrome- the burden of ALL GU consequences?
Occupationally-associated Male Genitourinary Conditions

Why this topic; Why Now?

- Workers on bikes with continued genital numbness and erectile dysfunction
- Unexplained increase in erectile dysfunction in young men: stress taking its toll?
- New knowledge of therapeutics and preventive approaches that block or minimize the effects of occupational exposure at the cellular level
- We’ve brought Erectile Dysfunction into the open, addressing possible work related risks (like BPA, heavy metals, stress, the aging worker – would this be part of Total Worker Health?)
- And lastly, to answer an enduring question that male workers may want to know...

The Challenge can be Overwhelming

**Occupational /Environmental Exposure**

includes: chemicals, pesticides, radiation, biological hazards, heat, sedentary postures, nano particles, psychosocial stress, lifestyle, drugs

**Unknowns:** 84,000 chemical compounds in the workplace; 2,000 new chemicals introduced each year. Only about 4,000 chemicals have been evaluated for reproductive toxicity...
• GnRH = Gonadotropin Releasing hormone
• FSH = Follicle Stimulating Hormone
• LH = Luteinizing Hormone

Blood-Testis Barrier:
• Prevents autoimmune destruction of sperm
• Blocks the body’s toxins
Spermatogenesis

Spermatogonium (begins outside the BTB) → Primary Spermatocyte

Primary Spermatocyte → Secondary Spermatocyte

Secondary Spermatocyte → Spermatid

Spermatid → Sperm

Takes About 5 weeks

What Parameters are important in Occupational/Environmental Repro Studies?

- **Sperm:** volume, density, liquefaction time, viability, motility, morphology
- **Seminal plasma:** total antioxidant capacity
  - (can measure the level oxidative stress by assay, which at high levels damages sperm)
- **Sertoli cells:** Mitochondrial Membrane potential
  - seen with early apoptosis (cell death)
  - We can measure the mitochondrial permeability transition pore using ELISA.

Guo et al, JOEM 58 (8) 2016
We’ve been able to Identify **Work Toxins** Affecting specific phases in sperm development

<table>
<thead>
<tr>
<th>Affected site</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epididymis</td>
<td>Epichlorohydrin, Chloromethane</td>
</tr>
<tr>
<td>Spermatid</td>
<td>Chloromethane</td>
</tr>
<tr>
<td>Spermatocyte</td>
<td>Heat</td>
</tr>
<tr>
<td>Spermatogonium</td>
<td>DBCP, ionizing radiation, cisplatin</td>
</tr>
<tr>
<td>Sertoli cell</td>
<td>Phthalate esters, BPA, cadmium, dinitrobenzene,</td>
</tr>
<tr>
<td></td>
<td>cisplatin</td>
</tr>
<tr>
<td>Leydig cells</td>
<td>Ethanol, ethane-1,2 dimethane sulfonate, cisplatin</td>
</tr>
</tbody>
</table>

We’ve Identified Morphological Effects on Sperm

<table>
<thead>
<tr>
<th>Type of Exposure</th>
<th>Lowered #</th>
<th>Abnormal Shape</th>
<th>Altered sperm transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dibromochloropropane</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbaryl (Sevin**)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toluenediamine and Dinitrotoluene</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Ethylene Dibromide</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Plastics (styrene and acetone)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethylene Glycol Monoethyl Ether</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Welding</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Perchloroethylene</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Military Radar</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kepone**</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Bromine Vapor**</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Radiation** (Chernobyl)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>2,4-Dichlorophenoxy Acetic Acid</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
Toxic Chemicals Break down the Blood-Testis-Barrier

- E.g., Cadmium and BPA enter Sertoli cells at the plasma mitochondrial membrane “pores”
- Causes oxidative stress, starts cytokine activity & interferes with endoplasmic reticulum, engulfs barrier proteins and destabilizes Blood- Testis-Barrier.
- Toxins also activate MAPK pathway & engulf more barrier proteins.

What’s new: Cadmium and BPA in the testes can be stopped!

- Knowing specific locations of toxic exposures disrupting the Blood-Testis-Barrier helps to develop controls to protect workers.
- We can modify the Arp2/3 membrane protein complex to stabilize the B-T-B when Cd and BPA are present.
- N-acetylcysteine, an antioxidant, can inhibit the effect of Cd on endoplasmic reticulum and prevent germ cell apoptosis in the testes.
Ebola Virus penetrates the blood testis barrier

- May hang out on outer side of Sertoli cells, infect spermatogonia, then surreptitiously sneak past the BTB, and remain in the infected sperm cell for maturation...
- Semen testing programs in West Africa have detected viral RNA in semen up to 1½ years after disease!

