

Update : réactions médicamenteuses

**Prof. Philippe Camus
Dijon**

Recalled drugs

- Mercury
- Hexamethonium
- Anorexigens: Aminorex; fenfluramine Fen-Phen, benfluorex
- Glitazones: pulmonary edema, congestive heart failure
- Aprotinin: severe coagulopathy
- Levamisole

CURRENT CONTROVERSY

3

The hexamethonium asthma study and the death of a normal volunteer in research

J Savulescu, M Spriggs

Death of a normal volunteer highlights problems with research review and protection of subjects



selected reports

Recreational Use of Aminorex and Pulmonary Hypertension*

Seán P. Gaine, MD, FCCP; Lewis J. Rubin, MD, FCCP;
James J. Knetzo, MD; Harold I. Palevsky, MD, FCCP; and
Thomas A. Traill, MD

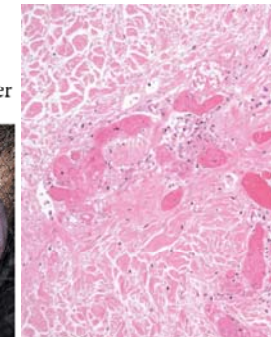
Pulmonary hypertension has been associated with ingestion of the appetite suppressant aminorex. A similar compound, 4-methyl-aminorex (street names, "U-4-E-uh" [pronounced euphoria] or "ice"), is a "designer" drug with central stimulant activity. This drug was discovered on the property of three individuals with diagnoses of pulmonary hypertension. The association between "recreational" aminorex manufacture and ingestion and the development of pulmonary hypertension is described.

(CHEST 2000; 118:1496-1497)

■ Levamisole present in ~70% of cocaine samples

- 10% in weight
- 10% present with DAH
- **Urine Drug Screen**

Toxic Effects of Levamisole in a Cocaine User



■ Propylthiouracil - PTU

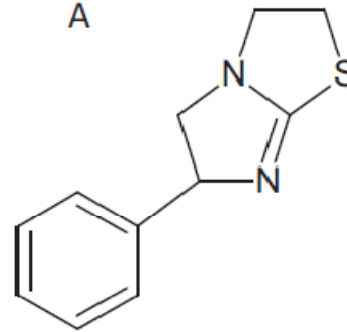
- 20~64% of patients develop anti-MPO ANCA
- Elevated titers
- Multiple targets: anti-lactoferrin, cathepsin-G, BPI protein
- anti-PR3 c-ANCA rare
- 5-10% develop vasculitis
 - ❖ ¼ develop ILD, AH, pulmonary capillaritis



FIG. 1. Hemorrhagic skin lesions involving the upper arm (right) with rapid onset.



A



B

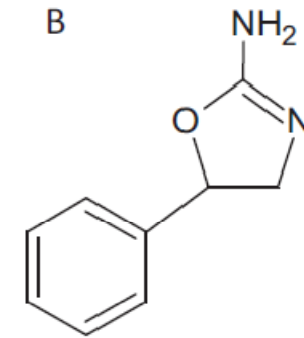


Fig. 1. Structure of levamisole (A) and aminorex (B).

- Amphetamine & PHTn
- OR: 2.99
- **Any PHT should include exposure to amphetamine**