Challenges with Ebola and Male GU Effects

- We still don’t know the pathophys. of virus & persistence in semen & eventual effect on the body.
- Has repercussions for workers who had Ebola and thought they were cured.
- Will infection reappear? Infectivity?
- Has repercussions for their employers, insurers, not to mention their families.
And then there is Zika Virus...

Zika virus (ZIKV) persists in semen, a 1st for flavivirus infection

- Can pass it to sex partners before, during, and after symptoms or NO symptoms
- Live Virus found in semen >69 days after symptoms onset
- Zika RNA found after 188 days

Mice infected with Zika had shrunken testicles & low testosterone levels. It preferentially infected spermatogonia, primary spermatocytes and Sertoli cells. It cause seminiferous tubule “death.”

Moreira J. et al. [2016] Clinical Microbiology and Infection 12.027

ZIKV in semen raises several important questions for workers, occup. professionals and businesses

1. What is true prevalence of ZIKV infection among male workers in affected countries?
2. What is the responsibility of employers to outdoor workers who get infected?
3. How do we deal with workers who have a persistence of an uncharted disease? Of those with a permanent loss in fertility?
4. Is Zika virus a “take-home toxin”?
CHEMICAL HAZARDS: CASE Study:

Low level Carbon disulfide exposure and Male Repro Effects (2014, 2016)

Industries use carbon disulfide as a raw material to make such things as viscose rayon, cellophane, sausage casings, and carbon tetrachloride.

Carbon Disulfide: Does it Cause Male Repro Effects at < 10 mg/m3?

- Since 1970s: high CS₂ exposure leads to decreased libido, male potency, decreased sexual hormones & semen quality
- At lower conc (~10 mg/m3), repro effects are unanswered...
- 2014, found CS₂ at low levels induce rat testicular injury via the mitochondrial permeability transition pore (MPTP).
- But mechanism in humans unknown...

Guo et al. 2014
Case- Control Study of Low Carbon Disulfide Exposure and Male Repro, 2016

76 male workers exposed to CS₂ and 94 unexposed workers: matched by age, BMI, tenure, education, alcohol, cigarettes

- Questionnaire
- Blood measured for FSH, LH, testosterone, sex hormone binding protein (SHBG)
- Semen samples

CS₂ area conc: Ave 9.7 mg/m³ for previous 2 yrs
(TWA in China is 5 mg/m³)

Compared Sex Hormone Levels Male Workers Exposed to CS₂ vs Unexposed

<table>
<thead>
<tr>
<th>Hormone Levels</th>
<th>Unexposed (94)</th>
<th>Exposed (n=76)</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH mIU/ml</td>
<td>7.9 ± 1.9</td>
<td>19.2 ± 2.5*</td>
<td>1.24~8.62</td>
</tr>
<tr>
<td>FSH, mIU/ml</td>
<td>10.2 ± 3.3</td>
<td>17.2 ± 3.9*</td>
<td>1~14</td>
</tr>
<tr>
<td>Testosterone, ng/dl</td>
<td>428.7 ± 3.9</td>
<td>68.8 ± 4.2*</td>
<td>260~1320</td>
</tr>
<tr>
<td>SHBG, nmol/L</td>
<td>68.5 ± 3.2</td>
<td>43.3 ± 1.5*</td>
<td>15~100</td>
</tr>
</tbody>
</table>

*P<0.05.

Guo at al, JOEM 58 (8) 2016
CS₂ = carbon disulfide
**Compared Semen in Male Workers Exposed to CS$_2$ vs Unexposed**

**Results:** Had Decrease in sperm quality parameters

- **Increased** liquefaction time, deformed chromatin structures, rates of apoptosis
- **Decreased** semen viability, motility, total antioxidant capacity, sperm mitochondrial membrane potential*;
- **High expression** of mitochondrial permeability transition pore proteins

**CS$_2$** even at low levels has deleterious effect on sex hormones and sperm.

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**Phthalates, BPA, and Male Repro and NIOSH work**

- High molecular weight plasticizers – can increase flexibility, durability, and the longevity of plastics.
- Used in resins, pesticides, antiparasitic agents, cosmetics, perfumes, lubricants, solvents, and anti-foam agents...
- Phthalates are **not** chemically bound to the plastic matrix or to other chemicals so migration & leaching occur.

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* Sapna S et al. [2015] Urology Vol 12 No 05 S 2309

**Guo et al, JOEM 58 (8) 2016**

- Breakdown of $\Delta \psi$m is characteristic
- of early apoptosis in testicular cells
BPA and Phthalate compounds’ effects upon spermatogenesis

- Bisphenol A (BPA), 4-nonylphenol, (NP) and di(2-ethylhexyl) phthalate (DEHP), and its metabolite mono-2-ethylhexyl phthalate (MEHP) have been shown to:
  - Disrupt the blood-testis-barrier
  - Generate reactive oxygen species
  - Cause spermatogonia sloughing
  - Cause spermatogonia apoptosis
Bisphenol-A (BPA)

- Affects androgen receptors, hormone levels, all male repro. organs, and spermatogenesis
- In animal studies, is an endocrine disruptor, has estrogenic & anti-androgenic effects.
- Causes epigenetic modifications, such as DNA methylation, which can alter chromatin structure, results in azoospermia, low sperm number, abnormal morphology, and infertility.

(Richter et al, 2007; National Toxicology Program, 2008; Bouskine et al, 2009; Salian et al, 2009a,b; Li et al, 2010; Vom Saal and Hughes, 2005, Bonefeld-Jorgensen et al., 2007; Wetherill et al., 2007).

Let’s look at BPA and Semen Parameters in Workers

- 230 Chinese Factory Workers exposed to BPA compared to 234 unexposed workers
- 2 semen samples, 2 urine samples for BPA

Found increased BPA level associated with decreased: sperm concentration, total sperm count, sperm vitality, sperm motility. (Controlling for confounders*).

*smoking, alcohol use, chronic diseases, history of subfertility, and exposure to other chemicals and heavy metals; recent heat sources, i.e., steam bath.
Also found worsening male sexual function; as urine BPA levels increased, there was:

- Reduced **sexual desire** *(P < .001)*
- Lowered **ability for erection** *(P < .05)*
- Increased difficulty having erection *(P < .001)*
- Increased difficulty with **ejaculation** *(P < .02)*
- Lowered **ejaculation strength** *(P < .001)*
- Lowered overall satisfaction with sex life *(P < .003)*
- Reduced ability to have an erection hard enough for penetration *(P < .24)*

Adjusted for age, marital status, chronic diseases, education, work hx, previous exp. chemicals and heavy metals, smoking, drinking, study site

Then, another study looked at BPA and reproductive hormones among workers

- Cross-sectional study of 592 male workers found increased urine BPA level was associated with:
  - increased prolactin *(p < 0.001)*
  - Increased estradiol *(p < 0.001)*
  - Increased sex hormone-binding globulin level *(p = 0.001)*
  - Reduced androstenedione *(p < 0.001)* & reduced free androgen index level *(p = 0.021).*

- **Conclusion:** Another confirmation that BPA exposure contributes to male infertility.

controlling for age and smoking status

NIOSH has recently looked at BPA exposure in 6 companies

- Workers producing polycarbonate resins, phenolic resins, handled raw BPA, and exposed by inhalation & dermal absorption.

- 78 workers gave 7 urine samples over 2 days.

**RESULTS:** Workers found to have BPA levels in their urine ~70 times higher than U.S. male pop. (2013/14 NHANES data) [88.0 µg g⁻¹ vs 1.27 µg g⁻¹].

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So what does NIOSH recommend for Phthalates & BPA?

**For Now, Rely on the Hierarchy of Controls:**

- Eliminate/substitute for BPA.
- Fully enclose or local exhaust ventilation.
- Minimize worktime in BPA production areas.
- Improve housekeeping
- Last resort, PPE with appropriate fit testing
- Implement sampling program for BPA
The European Union just issued its expert panel report “Burden of Endocrine Disruptors on Male Genitourinary System”.

Strong toxicological evidence for phthalates:

• male infertility & resultant reproductive procedures, costing $5 billion annually.
• lower testosterone conc. with 24,800 associated deaths annually; lost economic productivity of $8.45 billion.