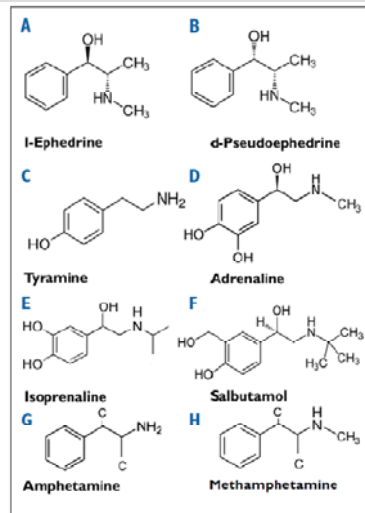


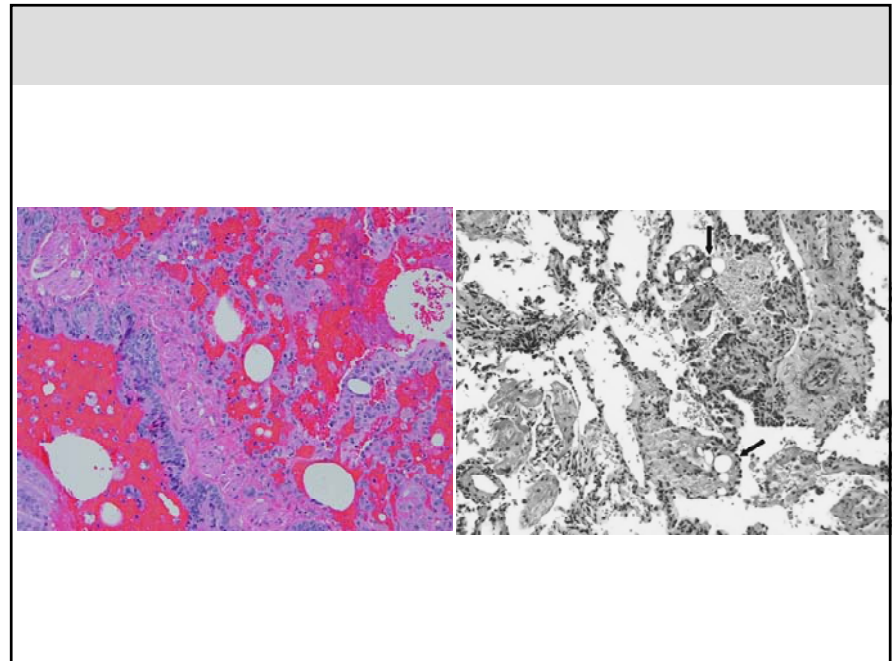
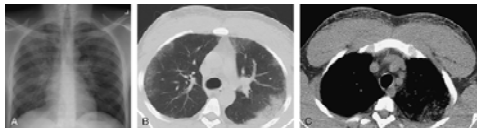
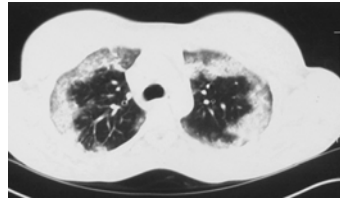
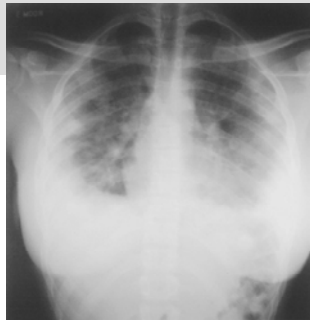
FIGURE 3 The chemical structures of important catecholamines: l-ephedrine (A), d-pseudoephedrine (B), tyramine (C), adrenaline (D), isoprenaline (E), salbutamol (F), and the amine amphetamine (G) and its methyl derivative methamphetamine (H).

Incidence

■ ILD	3.5%	Thomeer
■ ALI	9.5% 10%	Dhokahr Parambil
■ DAH	11-18%	
■ BOOP	28%	
■ EoP	10-18%	

Silicone (SES) (Ptox=48)

- ▣ Young women. Transsexualism
- ▣ Injection by physician - illegally
- ▣ Dyspnea, chest pain, hypoxemia
petechiae, altered consciousness
 - DAH
- ▣ Silicone in BAL / tissue
- ▣ ? Neurologic symptoms
 - 20%
 - 100% mortality



Abused and related substances

- ▣ DAH Cocaine, bong pipe
Sildenafil
- ▣ 'Crack lung' Cocaine
- ▣ ILD Cocaine
- ▣ BOOP Cocaine
- ▣ Pulmonary edema Cocaine, heroin
- ▣ Foreign body granuloma

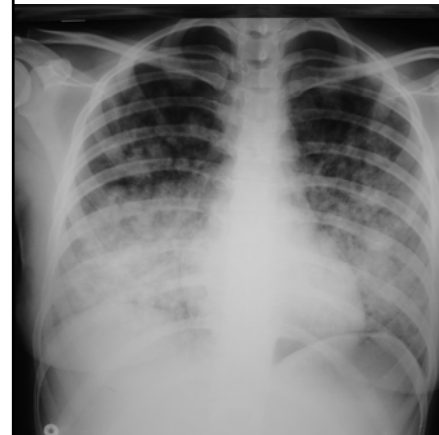
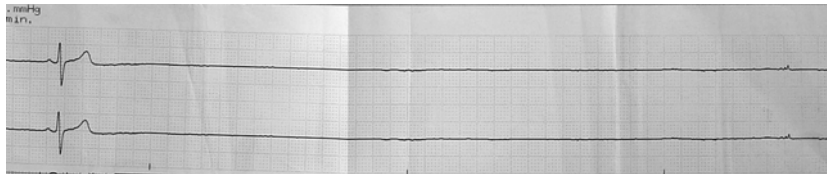
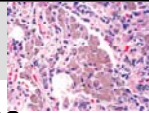
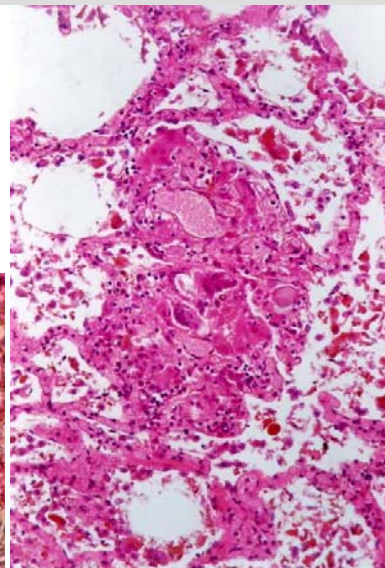
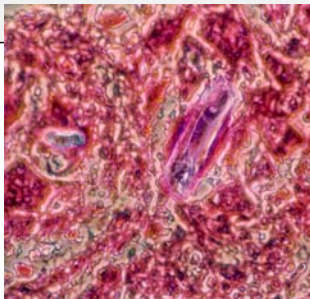


Figure 5. Mushroom plume from pulmonary oedema. This may be seen in opiate deaths.

Table 1

Frequently used additives/diluents to adulterate street drugs [22].

Quinine
Mannitol
Lactose
Glucose
Procaine
Caffeine
Inositol
Lidocaine
Starches
Methapyrilene
Sucrose
Acetylprocaine
Dextrose
Scopolamine
Paracetamol
Phenobarbital
Methaqualone



Acute transfixiating chest pain

- Crack cocaine
- Bleomycin, etoposide, methotrexate
- 5-FU
- Nitrofurantoin
- Adenosine, A5'TP, adrenaline
- Triptans: 1-4%
- Statins



Figure 1
ECG taken at time of chest pain

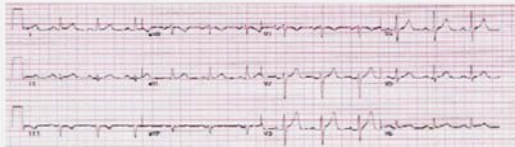
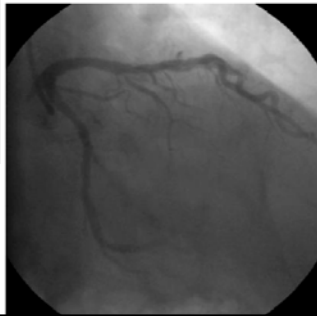


Figure 2
ECG after pain resolved



Angioedema

- ▣ I Face, lips
- ▣ II Tongue, mouth floor
- ▣ III Laryngeal and/or extrathoracic trachea



- ACEI OR x3.6)
 - ❖x4 in coloured people
 - ❖+50% in women
- ARB (ARB 1/10th-1/20th)
- Enalapril, isinopril > captopril
- No relationship with ACEI cough
- Incidence
 - ❖0.2-1% yearly
 - ❖-> **lifetime risk**
- 07/10,000 ED visits