Russ Hauser et al (2015), J Clin Endocrinol Metab. 2015 Apr; 100(4): 1267–1277

Heat and Increased Temperature Affect the GU System and are linked to infertility

- We know external heat exposure can affect male fertility...

- Classic studies have looked at Hot Work: e.g., welding, foundries, bakeries, and how increased temperatures cause differences between body core and scrotum temperatures.
Sperm are extraordinarily sensitive to even minor fluctuations in temperature.

- Sperm are ideally packaged in scrotum to deal with temperature changes
- Spermatogenesis: most efficient at 34 °C (93.2°F)
- Sperm thrive at body temp. from 50 min to 4 hrs, (the ave. time to go through female reproductive tract & fertilize the egg)
- >37°C (98.6°F), chances for successful insemination plummets...

Question: Can Laptops cause Elevated Scrotal Temps?

- Sheynkin et al. measured scrotal temps in 29 men working in 2 seated, 60 min sessions with and without laptops.
- Scrotal temps increase signif higher with laptops (2.8°C vs 2.1°C, p <0.0001). Happened in ~ 10 or 15 min., but men didn’t “feel it”. Ave. temp 36.5°C± 0.57 (97.7°F) [Recall, ideal is 34°F]
- In men using a lap pad and sitting with legs apart at a 70° angle, scrotal temp still was elevated by >1°C, indicating insufficient preventive effect.
Occupational Causes of Heat to GU: Can Laptops Impact male fertility?

- Concluded that long-term exposure to laptop computer-related repetitive transient scrotal hyperthermia may have a negative impact upon spermatogenesis.
- Sitting position with closely approximated legs found to be the major cause of scrotal hyperthermia with laptops.
- Scrotal shielding with a lap pad did not protect from scrotal temperature elevation.
- Prevention of scrotal hyperthermia required reduced computer time in lap.

Protection from Scrotal High Temps and Laptop use: What should men do?

- Keep scrotal temperature at the “safe” level by short-term use of a computer on the lap (maintaining scrotal temperature elevation within a 1°C margin can serve as a reasonable protective goal)
  - < 11 minutes with legs held together,
  - < 28 minutes with legs apart (70° angle)
Seated Work Position & Semen

- Duration of seated position assoc with increased scrotal temps, lower sperm counts
- Several previous studies on truck- and taxi drivers, show detrimental effects on semen quality
- Heated car seats increased temps 0.5°C, one-third of the exposure time versus unheated.

Besides Seated work and infertility, what other GU Problems Does Driving work cause?

- Mass, Goldfarb and Shah did a cursory review of overall genitourinary problems in Taxi cab drivers
- Concluded they have more voiding dysfunction, infertility, urolithiasis, prostatitis, ejaculatory duct abnormalities, bladder cancer, and urinary infections as compared with nonprofessional drivers
“Taxi Cab Syndrome:” Infrequent Voiding and GU Problems

For the Taxi drivers, the authors suggested interventions including:

- **Education**
  - Diet, fluid intake, adequate bladder emptying, techniques to limit heat exposure to genitals

- **Improved network of taxi relief stands & close, accessible toilets**

- **Urinary collection devices** encouraging drivers to urinate in sanitary, controlled setting in their vehicle.

Severe GU Injury to Military Soldiers (as workers)

**The Good News:** Improvements in battlefield medical care in Iraq and Afghanistan* conflicts have led to unprecedented rates of survival.

**The Bad News:** They resulted in more survivors with GU injuries than ever before in the history of war.

Epidemiology of Genitourinary Injuries among Male U.S. Service Members Deployed to Iraq and Afghanistan:

(Oct 2001 – Dec 2015)
Records from DoD Trauma Registry from 2001 to 2013

- Cohort: All U.S. military with 1 or more GU injuries.
  - 1,367 male GU injuries, 37% severe
- Demographics: 81% < 30 yrs., 60% junior-enlisted, Army or Marine
- 74% caused by explosive device

DOD Trauma Registry of Soldiers with GU Injuries

- 1,000 (73.2%) had 1 injury to external genitalia
  - 56% Scrotum
  - 30% Testes
  - 31% Penis
  - 9% And/or urethra
- 147 men had loss of entire penis and 1 or both testes was documented
  - 129 unilateral orchiectomies
  - 17 bilateral orchiectomies.
Soldiers with severe GU injuries had a higher % severe polytrauma

- Comorbid injuries:
  - 40% Traumatic brain injury
  - 25% Pelvic fracture
  - 22% Colorectal injury
- 29% had lower extremity amputation and GU injury
  - Most LE amputations at or above the knee

In GI’s with Pelvic blast injuries without overt testicular injury...

- Many developed testicular atrophy and biopsy-confirmed azoospermia – (no sperm!) despite no evidence of overt testicular injury at the time of initial presentation
- A delayed effect from the initial blast injury.
Why the increase in GU Injuries?

- Standard military PPE protects chest & abdominal organs but not external genitalia;
- Afghani rugged terrain required foot patrol, exposing genitals to injury from ground based explosive weapons;
- But increased survival following complex polytrauma...

How to Prevent GI GU Blast Injuries?

- Education
- Better PPE: new 2-tier systems:
  - **Tier 1: Kevlar, formfitting boxer-briefs:** reduces injury from low energy projectiles & penetration of dirt, debris into a pelvic wound;
  - **Tier 2: thicker, brief-type outer garment** worn over the combat trousers, designed to provide protection from high energy projectiles.
Other External Trauma to the urogenital tract affecting workers

- Acute trauma from direct impact to the perineum had lead to increased male erectile dysfunction.

- One 20-year old longitudinal study of 131 men found persistent changes in erectile function followed blunt pelvic or blunt perineum trauma.

- Estimated ~250,000 men are afflicted by sports injuries which involve blunt impact loading to the perineum or pelvis.

Bike Patrol and GU Problems: the NIOSH Evaluations

- > 50,000 public safety bike users
- Bike patrol officer –ave. 24 hrs/wk on bike
- Have continued pressure on perineal region in postures that may constrict the pudendal nerve and cause penile arterial compression.
- At risk for groin/genital numbness and erectile dysfunction
Police, Cycling and Genital Numbness

- NIOSH received a Health Hazard Evaluation request from a Police Dept. Union c/o genital numbness and sexual dysfunction.

- 29 police officers and 5 non-biking men (control group) were included in a prospective study to evaluate GU effects & bicycle riding.

Police, Cycling and Genital Numbness

Methods of NIOSH Evaluation

- 28 officers – bicycle seat pressure measurements
- 19 - surveyed on work hx, medical hx, and sex performance using International Index of Erectile Function Questionnaire
- 17 officers - blood samples for hormone analyses
- 16 officers had penile Rigiscan® measurements
- 5 - semen samples (All sperm counts, WBC, and sperm morphologies were normal.)
Assessing Riding Posture, Position and Pressure

- Each bike placed into stationary bicycle trainer, then pressure assessment mat aligned on bike seat
- Officer mounted bike and pedaled in normal riding position and in pursuit position.
- Each position monitored for ~ 30 seconds

Police Bicyclists and Evaluation of Genital Effects

- 16 participants had Rigiscan™ erection monitors - assesses erectile function during sleep. A monitor is worn on the leg, 2 loops on the penis.
- NIOSH compared # erections and % sleep time with an erection
Bicycling and Nighttime Erections

**RESULTS:** Police **Bicyclists** experienced erections 26% of the time asleep, measured by the Rigiscan, compared to 43% for non-bicyclists.

- As ave. # hrs /day the officer was on bike increased, the % sleeping time with an erection decreased.
- As measured pressure in PSI between the officer and the bicycle seat increased, % sleeping time with an erection was decreased.

Police, Cycling and Genital Numbness: Survey Results

- Police bikers reported normal erectile function (**Internal Index of Erectile Function Questionnaire.**)
- 93% of the 15 bikers had recurring numbness in buttocks, scrotum, testicles, or penis.
- Numbness occurred after 10 min to 3 hrs of riding;
- Numbness lasted 5 min to 24 hrs.
Assessing Riding Position and Pressure

- 22% weight was on nose of bike saddle;
- 78% weight on ischial tuberosity portion of saddle.

Ave pressures:
- 2.3 ± 1.7 psi on saddle nose;
- 2.9 ± 1.0 psi on wider part of saddle.

- The nose’s smaller surface area acts to increase the localized pressure on the rider.
- Pressure exerted on the nose is most detrimental to the nerves and blood vessels in the perineum.