- ≤12 hrs of 1st administration 1/3
- In a few weeks 1/3
- Months-to-years into treatment 1/3
- Average 12-14 mo
- Perioperative...
- ❑ **Hx of episodic macroglossia common**
- ❑ **Onset (4 - 6h)**
 - Sore throat
 - Drooling of saliva
 - Abdominal pain
- ❑ **Wanes or progresses**

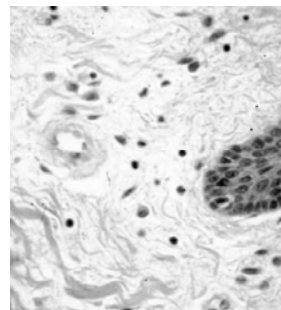
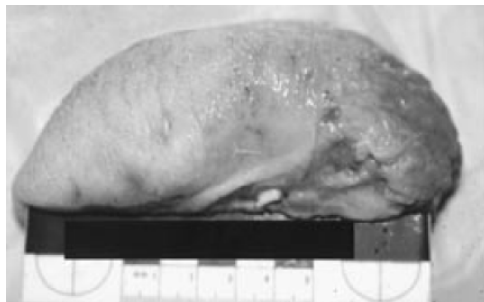


■ Dean
2001
n=7



FIGURE 1. Computed tomography scan of neck showing edema and airway compromise.

Minimal submental edema was also noted (Figure 1). Treatment included 0.3 mg epinephrine subcutaneously every 20 minutes for three doses, 300 mg cimetidine IV, 250 mg methylprednisolone IV, and 50 mg diphenhydramine IV for two doses. There was no response to this antiallergic treatment, and the soft-tissue swelling of the neck gradually increased. Because of the patient's inability to control



Clinical problems in cardiopulmonary disease

Are Physicians Aware of the Side Effects of Angiotensin-Converting Enzyme Inhibitors?*

A Questionnaire Survey in Different Medical Categories

Carlo Lombardi, MD; Mariangiola Crivellaro, MD; Annarita Dama, MD; Gianenrico Senna, MD; Sabrina Cargioni, MD; and Giovanni Passalacqua, MD

■ 2005

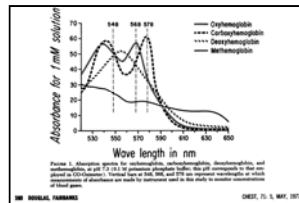
■ Cardiologists: 33.9%, GP: 40%, 'Allergists': 34%

▣ Methemoglobinemia

- MetHb: ferric Hb (Fe+++)
- Poor O₂ carrier

▣ Diagnosis

- Normal PaO₂
- Low - spurious SpO₂ readings
- Normal calculated SaO₂
- -> Saturation **gap**



▣ Methemoglobin

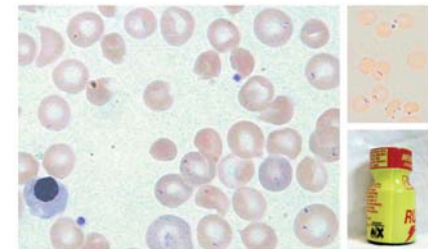
- Normal <1%
- Warning >2%
- Symptoms >15-20%
- Mortality > 50-70%

▣ Typical drugs

- Benzocaine, dapsone, NO

▣ Management

- Drug discontinuation
- Oxygen therapy
- Methylene blue
- Exchange transfusion, HBO



▣ **Audit on methemoglobin**

- Nurses: 32%
- Doctors: 50%

▣ **Make sure that:**

- **People know**
- **Methylene blue is available**

■ Abciximab (ReoPro®)

■ Tirofiban, eptifibatide, clopidogrel, ticlopidine

■ DAH

- ❖ Abciximab: 0.14-0.58% 5.5-12 v. unexposed
- ❖ Eptifibatide: 0.33-0.83%

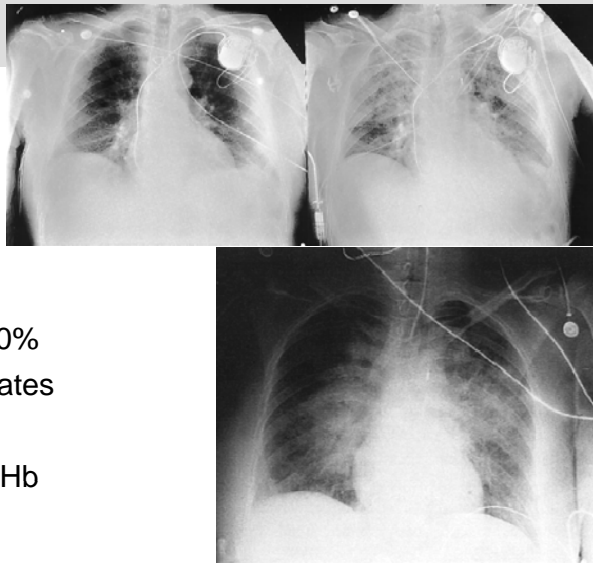
■ **Onset**

- 15min-2 d

■ **Easily mistaken**

■ **Presentation**

- Dyspnea
- Hemoptysis in 60%
- Pulmonary infiltrates
- Hypoxemia
- ≥ 2 g/dL drop in Hb



■ **Rebound pulmonary hypertension**

- Abrupt stoppage of NO, prostacycline
- Parameters worse than the baseline
- Marked CV instability
- Can be fatal

■ **Plentiful supply...**

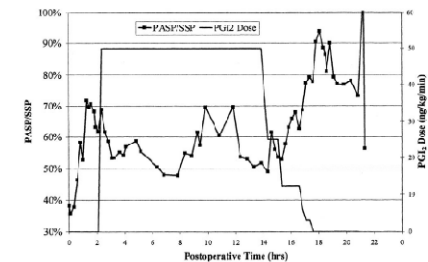
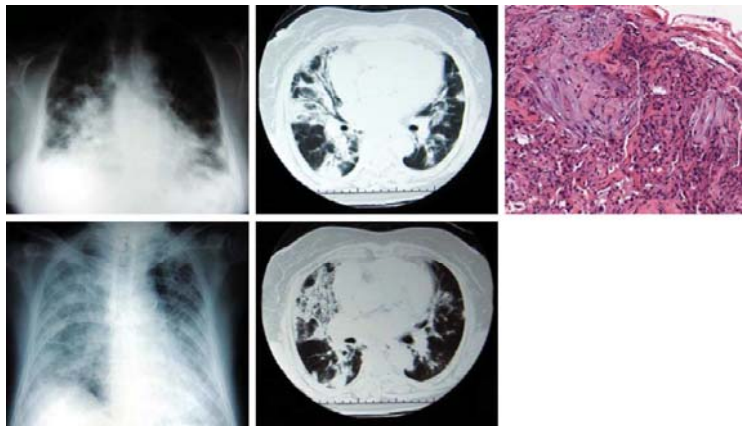


Fig. 1. Relationship of pulmonary hypertension to withdrawal of inhaled prostacycline. PASP = pulmonary artery systolic pressure; PGI₂ = inhaled prostacyclin; SSP = systemic systolic pressure.

Outpatients

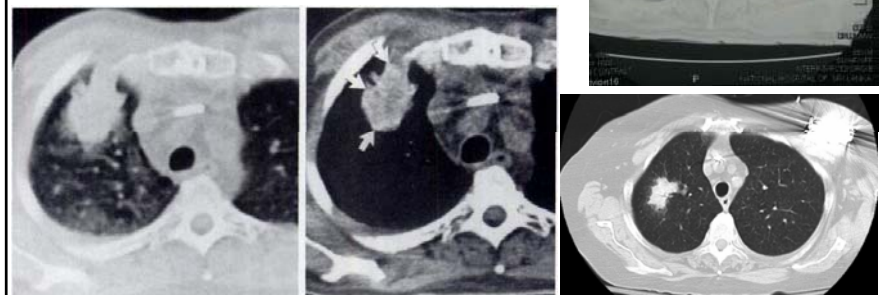
■ Dronedaronone – Multaq®

Siu et al. Fatal lung toxic effects related to dronedarone use. Arch Intern Med 2012; 172: 516-7