Nose of the Bicycle Saddle was Assessed by NIOSH

- NIOSH measured magnitude and distribution of pressure on perineal region of 33 bike police pedaling on stationary bicycle with different saddle types:
  - traditional sport/racing saddle with a protruding nose,
  - 3 saddles without a nose.
- The traditional sport/racing saddle had twice the pressure in the perineal region than no-nose saddles
- Penile perfusion was not assessed.
FOLLOW-UP: 2\textsuperscript{nd} NIOSH Longitudinal Study of No-Nose Saddle Use

- 121 Bicycle Police recruited in 5 metro Areas. Completed:
  - Erectile function survey
  - Pressure measurements on bicycle: handlebars, pedals, saddle
  - Nocturnal Rigiscan\textsuperscript{®} assessment
  - Penile Vibrotactile Sensitivity Threshold
  - Officers selected a no-nose bicycle seat and used them exclusively for 6 months,
  - Then retested 6 months later

assessed by computerized bio-thesiometry.
Results of NIOSH Longitudinal Study of No-Nose Saddle Use by Police (1 of 2)

- 90/121 (74%) men were reassessed at 6 months.
- Only 3/121 men had returned to a traditional saddle.
- 66% had reduced saddle contact pressure in the perineal region ($P < 0.001$).
- Signif improvement in penis tactile sensation ($P = 0.015$).

Results of NIOSH Longitudinal Study of No-Nose Saddle Use by Police (2 of 2)

- Signif improvement in erectile function assessed by IIEF ($P = 0.015$).
- No change in the Rigiscan® measures.
- Having “NO urogenital paresthesia while cycling” for the preceding 6 months rose from 27% to 82% using no-nose saddles.

*IIEF=International Index of Erectile Function Questionnaire*
FOLLOW-UP: 2nd NIOSH Longitudinal Study of No-Nose Saddle Use

**Conclusions.** With few exceptions, bicycle police officers were able to effectively use no-nose saddles in their police work.

Use of no-nose saddles reduced most perineal pressure.

Penile health improved after 6 month using no-nose saddles as measured by biothesiometry and IIEF.

*IIEF=International Index of Erectile Function Questionnaire*

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**Cycle Saddle Seats and Penile Cavernosal Blood Pressure**

Goldstein et al. found with penile hemodynamics and perineal compression forces:

Cycling on slim saddles with nose extensions resulted in 97.4% reduction of penile cavernosal peak systolic velocity (CA PSV) values.

Straddling on two-cheek noseless seats resulted in only a 2.2% reduction in CA PSV, in addition to producing dramatic increases in perineal pressures.
**NIOSH Recommendation for Workplace Bicycling**

- Use a no-nose saddle for workplace bicycling. It takes time to get used to it.
- Get fit for your bike from a trained bicycle fit specialist.
  - may require different saddle height and angle adjustments.
- Dismount the bicycle when at a standstill.
- Dismount the bicycle if you begin to have numbness, tingling, or loss of feeling in any part of your body.

**The no-nose bike saddle faces a marketing problem**

- The answer comes from a bike shop owner quoted in the article who said, “This saddle screams out: I’ve got a problem.”
- That could be why so few cyclists -- from hard-core racers to spinning-class addicts -- are rushing to buy noseless saddles.
Summary Of Male GU and Occupational Exposures

- Why this topic: testicular dysgenesis syndrome, metals, nano, chemicals
- Testicular function, hormonal cascade, spermatogenesis,
- Toxins affecting sperm development and the blood testis barrier
- Infectious agents: Ebola and Zika
- Chemicals: Carbon disulfide, Phthalates & BPA
- Physical factors: Heat, Laptops, Drivers, Taxi Cab syndrome
- Physical Factors: GU injury as Soldier
- Physical factors: sports and Bicycle and erectile dysfunction

Thank You for Your Attention!

QUESTIONS?

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The findings and conclusions in this presentation do not necessarily represent the views of the CDC, NIOSH, or the USPHS.
ANOTHER TOPIC FOR STUDY:
Bladder cancer Incidence and Mortality 1975-2013

What’s new?
The On-going Controversy in Bladder Cancer, Gene testing, and Occupational Exposure

- N-acetyltransferase 2, (NAT2) is encoded in our genes
- We either have rapid, intermediate, or slow acetylator phenotypes
  - Type may activate or deactivate carcinogens.

Does having a slow acetylator type make you more prone to Bladder Cancer with occupational exposure to workplace carcinogens?
NAT-2 Slow Acetylation and Workplace Testing

Do we test men with exposure to recognized bladder carcinogens for NAT-2, to identify those at higher risk for Bladder cancer?

Is this Genetic testing useful for purposes of identification, preventive action for workers, compensation, OR because of insufficient scientific evidence and lack of specificity, is this an ethical test?

NAT-2 \(=\) N-acetyltransferase 2 slow acetylation

In 2013, a nested case-control study of the *European Prospective Investigation into Cancer and Nutrition* (EPIC) Cohort

- Evaluated the association between N-acetyltransferase 2 slow acetylation (NAT2) and bladder cancer.
- Using ~750 bladder cancer cases and ~830 controls, and a semi-quantitative job-exposure matrix to categorize exposure to aromatic amines and (PAHs)
- They genotyped participants’ blood DNA into NAT2 acetylation status to categorize as “slow” or “fast” acetylators.

N-acetyltransferase 2 phenotype, occupation, and bladder cancer risk: results from the EPIC cohort.

**Results:** Increased Bladder Cancer Risk and occupational exposure to
- Aromatic amines [OR = 1.37; 95% CI, 1.02-1.84]
- PAHs [OR = 1.50; 95% CI, 1.09-2.05]

**BUT** NAT2 slow acetylation did not modify these risk estimates and was not associated with bladder cancer risk (OR = 1.02; 95% CI, 0.81-1.29).

**2013 CONCLUSIONS:**
- Confirmed occupational risk factors for bladder cancer **but not** the anticipated role of NAT2 slow acetylation.
- No interaction was detected between NAT2 and any exposures of interest, including smoking.

**IMPACT:** Genetic testing for NAT2 would be inappropriate in occupational settings.
The Saga Continues: 2016 NAT2 Slow Acetylation and Bladder Cancer Risk

In 2016, Wu et al. published a meta-analysis of 18 studies, included 4473 bladder cancer cases and 7204 matched controls

- NAT2 slow acetylators had increased risk of BCA compared to rapid acetylators
  - (OR, 1.6; 95% CI, 1.33-1.82; P < .00001)
- NAT2 slow acetylators had increased risk of BCA in smokers (OR, 0.75; 95% CI, 0.62-0.90; P = .002)
- Wu’s results suggest that NAT2 slow acetylator, in particular, the NAT2 slow acetylator combined with smoking, are associated with an increased bladder cancer risk.

Is Genetic screening of workers for susceptibility to cancer Appropriate?

- it must be demonstrated that:
  - a specific metabolic phenotype is a risk factor for cancer
  - Available tests accurately classify the subjects as to the phenotype.
  - Bias, arising as a consequence of enzyme induction by specific substrates, must be ruled out.
  - NIOSH previously thought this to be ethically unacceptable and premature application of the science.
Limitations of Male Repro Occup/Environ Studies:

- Question of validity, reliability & representativeness in looking at semen parameters
- Workplace masturbation puts logistical and emotional obstacles which limit the ability of obtaining semen in a timely and well-controlled manner
- Workplace approach is to identify exposure groups, then randomly choose from among these lists.
- Unfortunately, in practice, these procedure generate so many refusals that it leads to another form of ‘volunteer’ selection.
- Selection Bias: Inability to study a truly random population of men

Regarding Carbon Disulfide as a Reproductive Toxin, which answer is FALSE?

A. Since 1970s, we have known that high $\text{CS}_2$ exposure leads to decreased libido, male potency, decreased sexual hormones & semen quality
B. $\text{CS}_2$ effects on sperm include decreased liquefaction time, decreased apoptosis, increased mitochondrial membrane potential
C. Studies have found exposure to lower concentration levels (~10 mg/m3) of $\text{CS}_2$ are associated with reproductive effects.
Regarding Police on Bicycles and nighttime erections: Which is Correct?

A. As the average number of hours per day the officer was on bike increased, the % sleeping time with an erection decreased.
B. The wider the bicycle seat on the ischial tuberosity, the stronger and longer the reported erection.
C. As measured pressure in PSI between the officer and the bicycle seat increased, % sleeping time with an erection increased.

PSI = pounds per square inch

We need to know about the specific phases of sperm development and Occupational exposure. Occupational Exposures at which phase will have the most lasting effects on infertility?

A. Spermatocyte
B. Spermatogonium
C. Spermatid
D. Spermatoli