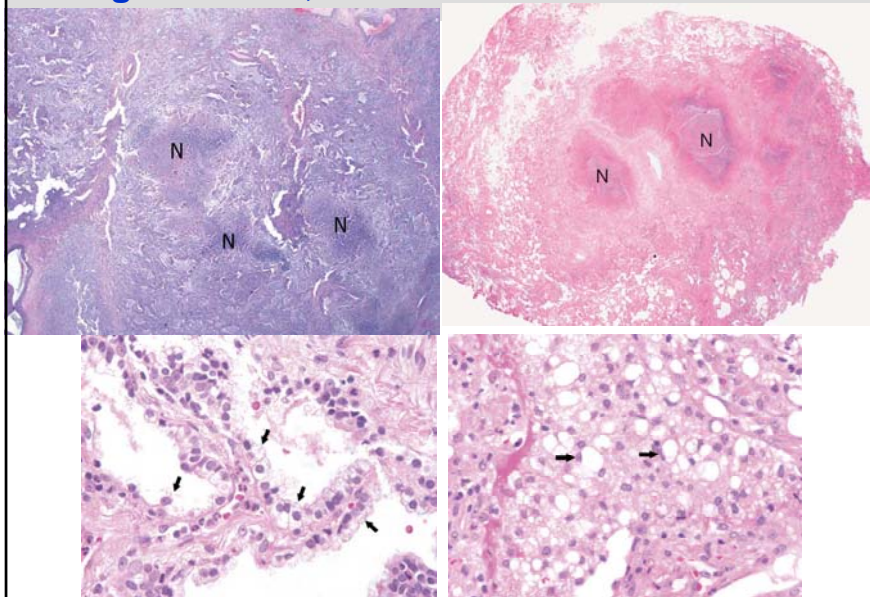


Amiodaronoma

- Electron-dense mass
- Can be 18F-DOG-avid
- 15/15 vanished in a few weeks after DTW



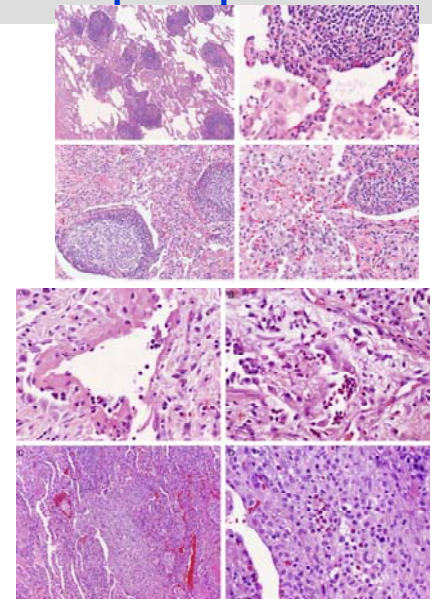
Ruangchira-Urai, 2008



Lymphoid hyperplasia - Eosinophilic pneumonia

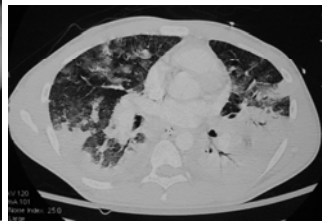
■ Larsen *et al.* 2012

- Twelve patients (7M)
- Diffuse infiltrates
- Histologic review
 - ❖ LH 8
 - ❖ Acute EoP 2
 - ❖ Chronic EoP 2



▣ **Anticonvulsants, minocycline (44 drugs)**

- Drug rash, fever, eosinophilia
- Atypical lymphocytes
- HHV 6, 7
- Internal organ involvement
 - ❖ Lung: 5-17%
 - ❖ Mortality ~5%



TKIs

▣ **Gefitinib Min 2011: 196 cases**

- Overall incidence
 - ❖ Japan 2.8
 - ❖ ROW 0.8
- GGO, septal thickening, diffuse disease
- Incidence 2.4 – 8.3%
- Mortality (ARDS) 40 - 70%
1.3 – 4.3%

▣ **Erlotinib**

- 7 reports – 2 fatalities
- Onset 5d – 2 mo

▣ **'DAD, BO, COP, HP, NSIP, UIP'**